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Posterior ocular blood flow in preeclamptic patients evaluated with optical coherence tomography angiography

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ABSTRACT

Objective: The aim of the present study was to examine the effects of preeclampsia on posterior ocular blood flow through optic coherence tomography angiography (OCTA).
Study design: The study included preeclamptic pregnant women (group PPW), healthy pregnant women (group HPW) and control non-pregnant women (group CNPW). The blood flow area of retina, optic nerve head and choriocapillaris were assessed through OCTA.
Results: Retinal superficial blood flow area (RSBFA) was similar in group PPW, HPW and CNPW ($p = 0.101$); likewise, there was not any difference in retinal superficial parafoveal vessel density (RSPFD) between the groups ($p = 0.685$). There was not any difference detected in retinal deep blood flow area (RDBFA) in group PPW, HPW and CNPW), likewise retinal deep parafoveal vessel density (RDPFD) was found similar between the groups ($p = 0.184$).

The choriocapillaris blood flow area (CBFA) was different between the groups ($p = 0.000$) and less in the group PPW than in group HPW. The CBFA was $1.875 \pm 0.05\ mm^2$ in group the PPW, $1.928 \pm 0.05\ mm^2$ in the group HPW and $1.464 \pm 0.06\ mm^2$ in the group CNPW. Similarly, the optic nerve head blood flow area was lower in the group PPW compared to the group HPW ($1.567 \pm 0.38\ mm^2$, $1.690 \pm 0.20\ mm^2$ and $1.592 \pm 0.25\ mm^2$ in the group PPW, group HPW and group CNPW respectively; $p = 0.002$).
Conclusion: Posterior segment ocular blood flow may be diminished in preeclamptic women. OCTA may enable to monitor ocular blood flow dynamics and give important clues in the diagnosis of retinal vascular pathologies accompanied by systemic diseases.

1. Introduction

Preeclampsia is a severe condition characterized by proteinuria, hypertension and multiorgan failure appearing during gestation and the convulsions accompany the disease in eclampsia [1]. Although the exact cause for preeclampsia is not clear, abnormal placentation through trophoblastic invasion in the uterus, diffuse endothelial cell dysfunction linked to the release of cytokines after the onset of the pregnancy, vasoconstriction, and platelet activation are all accused. Increased systemic blood pressure creates the clinical picture in pregnant women through disruption of micro-circulation in target organs such as central nervous system, liver, kidneys and eyes [2].

The ocular conditions arising from hormonal, metabolic, and immunologic mechanisms in preeclampsia may range widely from benign physiological changes to severe pathologies presenting visual loss and urgent treatment [3]. Some ophthalmological symptoms including decreased or blurred vision, photopsy, visual field defects, and focusing failure may ensue, which are encountered more frequently in severe

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preeclampsia and eclampsia. The most common eye related complications observed in preeclamptic pregnant women presenting the aforesaid symptoms are hypertensive retinopathy, exudative retinal detachment and cortical blindness [4].

Optic coherence tomography (OCT) is a device analyzing ocular structures in 3 dimensional scale using a laser source. The pursuit on functional extensions of its applications yielded the invention of OCT angiography (OCTA), which is a novel ocular imaging modality relying on the detection of blood flow in the vessels without requiring any dye. It is used as a fast and important diagnostic tool for morphological assessment of retinal vascular structures in retinal diseases such as diabetic retinopathy, retinal vein obstructions, central serous chorioretinopathy and age related macular degeneration [5].

Although there are several studies evaluating retinal vessels qualitatively or choroidal and macular thickness quantitatively by OCT without angiographic component in preeclamptic women, there is not yet any study assessing retinal or choroidal blood flow quantitatively in these patients [6–8]. The aim of the present study was to examine, for the first time, the effect of preeclampsia on ocular blood flow in posterior segment with an OCTA device.

