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ORIGINAL PAPER

Choroidal thickness in preeclampsia measured by spectral-domain optical coherence tomography

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Abstract

Purpose To compare choroidal thickness (CT) measurements in preeclamptic and healthy women in the third trimester of pregnancy using optical coherence tomography.

Methods This cross-sectional study included 148 eyes of 74 women, divided into two groups: 27 healthy pregnant women in the third trimester (control group) and 47 age-matched pregnant women in the third trimester with preeclampsia (PE group). Of the 47 subjects in preeclampsia group, 26 were classified as having mild PE and 21 as having severe PE. Choroidal thickness was measured at ten different locations: at the fovea and every 500 µm from the fovea up to 2500 µm temporally and up to 2000 µm nasally.

Results Comparing CT of both groups, choroid always tended to be thicker in subjects with preeclampsia in comparison with healthy pregnant women, with statistical significance in nasal measures. Dividing PE group according to disease severity, women with severe preeclampsia tended to have thicker choroids in comparison with mild preeclamptic and healthy pregnant women. Choroid was also significantly thicker in preeclamptic patients with serous retinal detachment (SRD) in comparison with preeclamptic patients without SRD ($P < 0.01$ in all macular points).

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Conclusion Our study showed that choroid tends to be thicker in patients with preeclampsia, with statistical significance only in nasal measures. In patients with SRD, however, choroid is markedly thicker at all points analyzed. From these findings we can hypothesize that preeclampsia can cause a choroidal thickening, which begins in the peripapillary area. As the imbalance increases, the entire choroid becomes thickened.

Keywords Preeclampsia · Pregnancy · Choroidal thickness · Optical coherence tomography · Serous retinal detachment

Introduction

Preeclampsia (PE) is a pregnancy-specific multisystem hypertensive disorder and a leading cause of maternal, neonatal morbidity and mortality. PE is associated with new onset hypertension in the second half of pregnancy, often associated with proteinuria. Although the exact pathophysiology of this disease is not completely known, preeclampsia is associated with an inadequate maternal vascular response to placentation, with increased systemic vascular resistance and dysfunctional condition of the endothelium [1].

Some ocular changes that occur in physiological pregnancy are well known, including increased central corneal thickness and curvature and decreased corneal sensitivity and intraocular pressure [2]. Preeclampsia can also lead to numerous ocular changes, including optic neuropathy, retinal edema, central serous chorioretinopathy, retinal hemorrhages, Elschnig's spots, cotton wool spots, segmental or generalized constriction of the retinal arterioles and retinal detachment. Visual symptoms as decreased vision, photopsia and visual field defects may also occur [3].

Changes in choroidal circulation and choroidal ischemia in patients with preeclampsia have also been reported [4–6]. Choroidal ischemia involves the retinal pigment epithelium, causing breakdown of the blood–retinal barrier, resulting in leakage of proteins and fluid through the retinal pigment epithelium. This abnormal choroidal vascular pattern seen in preeclamptic patients could be the main cause of the serous retinal detachment rarely seen in these patients [7, 8].

Traditional imaging modalities such as indocyanine green [6] and fluorescein [4] angiography and Doppler ultrasonography [9] were used in the past to assess choroidal function during pregnancy. The development of the enhanced depth imaging (EDI) technique of spectral-domain optical coherence tomography (SD-OCT) systems has allowed adequate analysis of choroidal morphologic features [10]. EDI-OCT dramatically increased image resolution of choroid by decreasing signal strength posterior to the retinal pigment epithelium. Since it is a noninvasive diagnostic method, EDI-OCT is an important technique for the study of choroidal changes during preeclampsia [11, 12].

The aim of this study was to compare choroidal thickness measurements in preeclamptic and healthy women in the third trimester of pregnancy using the EDI-OCT.

