Evaluation of Retinal and Choroidal Microvascular Changes in Healthy Pregnant Women Using Optical Coherence

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ABSTRACT

Purpose: To evaluate retinal and choroidal micro-vascular changes in healthy pregnant women using optical coherence tomography angiography (OCTA).

Materials and Methods: This cross-sectional cohort study was conducted on healthy pregnant and non-pregnant women. Macular flow area (superficial, deep, and choriocapillaris [CC]), superficial and deep vessel density, foveal avascular zone (FAZ) area, central foveal thickness (CFT), and subfoveal choroidal thickness (SFCT) were measured using OCTA.

Results: We evaluated 23 eyes of 23 pregnant women with mean age of 31.5±4.1 (26-43) years and 23 eyes of 23 age-matched controls (mean age: 30.5±3.9 [23-43] years). Superficial, deep, and CC macular flow areas were measured as 16.48±2.1, 14.55±0.8, and 18.71±1.1 in the pregnant women and 13.64±1.1, 13.97±0.6, and 17.63±0.4 in controls, respectively. In addition, superficial and deep vessel densities were significantly greater in the pregnant women than controls in all areas (foveal, parafoveal, temporal, superior, nasal, inferior) ($P<0.05$ for all). There were no significant differences in FAZ area, CFT or SFCT between the groups ($P>0.05$ for all).

Conclusion: Retinochoroidal micro-vascular flow and vessel density in the macular area were increased in pregnant women compared to non-pregnant controls. The clinical relevance of these alterations should be evaluated in further studies.

Keywords: Macular micro-circulation, Optical coherence tomography angiography, Pregnancy.

INTRODUCTION

Pregnancy involves a series of hormonal, metabolic, vascular, and immunologic changes that can affect ocular function.[1-4] Although most of these changes are normalized in the postpartum period, some alterations such as diabetic retinopathy may persist.[2] The progression of diabetic findings, increased incidence of central serous retinopathy and fluctuations in vision have been reported later in pregnancy, especially in patients with preeclampsia.[5]

The retinochoroidal disease has been documented in healthy pregnant women and attributed to hormonal hypercoagulability or hemodynamic changes during pregnancy.[1,2,6] However, the use of fluorescein or indocyanine green angiography is limited in pregnant women because of their teratogenic effects and concerns regarding breastfeeding.[7]

Since the recent commercial availability of optical coherence tomography angiography (OCTA) devices, which relies on the Doppler effect principle, OCTA is now being used in these patients. OCTA is a dye-free modality that provides valuable data for the evaluation of retinal circulation in both the superficial and deep capillary plexus as well as choroidal circulation in certain retinal diseases like diabetic retinopathy, central serous chorioretinopathy, and age-related macular degeneration.[8-10]

The aim of this study was to compare retinal superficial capillary plexus (SCP), deep capillary plexus (DCP), choroidal thickness (CT), and foveal avascular zone (FAZ) area between healthy pregnant and non-pregnant women using OCTA imaging.

Authors report no conflict of interest. The work has not been presented in any meeting.

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MATERIALS AND METHODS

Participants

Twenty-three healthy pregnant women and 23 age-matched controls were enrolled to the study. Both the study and control groups were selected from individuals who had no chronic ocular or systemic disease. The study protocol was approved by Izmir University Hospital Institutional Review Board and Ethics Committee. The research was conducted in accordance tenets of the Declaration of Helsinki, and detailed written informed consent was obtained from each subject before participation.

Study Design

This was a cross-sectional cohort study. Exclusion criteria for both groups included any systemic disease (e.g. diabetes mellitus, arterial hypertension, anemia, renal disease, and cardiovascular disease), epilepsy, migraine, and history of any chronic drug use including analgesics, antihistamines, vasodilators, decongestants, anticoagulants, oral contraceptives, and sildenafil. In addition, subjects with nystagmus, corneal opacity, cataract, glaucoma, congenital or acquired retinal disorders including any vascular disease, history of ocular trauma or surgery, and refractive spherical error >5 D or cylinder error >3 D were excluded. Women who were pregnant or breastfeeding were excluded from the control group.