2. Material and methods

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments. Approval for the study was granted by the Scientific Research Ethics Committee of Kahramanmaras Sütcü Imam University (KSU) Medical Faculty (approval number-date: 277-03.01.2018).

The present study had a prospective cross-sectional design. The study content was explained and the study started after obtaining the written consent of the participants. The diagnosis of non-severe preeclampsia was based on the criteria established by American College of Obstetricians and Gynecologists Association, which is a blood pressure over 140/90 mmHg but less than 160/110 mmHg detected on two occasions, proteinuria more than 0.3 gr/24 h and appeared after the 20 week gestational age. In addition, signs suggestive of severe preeclampsia such as pulmonary edema, myocardial infarction, stroke, thrombocytopenia, renal failure, etc. were used as an exclusion criteria [9].

All participants underwent a general ophthalmologic examination and subjects with previous history of ophthalmologic pathology (cataract, glaucoma, retinal diseases, uveitis, iridocyclitis etc.) and/or any previous ophthalmologic surgery as well as the patients with any systemic disease such as cardiac disease, hypertension, central nervous system disease, systemic vasculitis etc. were excluded from the study. Also, incompliant patients or the patients with poor image quality were excluded.

Optic coherence tomography angiography measurements were performed via AngioVue device (Optovue, Fremont, CA, USA).

Optic coherence tomography angiography measurements of the retina and optic nerve head were performed via AngioVue device (Optovue, Fremont, CA, USA). We followed recommendation of the manufacturer to scan and capture the images. Shortly, the patient was positioned in front of the device, placedher chin on the chinrest and requested to maintain a steady gaze. The internal fixation target of the device helped the patient align the eye. The accurate focus and resolution of the ocular images were obtained by the autofocus function of the device. Although the images were tried to be taken at one time, the patients were allowed to blink or reposition their heads between the scans.

The images with poor resolution, motion artifacts and a signal strength index under 50 were eliminated. All measurements were recorded and calculated by the device, obviating any manual calculation. The measurements were done on both eyes but the only the values obtained from the right eye were taken into assessment. Retinal, choroidal and optic nerve head measurements were taken sequentially without dilatation of pupilla under normal lighting conditions.

Retinal and choriocapillaris images were taken from acube with a predetermined thickness of 6 × 6 mm centered around the fovea. The vascular layers investigated in the retinal cube are identified as follows. Superficial retinal vascular plexus is between internal limiting membrane and posterior margin of internal plexiform layer; deep retinal vascular plexus is between posterior margin of internal plexiform layer and posterior margin of outer plexiform layer and the choriocapillaris is the vascular plexus of 30 μm thickness located just beneath the retinal pigment epithelium. The images from optic nerve were taken from a cube with a predetermined thickness of 6 × 6 mm around optic nerve head and superficial vascular layer was analyzed in this cube.

AngioAnalytics software of the device was used to make the calculations. The software can calculate two parameters in a specified cube. One is the flow, which is defined as the area occupied by the vessels in a circle of 1 mm in diameter and the unit is expressed as mm^2. The other parameter is the vessel density, which is the percentage of vascular structures in the specified cube and the unit is given as percentage (%). The flow and the density parameters are interpreted as indirect index of blood flow for that segment.

In the retina, the flow was analyzed in superficial vascular plexus, deep vascular plexus and choriocapillaris plexus, which yielded the retinal superficial blood flow area (RSBFA), retinal deep blood flow area (RDBFA) and choriocapillaris blood flow area (CBFA). The vessel density in the retina was calculated as the parafoveal vessel density (PFD), which is defined as the percentage area of the vessels in a parafoveal circle of 3 mm centered around the fovea excluding the fovea. The parafoveal density was calculated for retinal superficial vascular plexus (RSPFD) and deep retinal vascular plexus (RDPFD). In the optic nerve, the flow calculation in the superficial optic nerve head yielded optic nerve head blood flow area (ONHBFA).