Materials and methods

This cross-sectional study included 148 eyes of 74 women, divided into two groups: 27 healthy pregnant women in the third trimester (control group) and 47 age-matched pregnant women in the third trimester with preeclampsia or eclampsia (PE group). The participants were recruited between March and September 2016 at Hospital de Clinicas de Porto Alegre (HCPA), Brazil. All participants received in person full explanation about the study and provided written informed consent. This study was approved by HCPA research ethics committee and was conducted in accordance with the Declaration of Helsinki guidelines.

All participants were receiving prenatal care at HCPA and were in their third trimester of singleton pregnancy. Preeclampsia cases were defined according to criteria of the American College of Obstetricians and Gynecologists (ACOG) [13]. The distinction between mild and severe preeclampsia also followed ACOG criteria. Subjects with the previous ocular surgery, any ocular pathology, refractive disorders with the spherical equivalent greater than $\pm$ 1.0 diopters or intraocular pressure higher than 21 mmHg were excluded. Subjects with any chronic diseases,

including chronic hypertension, pre-gestational or gestational diabetes, were also excluded.

All study participants underwent an interview with demographic and background history. The ophthalmic examination included uncorrected visual acuity, best-corrected visual acuity, Goldmann applanation tonometry, slit-lamp-assisted biomicroscopy, indirect ophthalmoscopy and SD-OCT. All OCT scans were performed in the morning (8:00 am to 12:00 pm) to avoid diurnal variations of choroidal thickness [14, 15]. The same experienced ophthalmologist (CB) performed all ophthalmic examinations and OCT scans, using Heidelberg Spectralis OCT (Heidelberg Engineering Co, Heidelberg, Germany). Choroid was imaged with a six-line radial scan (30°, 9.2 mm) using the EDI setting, with 100 images averaged per section. All scans were reviewed before being included in the study. Those with image artifacts or inaccurate choroidal limits were excluded.

Choroidal thickness was determined as the vertical distance from the outer surface of the line formed by the retinal pigment epithelium to the choroidal–scleral interface using the Spectralis OCT measurement software. The measurements were taken by an experienced ophthalmologist (DL) masked to the participant group. Previous studies have already demonstrated the reproducibility of this technique, even across different OCT systems [16–18]. Choroidal thickness was measured at ten different locations: at the fovea and every 500 μm from the fovea up to 2500 μm temporally and up to 2000 μm nasally. We used the following abbreviations for the macular points: T5: choroidal thickness at 2500 μm temporally to the fovea; T4: choroidal thickness at 2000 μm temporally to the fovea; T3: choroidal thickness at 1500 μm temporally to the fovea; T2: choroidal thickness at 1000 μm temporally to the fovea; T1: choroidal thickness at 500 μm temporally to the fovea; SF: choroidal thickness at the fovea; N1: choroidal thickness at 500 μm nasally to the fovea; N2: choroidal thickness at 1000 μm nasally to the fovea; N3: choroidal thickness at 1500 μm nasally to the fovea; N4: choroidal thickness at 2000 μm nasally to the fovea.

Statistical analysis

Statistical analyses were performed using SPSS V.15.0 (SPSS Science, Chicago, Illinois, USA). Quantitative variables were presented as mean (± SD). Categorical variables were described by absolute and relative frequencies. To compare variables between groups, a *t* test was used for quantitative data and a χ^2 test for qualitative data. Differences in choroidal thickness were analyzed using generalized estimating equations (GEE) with Bonferroni adjustment. GEE eliminates the effect of laterality and identifies possible discrepancies between eyes. A P value ≤ 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the subjects are summarized in Table 1. The OCT scans were performed in 148 eyes of 74 women: 27 healthy pregnant women in the third trimester and 47 age-matched pregnant women in the third trimester with preeclampsia. Of the 47 subjects in preeclampsia group, 26 were classified as having mild preeclampsia and 21 as having severe preeclampsia. None of the subjects progressed to eclampsia. Five individuals with severe preeclampsia had serous retinal detachment at the ophthalmologic examination and OCT.