Examination

Age, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded. All participants underwent a comprehensive ophthalmic examination including autorefractometry and keratometry, best-corrected visual acuity assessment, slit-lamp anterior segment examination, axial length (AL) measurement by IOLMaster (ver. 3.02; Carl Zeiss, Meditec, Jena, Germany), intraocular pressure (IOP) measurement using Goldmann applanation tonometry, and fundus examination including indirect ophthalmoscopy with a 90 D lens and OCTA.

Macular flow area in the SCP, DCP, and choriocapillaris (CC), superficial and deep vessel density, FAZ area, central foveal thickness (CFT), and subfoveal choroidal thickness (SFCT) were measured using OCTA in all subjects. The participants and controls were asked not to consume any caffeinated beverages, chocolate, or any medication for at least 24 h before OCTA measurement. The study participants were non-smokers. All OCTA scans were performed during the same time of the day (between 10:00 and 12:00 am) to avoid diurnal fluctuations. Participants in both groups were instructed not to eat or drink until the end of the evaluations.

Optical Coherence Tomography Angiography Measurements

XR Avanti AngioVue spectral domain OCTA (Software Version 2015.1.1.98, Optovue Inc, Fremont, CA) is a device which obtains volumetric 304 ×304 A-scans at 70,000 A-scans per second, using a light source of 840 nm and an axial resolution of 5 µm. The OCTA system based on split-spectrum amplitude-decorrelation angiography algorithm that yses blood flow as intrinsic contrast.[11] All OCTA scans were performed using AngioVue OCTA with a scanning area of 6×6 mm. Three dimensional (3D) OCTA scans were acquired over 6×6 mm regions by using five repeated B-scans at 216 raster positions, each B-scan consisting of 216 A scans, and 304×304 pixels in the transverse dimension. In previous studies, a cut-off value of signal strength index was set at ≤40.[12] However, scans with signal strength index <60, motion artifacts, and low-quality images because of poor fixation were excluded from the study to use more qualified scans in analyses. Optovue Angio-Vue system technology allows for quantitative analysis. It provides numerical data about flow area or vessel density. For measurement of retinal density, a 6×6 mm macular angiogram of superficial layer was analyzed using Optovue software with density function. Automatic segmentation was performed using the viewing software to generate en face projection images of the SCP and DCP. The SCP en face OCTA image was segmented using an inner boundary 3µm below the internal limiting membrane and an outer boundary 16µm below the inner plexiform layer and the DCP image 16µm to 70 µm below the inner plexiform layer. Outer retina is described as 70µm below the inner plexiform layer and 30µm below the retinal pigment epithelium.[13] The flow area was defined as the percentage area occupied by vessels in a 6×6 mm square region of interest centered in the center of the FAZ. The Angio-Vue software automatically outputs the flow area value within the region of interest (Figure 1.A). Vessel density is calculated as the percentage area occupied by vessels and microvasculature in the selected region. The vessel density was separately calculated in five regions (fovea, temporal, superior, nasal and inferior) based on the Early Treatment Diabetic Retinopathy Study contour (Figure 1.B). This tool works both on SCP and DCP. To measure choriocapillaris (CC) flow area, a 6×6mm macular angiogram of the CC layer (from retinal pigment epithelium with a retinal pigment epithelium offset of 31µm to the deeper layer with a retinal pigment epithelium off-set of 59 µm) was analyzed using Optovue software with flow function.[13] Flow area of CC was calculated automatically as vessel areas of CC divided by selected areas (Figure 1.C). Avascular area is a significant area (larger than the normal gap between capillaries) devoid of flow signal on an en face angiogram. On the OCTA of macula, the FAZ