2.1. Statistical analysis

Given the median and standard deviation, sample size is decided by an online sample size calculators. To detect a 10% change between the groups with a power of 95 and type 1 error of 5%, the total number of subjects required in the study was found 69 with a minimum number of 23 subjects in each group. The categorical data were expressed as frequency and percentage (%) while numerical data were expressed as mean ± standard deviation.

For group comparisons, ANOVA was used after the normality of distribution was confirmed with Kolmogorov-Smirnov test and the homogeneity of the variances with Levene's test and post hoc comparisons were done with Tukey's HSD test. Kruskal Wallis test was used in case these assumptions were not sustained and Scheffe test was used for post-hoc comparisons. The categorical data was assessed with Chi square test. The statistical significance level was accepted as $p < 0.05$ for all analyses. The statistical analyses of the data were performed by using SPSS 20.0 software (SPSS Inc., Chicago 2, USA).

3. Results

A total of 78 subjects were enrolled in the research according to the study protocol. Twenty seven pregnant women (34.6%) with a gestational age of 20 weeks and later diagnosed with non-severe preeclampsia comprised preeclamptic pregnant women group (PPW), 26 healthy pregnant women (33.3%) with gestational age of 20 weeks and later comprised healthy pregnant women group (HPW) and 25 healthy non-pregnant control women (32.1%) of similar age comprised control non-pregnant women group (CNPW). The average age was 31.44 ± 5.89 (22–43) years in PPW, 28.07 ± 5.95 (20–43) years in HPW and 30.32 ± 4.44 (24–41) years in CNPW respectively and there was not any significant difference between the groups ($p = 0.08$). The

Table 1
Demographic data of patients.

	Groups			P value
	Group PPW (n = 27) Mean ± SD	Group HPW (n = 26) Mean ± SD	Group CNPW (n = 25) Mean ± SD	
Age (y)	31.44 ± 5.89	28.07 ± 5.95	30.32 ± 4.44	0.08
Gestation (wk)	32.66 ± 3.60	31.92 ± 2.93		0.415
Systolic pressure (mmHg)	140.63 ± 10.04	103.23 ± 8.41	124.44 ± 17.96	
Diastolic pressure (mmHg)	78.78 ± 7.68	52.42 ± 4.21	68.52 ± 7.08	
Gestational age at delivery (wk)	35.7 ± 3.67	39.5 ± 1.27		0.000*
Birth weight (gr)	2711.48 ± 737.66	3192.31 ± 165.37		0.005*

Mann Whitney-*U* test and One-way ANOVA; Post hoc test: Scheffe test; Welch test and Tamhane's T2 test.
PPW: Preeclamptic pregnant group, HPW: Healthy pregnant women, CNPW: Control non-pregnant women.
* $p \leq 0.05$. The difference between the three groups were statistically significant

gestational age was similar between PPW (32.66 ± 3.60 weeks) and HPW (31.92 ± 2.93 weeks) (p = 0.415). All healthy pregnant women maintained a healthy status throughout the study. Severe preeclampsia developed in 6 non-severe preeclamptic pregnant women during the course of the pregnancy and five of them resulted in preterm delivery. Table 1 shows the demographic data of the pregnant women during pregnancy and delivery. Evaluation of retinal superficial blood flow area revealed no difference between group PPW (1.452 ± 0.08 mm^2), group HPW (1.488 ± 0.07 mm^2) and group CNPW (1.445 ± 0.08 mm^2) (p = 0.101). Similarly, retinal superficial parafoveal vessel density (RSPFD) was found similar in group PPW, group HPW and group CNPW (55.88% ± 3.52%, 55.98% ± 2.40%, 55.30% ± 3.02%, respectively; p = 0.685). Retinal deep blood flow area (RDBFA) was similar between the groups (1.525 ± 0.11 mm^2, 1.581 ± 0.12 mm^2, 1.549 ± 0.10 mm^2, in group PPW, HPW and CNPW respectively; p = 0.189), and no difference was found between the groups with regard to retinal deep parafoveal vessel density (RDPFD) (63.66% ± 2.23%, 64.09% ± 2.31%, 64.78% ± 1.99%, in group PPW, HPW and CNPW respectively; p = 0.184).