Comparing the 10 choroidal thicknesses measurements of both groups, choroid always tended to be thicker in subjects with preeclampsia, especially in nasal measurements. This difference was statistically significant in the N4, N3 and N2 macular points (Table 2).

We also performed the analysis dividing subjects into mild and severe preeclampsia. Pregnant women with severe preeclampsia tended to have thicker choroids in comparison with the other groups (Table 3). In N3 macular point, macular thickness was significantly higher in mild preeclampsia group in comparison with healthy pregnant group. In N4 macular point, macular thickness was significantly higher in mild and severe preeclampsia group in comparison with healthy pregnant group.

As an expressive number of women with severe preeclampsia were diagnosed with serous retinal detachment, we also analyzed the choroidal thickness of these patients (Table 4 and Fig. 1). Choroid was significantly thicker in preeclamptic patients with serous retinal detachment in comparison with

Table 1 Demographic and clinical characteristics of the study and control groups

	Healthy pregnancy group (n = 27)	Preeclampsia group (n = 47)	P value
Age (years) mean + SD	28.1 ± 7.0	28.3 ± 6.7	0.902*
Ethnicity—n (%)			
Caucasian	25 (92.6)	33 (73.3)	0.091**
African-American	2 (7.4)	12 (26.7)	
Gestational age (weeks) mean + SD	33.3 ± 2.6	32.6 ± 3.4	0.369*

*t test

**χ^2 test

Table 2 Comparison of choroidal thickness measurements between healthy pregnant women and women with preeclampsia

	Healthy pregnancy group (n = 27) Mean + SE (μm)	Preeclampsia group (n = 47) Mean + SE (μm)	P value
T5	278.5 + 13.9	285.5 + 12.4	0.708
T4	291.5 + 15.2	301.8 + 12.4	0.600
T3	300.9 + 14.3	312.4 + 13.2	0.557
T2	308.2 + 14.8	324.8 + 13.9	0.413
T1	311.2 + 14.8	340.0 + 13.9	0.155
SF	318.1 + 15.6	346.7 + 14.9	0.184
N1	291.3 + 14.9	332.0 + 14.8	0.052
N2	267.1 + 14.7	315.2 + 14.3	0.019
N3	239.4 + 13.9	294.4 + 13.8	0.005
N4	210.2 + 12.2	269.8 + 13.8	0.001

GEE with Bonferroni adjustment

N1: choroidal thickness at 500 μm nasal to the fovea; N2: choroidal thickness at 1000 μm nasal to the fovea; N3: choroidal thickness at 1500 μm nasal to the fovea; N4: choroidal thickness at 2000 μm nasal to the fovea; SF: choroidal thickness at the fovea; T1: choroidal thickness at 500 μm temporal to the fovea; T2: choroidal thickness at 1000 μm temporal to the fovea; T3: choroidal thickness at 1500 μm temporal to the fovea; T4: choroidal thickness at 2000 μm temporal to the fovea; T5: choroidal thickness at 2500 μm temporal to the fovea

preeclamptic patients without serous retinal detachment ($P < 0.01$ in all macular points).

Discussion

Preeclampsia affects 2–8% of all pregnancies and is associated with significant morbidity and mortality to the mother and the fetus [19]. PE is defined by the development of hypertension and proteinuria after 20 weeks gestation. In the absence of proteinuria, additional features contribute to diagnosis (thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual symptoms). The physiopathological process of PE begins with inadequate trophoblast invasion early in pregnancy. Placental ischemia leads to the release of factors associated with maternal systemic endothelial dysfunction [1]. The enhanced formation of endothelin and superoxide, the increased vascular sensitivity to angiotensin II and the decreased formation of vasodilators such as nitric oxide result in a generalized vasoconstriction throughout the body. Endothelial cell dysfunction and hyperpermeability are major causes of multiorgan failure in preeclampsia, causing cytotoxic and vasogenic edema [20].