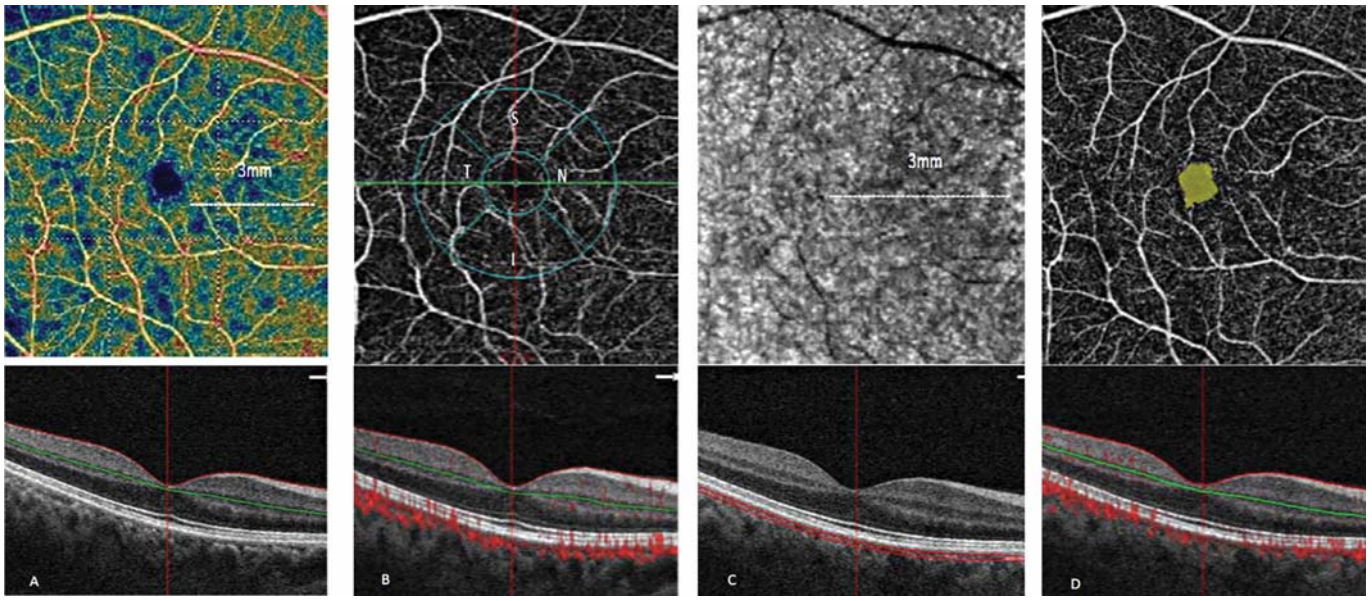

Figure 1: *Macular perfusion parameters of a 6 mm · 6 mm angiography scan size using OCTA. A. The flow area within a 3-mm radius is represented by the color yellow. B. The vessel density of five areas of interest, including the fovea (1-mm diameter) and temporal, inferior, nasal, and superior quadrants (1-mm annular ring); (C) the choroidal capillary flow area within a 3-mm radius is represented by the color yellow; (D) the FAZ is automatically delineated using the included software and represented by the color yellow.*

produces a normal avascular area. FAZ and central foveal thickness (CFT) are measured automatically using OCTA (Figure 1.D). Subfoveal choroidal thickness (SFCT) defined as the distance between the hyper-reflective line corresponding to the base of the RPE and the hyper-reflective line corresponding to the chorioscleral interface was measured three times by two independent observers with manual calipers in the horizontal and vertical sections beneath the fovea and average values were recorded and included into analysis.

Statistical Analysis

One eye from each subject was randomly selected for analysis. Statistical analysis was performed using SPSS for Windows 21.0 (SPSS Inc, Chicago, IL). For each continuous variable, normality was determined using Kolmogorov–Smirnov test. All parameters showed normal distribution. Categorical variables were analyzed using chi-square test. Baseline OCTA measurements of the groups were compared using independent t-test. A p value < 0.05 was considered as statistically significant.

RESULTS

Mean age was 31.5±4.1 (26-43) years in the pregnant and 30.5±3.9 (23-43) years non-pregnant groups (p=0.986). Mean gestational age was 21.9±9.1 (6-40) weeks in 23 pregnant women including 7 women in the first trimester (0-13 weeks), 8 in the second trimester (14-26 weeks), and 8 in the third trimester (26-40 weeks). Table 1 shows he mean age, spherical equivalent (SE), axial length (AL), systolic blood pressure (SBP), diastolic blood pressure (DBP), and intraocular pressure (IOP) values of the groups. There were no significant differences between the groups in any of these parameters.

Superficial, deep, and CC macular flow area measurements of the pregnant and control groups revealed significant differences between groups ($P<0.05$ for all, independent t-test) (Table 2). However, there was no significant difference in FAZ area measurements between the pregnant and control groups (p=0.903) (Table 2).