Choriocapillaris blood flow area was significantly different between the groups. The CBFA was 1.875 ± 0.05 mm^2 in PPW group, 1.928 ± 0.05 mm^2 in HPW group and 1.464 ± 0.06 mm^2 in CNPW group (p = 0.000). Post-hoc analysis revealed that the CBFA was lower in group PPW than in group HPW (p = 0.004). The analysis also showed that CBFA was higher in both pregnant women groups compared to the control non-pregnant women group (p = 0.000, for both comparisons).

A change in the blood flow area in superficial layer of optic nerve head was detected between the groups (1.567 ± 0.38 mm^2, 1.690 ± 0.20 mm^2, 1.592 ± 0.25 mm^2 in PPW, HPW and CNPW respectively; p = 0.002). Post-hoc analysis revealed that optic nerve head blood flow area in HPW was higher than in PPW (p = 0.006) and CNPW (p = 0.005). Preeclamptic and non-pregnant women were similar with regard to ONHBFA (p = 1.00).

Comparison of age, RSBFA, RSPFD, RDBFA, RDPFD, CBFA and ONHBFA between the groups was shown in Table 2. Additionally, optic nerve head blood flow area, retinal superficial-deep blood flow area and choriocapillaris blood flow area of patients in three different groups were shown in Fig. 1 and retinal superficial-deep parafoveal vessel density were shown Fig. 2.

Table 2
Comparison of Retinal superficial blood flow area/parafoveal vessel density, Retinal deep blood flow area/parafoveal vessel density, Choriocapillaris blood flow area and Optic nerve head blood flow area among the three study groups.

	Groups			P value
	Group PPW (n = 27) Mean ± SD	Group HPW (n = 26) Mean ± SD	Group CNPW (n = 25) Mean ± SD	
RSBFA (mm^2)	1.452 ± 0.08	1.488 ± 0.07	1.445 ± 0.08	0.101
RSPFD (%)	55.88 ± 3.52	55.98 ± 2.40	55.30 ± 3.02	0.685
RDBFA (mm^2)	1.525 ± 0.11	1.581 ± 0.12	1.549 ± 0.10	0.189
RDPFD (%)	63.66 ± 2.23	64.09 ± 2.31	64.78 ± 1.99	0.184
CBFA (mm^2)	1.875 ± 0.05#	1.928 ± 0.05	1.464 ± 0.06#	0.000*
ONHBFA (mm^2)	1.567 ± 0.38#	1.690 ± 0.20	1.592 ± 0.25#	0.002#

Independent-Samples T test and One-way ANOVA; Kruskal-Wallis H test.
Post hoc test: Scheffe test; Independent samples test-pairwise comparisons analyze.
PPW: Preeclamptic pregnant group, HPW: Healty pregnant women, CNPW: Control non-pregnant women RSBFA: Retinal superficial blood flow area, RSPFD: Retinal superficial parafoveal vessel density, RDBFA: Retinal deep blood flow area, RDPFD: Retinal deep parafoveal vessel density, CBFA: Choriocapillaris blood flow area, ONHBFA: Optic nerve head blood flow area
* $p \leq 0.05$, The difference between the three groups were statistically significant.
# $p \leq 0.05$, compared with group 2.

4. Discussion

The present study has the characteristics of being the first study in which the impact of preeclampsia on posterior ocular circulation was assessed objectively by optic coherence tomography angiography. Although OCT has been accepted widely in ocular armamentarium for more than a decade, it wasn't until recently that ocular blood flow area and vascular structures could be analyzed quantitatively using OCT [10–14]. OCTA enables both structural and flow data simultaneously, giving additional circulatory information superimposed on classical OCT slices. Analyzing retinal slabs allows assessing retinal vascular plexus spreaded throughout a retinal cube.