Changes in choroidal circulation and choroidal ischemia in preeclampsia have already been reported [5]. The choroid is a complex vascular network which provides vascular supply for the retinal pigment

Table 3 Comparison of choroidal thickness measurements between healthy pregnant women, women with mild preeclampsia and women with severe preeclampsia

	Healthy pregnancy group (n = 27) Mean + SE (μm)	Mild preeclampsia group (n = 26) Mean + SE (μm)	Severe preeclampsia group (n = 21) Mean + SE (μm)	P value
T5	278.5 + 13.9	262.8 + 11.0	312.9 + 22.5	0.129
T4	291.5 + 15.2	282.8 + 12.4	324.9 + 21.9	0.247
T3	300.9 + 14.3	295.4 + 13.6	332.8 + 23.5	0.380
T2	308.2 + 14.8	309.1 + 14.8	344.3 + 24.6	0.409
T1	311.2 + 14.8	328.2 + 13.4	354.4 + 25.7	0.328
SF	318.1 + 15.6	337.9 + 15.2	357.6 + 27.3	0.401
N1	291.3 + 14.9	324.4 + 15.2	341.5 + 27.1	0.150
N2	267.1 + 14.7	308.6 + 14.3	323.5 + 26.4	0.060
N3	239.4 + 13.9a	287.1 + 13.0b	303.4 + 26.2ab	0.017
N4	210.2 + 12.2a	260.3 + 12.3b	281.4 + 26.5b	0.004

a,b same letter do not differ from each other at a 5% of significance by GEE with Bonferroni adjustment

N1: choroidal thickness at 500 μm nasal to the fovea; N2: choroidal thickness at 1000 μm nasal to the fovea; N3: choroidal thickness at 1500 μm nasal to the fovea; N4: choroidal thickness at 2000 μm nasal to the fovea; SF: choroidal thickness at the fovea; T1: choroidal thickness at 500 μm temporal to the fovea; T2: choroidal thickness at 1000 μm temporal to the fovea; T3: choroidal thickness at 1500 μm temporal to the fovea; T4: choroidal thickness at 2000 μm temporal to the fovea; T5: choroidal thickness at 2500 μm temporal to the fovea

Table 4 Comparison of choroidal thickness measurements between preeclamptic subjects without serous retinal detachment and preeclamptic subjects with serous retinal detachment

	Preeclampsia without RD (n = 42) Mean + SE (μm)	Preeclampsia with RD (n = 5) Mean + SE (μm)	P value
T5	266.7 + 10.2	441.1 + 27.0	< 0.001
T4	284.3 + 10.7	447.0 + 26.6	< 0.001
T3	294.9 + 12.0	456.9 + 25.2	< 0.001
T2	307.4 + 12.9	470.8 + 24.6	< 0.001
T1	321.9 + 12.6	489.7 + 25.7	< 0.001
SF	328.4 + 13.9	500.7 + 25.2	< 0.001
N1	313.7 + 13.7	486.0 + 28.6	< 0.001
N2	296.9 + 12.9	469.5 + 29.9	< 0.001
N3	276.6 + 12.3	443.4 + 35.1	< 0.001
N4	252.4 + 12.1	415.9 + 40.2	< 0.001

GEE with Bonferroni adjustment

N1: choroidal thickness at 500 μm nasal to the fovea; N2: choroidal thickness at 1000 μm nasal to the fovea; N3: choroidal thickness at 1500 μm nasal to the fovea; N4: choroidal thickness at 2000 μm nasal to the fovea; SF: choroidal thickness at the fovea; T1: choroidal thickness at 500 μm temporal to the fovea; T2: choroidal thickness at 1000 μm temporal to the fovea; T3: choroidal thickness at 1500 μm temporal to the fovea; T4: choroidal thickness at 2000 μm temporal to the fovea; T5: choroidal thickness at 2500 μm temporal to the fovea

epithelium and outer retina layers, representing the sole provider of oxygen and nutrients to the avascular fovea. Previous studies with indocyanine green angiography in patients with preeclampsia have demonstrated non-perfusion in the early phases of the angiogram and staining of the choroidal vasculature with subretinal leakage in the late phases of the angiogram, suggesting severe damage to choroidal