Superficial and deep vessel density measurements of the pregnant and control groups revealed significant differences in all macular regions (foveal, parafoveal, temporal, superior, nasal, inferior) ($p<0.05$ for all, independent t-test) (Table 2).

CFT and SFCT measurements of the pregnant and control groups showed no statistically significant differences (p=0.944, p=0.988; respectively) (Table 2).

Figure 2 shows Box plot analysis representing the macular flow area measurements (superficial, deep, and CC) and FAZ area in the pregnant and control groups.

Comparison by trimester revealed no differences among the pregnant women in superficial, deep, or CC macular flow area, FAZ area, superficial or deep vessel density, CFT, or SFCT ($p>0.05$ for all).

Table 1. *The Demographic and Clinical Characteristics of the pregnant and control groups,*

	Pregnant group (n =23)	Control group (n =23)	P value
Age (years)	31.5±4.1 (26-43)	30.5±3,9 (23-43)	0,986
SBP (mmHg)	113.13±4.9 (105-125)	115.58±5.2 (100-130)	0,933
DBP (mmHg)	70.0±3.7 (70-85)	75.2±4.1 (70-85)	0.681
IOP (mmHg)	13.8±1.4 (11-17)	13,7±1.23 (10-19)	0.815
SE (D)	0.142±0.44 (-0,5, 1.00)	0.168±0.4 (-0,5, 1,00)	0.825
AL (mm)	23.07±0.66 (22.1-24.0)	23,10±0.48 (22.01-24.12)	0.845
Values are mean ± SD. (range:min-max)			

Table 2. *Macular Perfusion Parameters of pregnant and Control groups.*

	Pregnant Group n:23	Control Group n:23	P value
Superficial retinal flow area (mm2)	16.48±2.1	13.64±1.1	0.011*
Deep retinal flow area (mm2)	14.55±0,8	13,97±0,6	0.044*
CC flow area (mm2)	18.71±1.1	17.63±0,4	0.020*
FAZ area (mm2)	0,324±0,01	0,323±0,01	0.903
Superficial vessel density (%)			
Fovea	36.7±0,5	34.6±0,4	0.031*
Parafovea	56.1±0.8	54.7±0.8	0.024*
Temporal	56.3±0.9	54.6±1.1	0.022*
Superior	56.7±1.2	54.3±1.3	0.015*
Nasal	56.7±1.4	53.9±1.1	0.011*
Inferior	56.8±1.5	54.5±1.4	0.027*
Deep vessel density (%)			
Fovea	38.1±0.8	36.5±0.6	0.025*
Parafovea	57.0±0.9	55.6±0.8	0.038*
Temporal	57.1±1.7	55.4±1.9	0.030*
Superior	57.2±0.8	55.0±0.7	0.039*
Nasal	56.1±0.9	53.1±0.9	0.043*
Inferior	55.4±0.5	53.3±0.4	0.031*
Central Foveal Thickness	256.25±16	254.55±34	0.944
Sub Foveal Choroidal Thickness	365.25±16	365.66±74	0.988
Values are mean ± SD.			

DISCUSSION

It is well-known that many hormonal, biochemical, and physiological changes take place during pregnancy. However, because of their possible teratogenic effects, invasive and dye-based imaging modalities are usually avoided. In this study, retinal and choroidal vascular structures were evaluated using OCTA, a new, non-invasive, dye-free imaging technique.