The OCT used herein makes 70,000 scans per second and utilizes a laser wavelength of 840 nm and operates with "split-spectrum amplitude-decorrelation angiography" algorithm perceiving intrinsic movement of erythrocytes in the vascular tree as contrast. This algorithm splits OCT spectrum to get narrower bands and ameliorates signal to noise ratio by averaging the signals detected in each band. The calculations of OCTA relies on "flow area" reflecting vessel area and "vessel density" which is the percentage area of blood vessels. The flow area and the vessel density are surrogate markers of real blood flow for that segment. These parameters have been shown to be reliable in both repeatability and reproducibility [15].

In preeclampsia, vascular dysregulation mechanisms have been suggested to explain the tissue ischemia. Cerebral blood flow dynamics in preeclampsia with magnetic resonance imaging showed that cerebral perfusion pressure is increased through decreased vascular resistance and hyperperfusion may cause vasogenic edema leading to tissue ischemia and other signs of organ insufficiency [16]. It is shown that increased perfusion pressure in preeclampsia may end up with

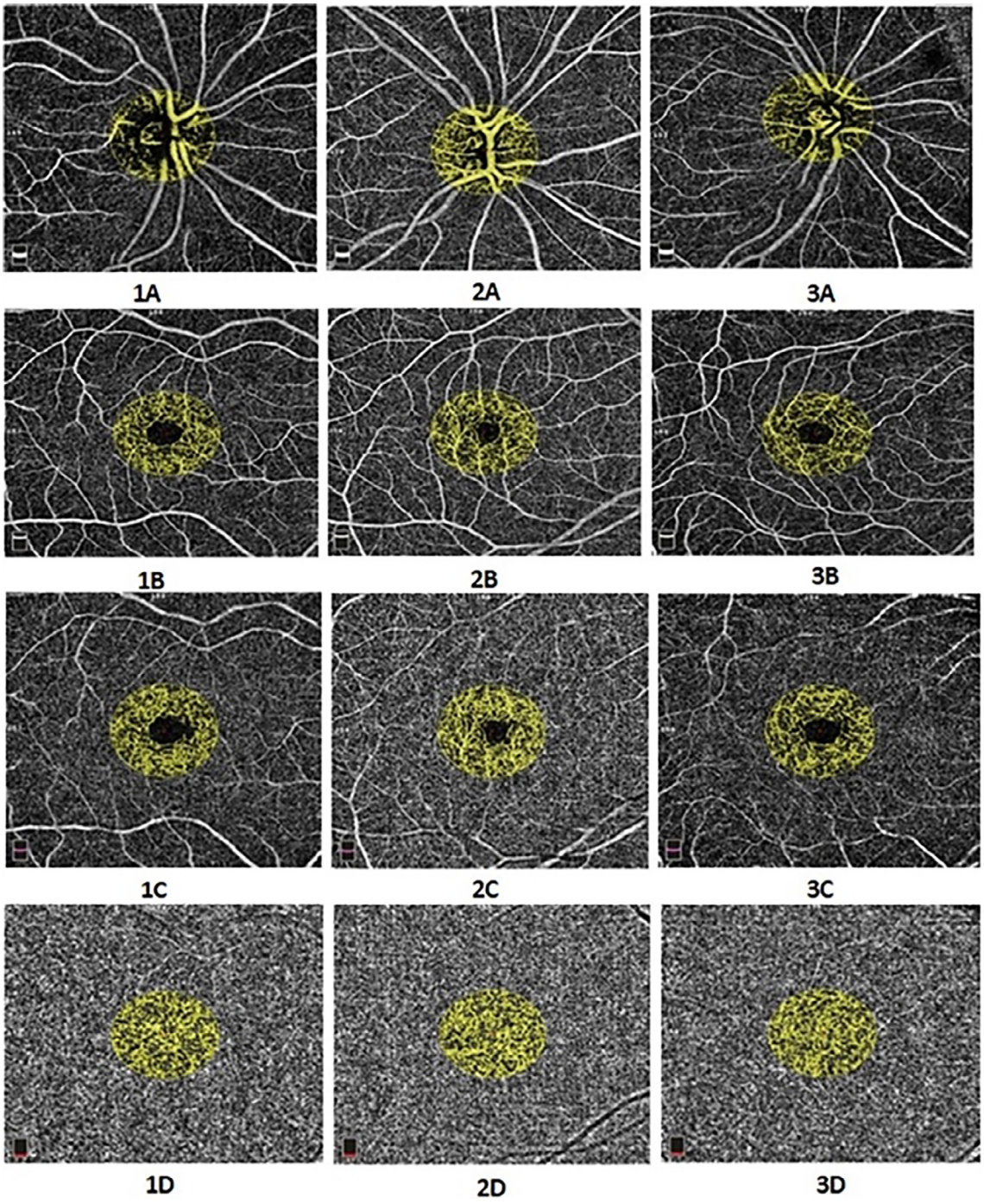

Fig. 1. Optic nerve head blood flow area, Retinal superficial-deep blood flow area and Choriocapillaris blood flow area of patients in three different groups. 1. Preeclamptic pregnant women 2. Healthy pregnant women 3. Control non-pregnant women. A. Optic nerve head blood flow area (ONHBFA) B. Retinal superficial blood flow area (RSBFA) C. Retinal deep blood flow area (RDBFA) D. Choriocapillaris blood flow area (CBFA).

decreased cranial blood flow [17]. Events taking place in preeclampsia is too complex and investigations are still ongoing to elucidate the entailing mechanism. Nonetheless, it appears that increased over-perfusion leading to hypoperfusion may be a common pathophysiological entity during the process. Although we didn't check cerebral blood flow in our patients, it would be better to include these analyses in new researches.

In this research, we demonstrated that preeclampsia created posterior ocular blood flow changes. In the eye, the optic nerve head and retinal vessels but choriocapillaris have an autoregulation system, which is not affected by autonomic nervous system. Although choroidal flow increases in proportion to systemic blood flow in case blood pressure is increased, the same is not true for retinal or optic nerve head flow, which brings about a balanced blood flow to these tissues under normal circumstances [18].

This study is unique in the literature for quantitatively establishing increased blood flow in posterior segment of the eye in pregnant women. We found a higher blood flow area in the choriocapillaris and optic nerve head in our healthy pregnant women compared to the control non-pregnant women ($p < 0.05$), as expected. Pregnancy is associated with increased blood flow to the organs including eye due to elevated cardiac rate and output, enlarged intravascular volume, and