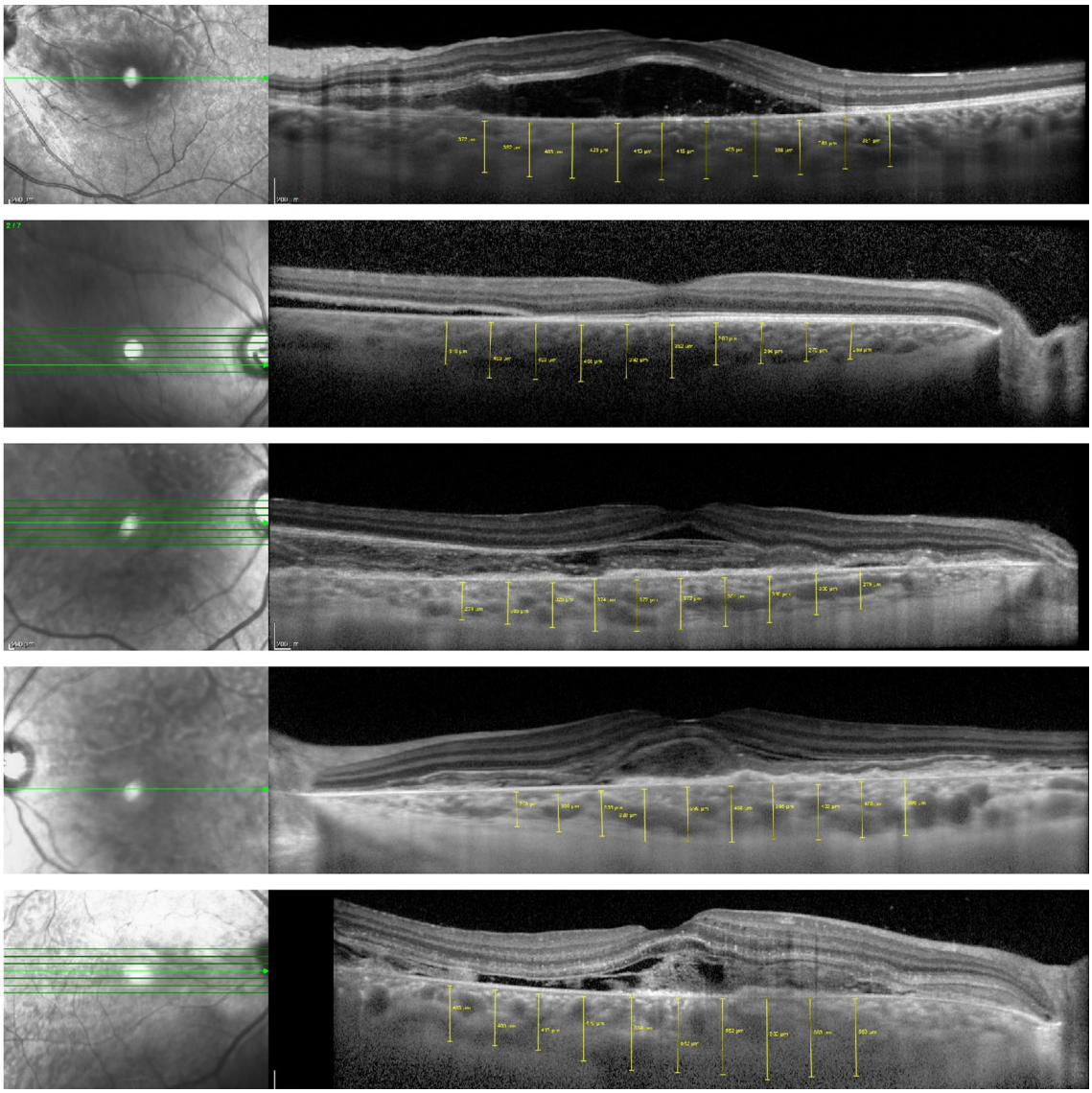

Fig. 1 Measurements of choroidal thickness in preeclamptic patients with serous retinal detachment