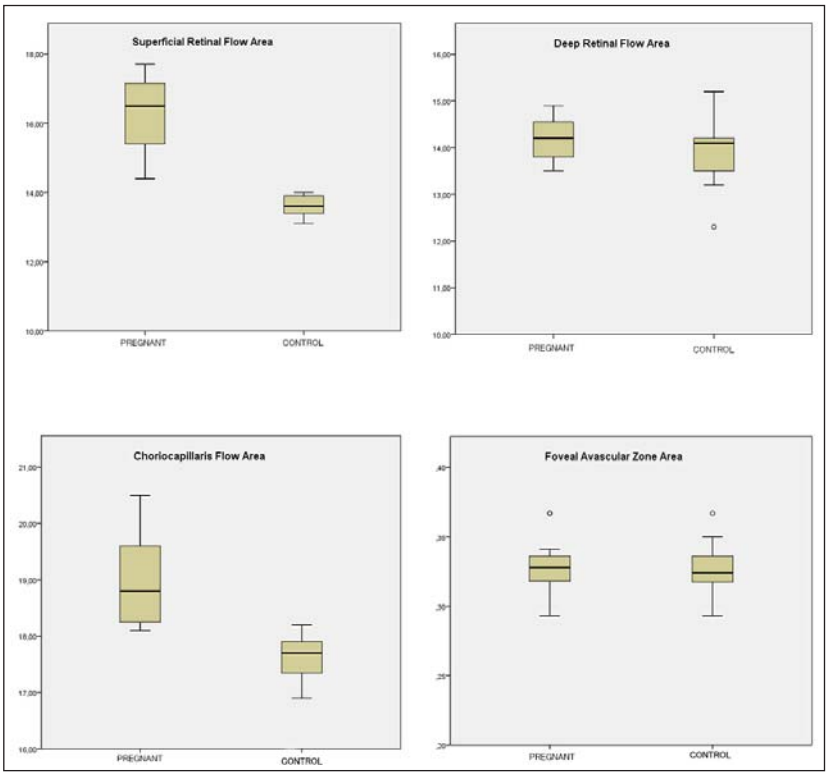

Figure 2: Box plot analysis representing the macular flow area measurements (superficial, deep, and Choriocapillaris) and FAZ area in the pregnant and control groups are shown.

In this study, we evaluated the flow area and vascular density of the SCP (3-15 µm from the retina surface), which is crucial to ganglion cell layer nutrition. Both values were found to be significantly greater in pregnant women than in non-pregnant controls. In pregnant women, we also observed significantly higher flow area and vascular density in the outer retina (15-70 µm from the retina surface) and DCP, which consists of photoreceptors. To evaluate the choroidal vascular structure, CC flow area and SFCT values were measured. Our analysis showed significantly higher CC flow area in pregnant women, although there was no significant difference in SFCT compared with controls.

It has been demonstrated that estrogen levels increase progressively during pregnancy and that estradiol, which is shown to have vasodilator activity, increases ocular blood flow by dilating the retrobulbar arteries.[14,15] A study comparing pregnant and non-pregnant women showed that pulse ocular blood flow progressively increases in pregnancy.[16] Centofanti et al.[14] reported that this increase in circulation in ocular and non-ocular tissues is a result of endothelial-dependent vasodilation mediated by estrogen. Another study reported increased blood flow in the optic nerve head and retina in postmenopausal women receiving estrogen hormone replacement therapy.[17] High peak systolic and end-diastolic velocities of the central retinal artery were measured in patients receiving beta-estradiol therapy.[18] Chen et al.[19] examined the retinal vasculature in diabetic and non-diabetic pregnant women and showed that both groups exhibited comparable changes in macular vessel caliber and the retina responded by increasing vascular flow velocity via auto-regulatory mechanisms. These findings all indicate that the elevated estradiol levels in pregnancy produce a vasodilatory effect and cause increased ocular blood flow. The increases in SCP density and DCP and CC flow in our study might be related to the elevated estrogen levels and higher flow velocity during pregnancy demonstrated in previous studies.[16-19] One factor to consider when evaluating OCTA studies is that the instrument measures by detecting the movement of erythrocytes circulating within the vascular structures.[11] For this reason, increased flow velocity and cardiac output during pregnancy may affect the number of erythrocytes passing through a specified area within a fixed time period, resulting in a higher value.

In the present study, we found that pregnant women had greater choroidal flow measured by OCTA compared to healthy non-pregnant women. Elevations in estrogen and endogenous serum cortisol levels have been demonstrated in pregnancy.[20] In addition to increased cardiac output and blood volume, elevated cortisol level in pregnant women increases ocular vascular permeability, disrupts the blood-

retina barrier, and damages the choriocapillaris.[21] The increase in choroidal flow may be a result of the increase in plasma volume caused by elevated cortisol level. Choroidal thickness and choroidal volume were shown to be increased by 4.3% and 3.9% in healthy individuals measured immediately after drinking 1 liter of water within 5 minutes.[22] Although the authors could not draw a definitive conclusion regarding mechanism for this change, one theory was that rapid volume influx changes the dynamics of the aqueous humor, which alters the episcleral venous pressure and results in expansion of the choroidal tissue[22]. The rapid increase in plasma volume that occurs in pregnancy may explain the increase in choroidal flow we observed in the current study.