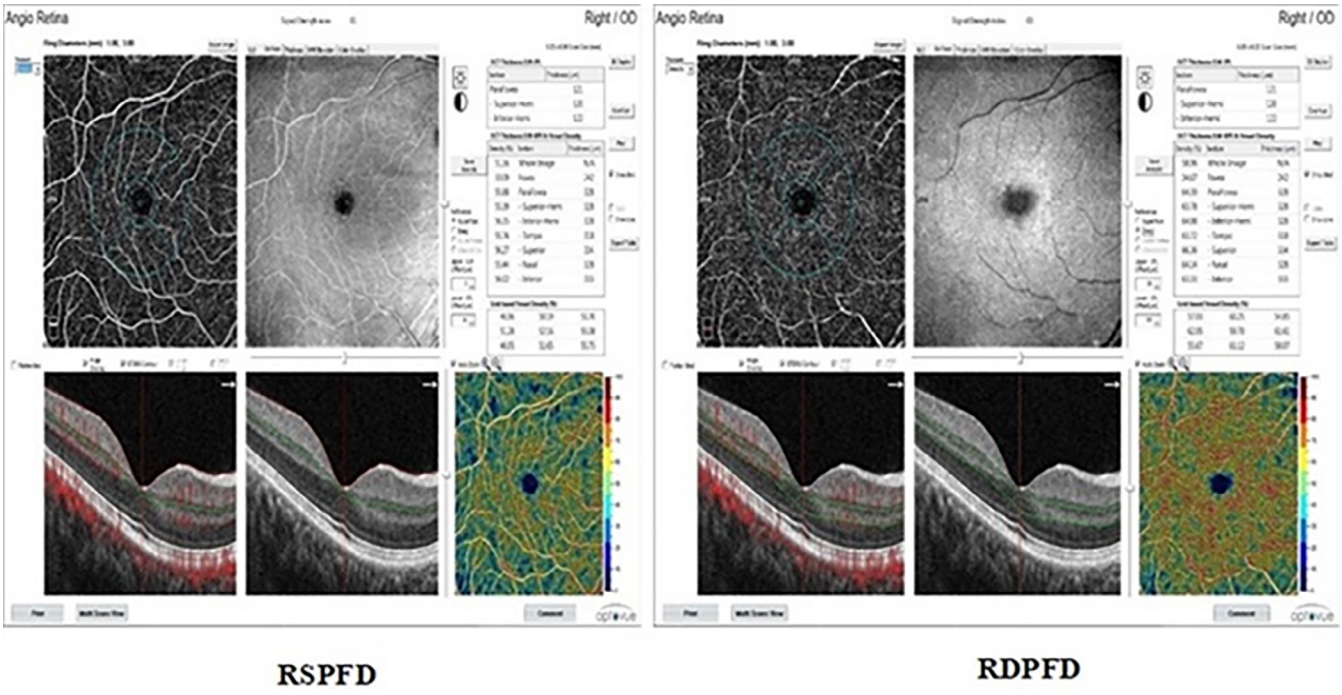

Fig. 2. Retinal superficial-deep parafoveal vessel density. RSPFD: Retinal superficial parafoveal vessel density. RDPFD: Retinal deep parafoveal vessel density.

peripheral vascular dilatation [19–23]. Since choriocapillaris are devoid of autoregulation, they are directly influenced by systemic vasoregulation and being subjected to increased vessel area in our healthy pregnant women.

In our study, preeclamptic group had lower choriocapillaris flow area than in healthy pregnant women ($p < 0.05$). Although needs confirmation, impaired choroidal flow may be related to choroidal overperfusion leading to vasogenic tissue edema, giving rise to a paradoxical perfusion decrease, a mechanism used to explain cerebral ischemia in preeclampsia as well [16,17]. The explanation for this situation may involve other mechanisms as well. Vasoconstrictor agents secreted by trophoblasts emerging from abnormal placental invasion may also be held responsible for ominous vasospasm leading to impaired blood flow [18].

It can be debated that if this deficit is important from a clinical point of view. Choriocapillaris are an essential supply for outer retina and, to some extent, fluctuations in this vascular bed can be tolerated by retina. But at above a certain threshold, this delicate balance may be destroyed, leading to a wide spread breakdown of outer blood retinal barrier, which is the clinical scenario seen in preeclampsia and eclampsia. It is possible that outer blood retinal barrier breakdown seen in preeclamptic patients may be related to choriocapillaris deficit detected in this study. It is not likely to ascertain that how much vascular compromise gives rise to the clinical symptoms and this question is yet to be answered. Whether this choriocapillaris loss is an early sign of other future significant morbidities encountered in preeclampsia and eclampsia can be investigated with further analyses as well.