vascular walls [6]. Sathish and Arnold [21] also reported a delayed perfusion of the choriocapillaris, with areas of non-perfusion and gradual fluorescein leakage in a patient with preeclampsia and serous retinal detachment. The presence of Elschnig's spots in preeclamptic patients also demonstrates the presence of ischemic infarcts of RPE and choroid. An ischemic RPE can cause breakdown of the blood–retinal barrier, allowing leakage of fluid from the choroid into the subretinal space [22].

Although indocyanine green or fluorescein angiography can provide important information about choroid vessels, its possible deleterious effects on pregnant women should be remembered. Recent studies have analyzed possible changes in choroidal thickness in patients with preeclampsia using OCT, with controversial results [23–27]. Choroidal thickness can be influenced by major factors such as age, refractive error and axial length (AL), with increasing age, AL and decreasing refractive diopter being associated with a reduction of choroidal thickness [28]. Atas et al., Duru et al. and Sayin et al. found that the choroid is thinner in preeclamptic pregnant women in comparison with healthy pregnant women. Kim

et al., however, reported that the choroid in preeclamptic subjects was significantly thicker than in non-pregnant and healthy pregnant women. Garg et al. also reported choroidal thickening in the setting of severe preeclampsia. Both Duru et al. and Kim et al. found a significant decrease in choroidal thickness after delivery in preeclamptic subjects.

In this study, subjects with preeclampsia had thicker choroids in comparison with healthy pregnants. However, this difference was statistically significant only in nasal measurements, where the difference was more expressive. These findings may lead to the hypothesis that choroidal thickening during preeclampsia begins by the peripapillary area. When we classified patients with preeclampsia by severity criteria, patients with severe preeclampsia had the highest choroid thickness measurements. Again, statistical significance was found only in the locations closest to the optic disk.

Of the 21 patients with severe preeclampsia, five had serous retinal detachment. The apparently high prevalence of SRD among subjects with preeclampsia can be explained since this institute is a tertiary care hospital. Patients with significant visual complaints are usually referred from other hospitals, which often do not provide ophthalmologic care. Choroidal thickness of patients with SRD was significantly higher in all macular points in comparison with other preeclamptic patients. Choroid thickening in these subjects is very significant, with much larger measures compared to the other subjects. Subretinal fluid in preeclamptic patients is probably originated by a complex imbalance of the choroid, which can be caused by endothelial cell dysfunction, choroidal and RPE ischemia, hyperpermeability and increased hydrostatic pressure.

Our study has some limitations, such as the small number of subjects. Also, the cross-sectional design allows us to analyze choroidal characteristics only from the third trimester of pregnancy.

However, we attempted to minimize possible confounding factors by excluding subjects with pregestational or gestational diabetes or with chronic hypertension from the analysis.

We also performed all the OCT examinations during the morning to avoid diurnal variations and excluded subjects with refractive disorders with spherical equivalent greater than $\pm$ 1.0 diopters.

In conclusion, our study showed that choroid tends to be thicker in patients with preeclampsia, with statistical significance only in the measurements nasal to the fovea. In patients with SRD, however, choroid is markedly thicker at all points analyzed. From these findings, we can hypothesize that preeclampsia can cause a choroidal thickening, which begins in the peripapillary area. As the imbalance increases, the entire choroid becomes thickened. Further prospective studies with a larger number of subjects should be performed to confirm these findings and to analyze if perhaps choroidal thickness could be a predictive marker for preeclampsia severity.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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