In our study, another finding was that the choroid is not thicker in pregnant women despite the increase in choroidal blood flow. In addition, we also found that retinochoroidal flow did not change significantly according to week of gestation. The literature generally reflects that, depending on the underlying cause, choroidal thickness is correlated with choroidal circulation in conditions such as central serous retinopathy, age-related macular degeneration, and Vogt-Koyanagi-Harada syndrome.[23-25] However, Fitzgerald et al.[26] showed that choroidal circulation measured by Doppler flowmeter showed no correlation with changes in choroidal thickness in an animal study.

Karahan et al.[27] recently reported no significant correlation between choroidal thickness and serum cortisol levels in 66 healthy women. Kim et al.[28] observed no difference in choroidal thickness in their comparison of healthy pregnant and non-pregnant women, but found that choroidal thickness was greater in pregnant women who developed preeclampsia compared to those who did not. Similarly, Takahashi et al.[29] and Kim et al.[28] observed no difference in choroidal thickness between healthy pregnant and non-pregnant women. However, several authors reported significantly thicker subfoveal choroid in healthy pregnant women.[30-32] There are a few studies in the literature that compared choroidal thicknesses between pregnant women at varying weeks of gestation. In one of those studies, Goktas et al.[33] evaluated 90 healthy pregnant women, 30 in each trimester, and 30 non-pregnant healthy women and found that choroidal thickness was significantly greater in the second trimester when compared with non-pregnant women. In another study, Dadaci et al.[34] showed that choroidal thickness significantly decreased at all measurement points during the third trimester compared to the first trimester. In the present study, we observed no significant mean SFCT increase at different stages of gestation, consistent with the findings of Takahashi and Kim. Based on this and previous studies, an increase in choroidal flow may not cause an increase in choroidal thickness, depending on the underlying pathophysiological mechanism. Although blood volume, estrogen levels, blood cortisol levels, and cardiac output may increase up to non-physiological levels in pregnant women, the response of the choroid to pregnancy may be increased choroidal flow while choroidal thickness remains within normal physiological range. Further prospective studies are needed to investigate the relationship between choroidal thickness and choroidal flow in pregnancy.

The known tendency for systemic hypertension in pregnant woman is a result of activation of the coagulation system by peripheral vasospasm of unknown cause.[1,2,35] Vasospasm and fibrin deposits due to vascular endothelial dysfunction cause mechanically damaged and deformed erythrocytes.[36,37] It has also been suggested that hypercoagulation secondary to elevated estrogen levels is a physiological adaptation to possible postpartum hemorrhages and in rare instances can cause retinal vein occlusion and branch retinal artery occlusion.[38,39] The possible teratogenicity of diagnostic and therapeutic procedures for vascular dysfunction that occurs naturally in pregnancy is associated with challenges for physicians and pregnant women. Therefore, new non-invasive, non-teratogenic, dye-free technologies such as OCTA may be useful to diagnose pathologies secondary to pregnancy.

Limitations of our study include the small sample size and cross-sectional design. There are studies in the literature evaluating the retinochoroidal vasculature in pregnant women, but this is the first study using OCTA for analysis of both vascular systems. Although many different assessment techniques are available, we believe that future studies will empirically demonstrate that OCTA is the ideal method for the measurement of retinochoroidal vascular circulation. However, a shortcoming of OCTA compared to fluorescein angiography (FA) is that OCTA does not show retinal leakage and therefore we cannot identify disruptions in the blood-retina barrier or leaks. It is not possible with current OCTA technology to visualize leakage as we are accustomed to doing with FA.

In summary, our findings using OCTA to evaluate the retinal and choroidal vasculature in pregnant women are an initial step in explaining and further investigating the impact of systemic vascular and hemodynamic changes in these patients. Moreover, the effectiveness and safety of OCTA combined with the capacity to analyze individual layers of the vascular structure make the results more valuable.

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