It is noteworthy that optic nerve head circulation is still subjected to physiological alterations during pregnancy. Despite autoregulation, blood flow area in optic nerve head of the healthy pregnant women ($1.690 \pm 0.20\,mm^2$) was surprisingly higher than that of the non-pregnant women ($1.592 \pm 0.25\,mm^2$), showing a profound response to pregnancy ($p = 0.006$). Our study interestingly found that the preeclamptic pregnant women had the lowest blood flow area ($1.567 \pm 0.38\,mm^2$), which may be explained with overperfusion injury or vasoconstriction mechanisms as explained above. Based on these variations in blood flow area, it can be claimed that optic nerve head autoregulation capacity might be very vulnerable to change in systemic hemodynamics and its physiological limit may be overwhelmed in abnormal increase of blood pressure such as in preeclampsia or malignant hypertension [24].

The retinal blood flow areas were similar in all three groups in our study. It was neither increased in healthy pregnant women nor decreased in preeclamptic pregnant women, contrary to what might have been expected. It means that retina can maintain autoregulation effectively without an overflow and sustain a consistent blood flow in elevated systemic pressure due to non-severe preeclampsia. Furthermore, our study may imply that retinal autoregulation capacity could be stronger and more resistant to surges in systemic blood pressure compared to that of optic nerve circulation.

There are some investigations regarding ocular pathologies in preeclamptic disorders. Atas et al. and Sayın et al. studied the choroidal thickness in healthy and preeclamptic pregnant women with OCT and both investigations reported a decrease in choroidal thickness of preeclamptic pregnant women compared to healthy pregnant women [7,8]. Although only the thickness measurements were done and blood flow couldn't be evaluated due to the technical inabilities of those times, the mentioned studies appear to confirm indirectly our findings.

Previous studies showed that retinal and choroidal layers are affected by microcirculatory disorder in preeclampsia, which included local or generalized vasoconstriction, diffuse retinal edema, hemorrhage, exudates and choroidal infarction [6,25–27]. These circulatory disorders have been shown via fundus fluorescein angiography or indocyanine green angiography in preeclampsia, though quantitative data is unable to obtain [28,29].

Since both methods are invasive procedures necessitating the intravenous administration of contrast agents, adverse effects of which are not known in pregnant women, use of such methods raises some concerns and is not suggested generally [30]. Although there are also other diagnostic approaches such as ocular perfusion pressure, ocular Doppler ultrasound to show ocular blood flow, the use of these techniques has remained limited because of their subjective nature [31,32]. Having no adverse effects and being more versatile and objective method, OCTA has started substituting other practices in diagnosis and monitoring of vascular diseases of posterior segment [14,33].

Our research was designed prospectively and contained age and

gestational week matched control group, which gave the strength to its result. In the present study, we report first time the OCTA data of the preeclamptic pregnant women in the literature. We detected quantitatively that choriocapillaris flow was lower in preeclamptic pregnant women than in healthy pregnant women. Besides, optic nerve head blood flow area in the preeclamptic pregnant women was even lower than in the control non-pregnant women, which may reflect a substantial flow deficit in the optic nerve head in these subjects. The OCT device we used was able to create high resolution pictures in most of the times due to its unique features including eye tracking system, motion correction technology and projection artifact prevention modality.

There are also some limitations of this study. We only enrolled patients with non-severe preeclampsia and the patients with severe preeclampsia and eclampsia were not included into the study due to probable difficulties we might have faced during measurements. Firstly, these patients generally need close monitoring and treatment in the delivery room and the urgent delivery of the baby could be necessary. Additionally, since severe preeclamptic and eclamptic pregnant women are severely debilitated, they are unlikely to cope with the challenges during OCTA measurements such as sitting on the chair and putting their chin on the chinrest. Another limitation of the study might be the lack of repeated OCTA assessments taken after the delivery. The another point is that the laser wavelength of the OCT device well enables visualisation of choriocapillaris, though, may be weaker to analyse deeper choroidal layers.

In this study we detected that blood circulation in choriocapillaris and optic nerve head is decreased. As a conclusion, OCTA is a new and promising innovation for evaluation of blood flow dynamics and may provide important information for diagnosis and follow-up of any ocular pathology arising from vascular layers of the globe.

Declaration of Competing Interest

The authors report no conflict of interest.

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