Retinal and Choroidal Microvascular Changes During Pregnancy Periods Detected with Optical Coherence Tomography Angiography: A prospective study

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Research Article

Keywords: choroidal thickness, foveal avascular zone, optical coherence tomography angiography, vascular density

Posted Date: August 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1964316/v1

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Abstract

**Purpose:** To investigate choroidal and retinal blood flow and thickness changes using Optic Coherence Tomography (OCT) and OCT Angiography (OCTA) during pregnancy.

**Methods:** This prospective study included 41 eyes of 41 pregnant and 45 eyes of 45 healthy nonpregnant women. Ocular perfusion pressure (OPP), Retinal thickness (RT), choroidal thickness (CT), foveal avascular zone (FAZ) area, superficial and deep capillary plexus (SCP, DCP) vessel density (VD), choriocapillaris VD measurements were evaluated with OCT and OCTA.

**Results:** There was no significant difference in OPP, RT, and CT during pregnancy. FAZ area increased as the gestational weeks progressed (p:0.011). The FAZ area of the first trimester was significantly lower than the control group (p:0.029). A decrease in central SCP and DCP VD in the third trimester and an increase in the choriocapillaris VD during pregnancy were detected (p:0.01, p<0.001, p<0.001 respectively). We observed an increase in mean VD for both SCP and DCP in the second trimester (p:0.02, p:0.027). In the second and third trimesters, SCP and DCP VD values were found to be significantly higher than the control group. During the pregnancy period a significant increase was detected in choriocapillaris VD when compared to the first trimester.

**Conclusion:** In conclusion, this is the first prospective study in the literature that evaluates the measurements in all trimesters of pregnancy with OCTA. We observed significant retinal and choroidal microvascular changes between trimesters of pregnancy and when compared with healthy women.

Clinicaltrials.gov registration ID: NCT04950855 11/01/2021

**Key Messages**

- This is the first prospective study in the literature that evaluates the measurements in all trimesters of pregnancy with OCTA.
- In previous studies, changes were observed in other ocular structures, especially in the choroid, during pregnancy.
- We observed an increase in FAZ area, SCP, DCP and choriocapillaris VD; but a decrease in central SCP and DCP VD. Choriocapillaris VD was found to be significantly lower in the first and second trimesters; higher in the third trimester compared to the control.

**Introduction**

Pregnancy is a physiological process that affects cardiovascular, pulmonary, renal, hematological, and ophthalmological systems, especially the endocrine system. While these effects are physiological and temporary in most pregnant women; sometimes it could be pathological and permanent [1]. The most common ocular pathologies in pregnancy are serous retinal detachment, central serous chorioretinopathy,
and vascular changes due to preeclampsia [2]. These findings mostly occur in the third trimester; and return to normal with the end of preeclampsia.

In previous years, studies about the retina in the pregnancy period were limited due to the potential risks of eye drops and fluorescein dye which were classified as category C according to the U.S. Food and Drug Administration [3]. Optical Coherence Tomography Angiography (OCTA) is a non-invasive method that can be used to visualize the retina in pregnant women. It detects the motion contrast in the blood flow and displays the capillary networks of the retina and choroid and the outer retina without using dye.

Previous studies generally focused on the changes in choroidal thickness and there are very few studies about retinal thickness, vessel density, and FAZ area measurements with OCTA during pregnancy. This study has the importance of being the first prospective study in the literature that evaluates the measurements in all trimesters of the pregnancy with OCTA. Ganglion cell layer (GCL) thickness and choriocapillaris vessel density haven’t been evaluated before in other studies.

In this study, we aimed to investigate retinal and choroidal microvascular changes with OCT and OCTA between trimesters during pregnancy and to compare them with the healthy age- and sex-matched control group.

**Materials And Methods**

This prospective and controlled study was approved by the local ethics committee of the Akdeniz University Hospital (Approval Number KAEK-221) and the study was conducted and in compliance with the ethical standards set out in the Declaration of Helsinki. Informed consent was obtained from the participants who met the inclusion criteria and agreed to participate in the study.

A total of 86 eyes, 41 eyes of 41 pregnant women, and 45 eyes of 45 healthy women were included in the study. Pregnant women who were followed up from the first trimester were also evaluated in the second and third trimesters. A total of 3 measurements were taken in the first, second, and third trimesters from the pregnant women and 1 measurement from the control group.

The inclusion criteria for the pregnant group were: gestational age less than 14 weeks in the first examination and uncomplicated pregnancy. The common inclusion criteria for all groups were: patients between the ages of 20–40, good OCT and OCTA image quality (signal strength index > 60). The common exclusion criteria for all groups were: history of systemic disease, ocular surgery or ocular pathology that may decrease visual acuity, pre-eclampsia, history of systemic and/or ocular drug usage, smoking, and having a refractive error more than 4 diopters.

All groups underwent a comprehensive ophthalmologic examination, including measurements of best-corrected visual acuity (BCVA), refractive error (Nidek AR600A), intraocular pressure (noncontact tonometer NIDEK NT-2000), systolic and diastolic blood pressures (SBP and DBP) with a sphygmomanometer. The ocular perfusion pressures (OPP) were calculated with the formula: (OPP = 2x [
DBP + (SBP-DBP)/3]/3- IOP). The BCVA was converted into the logarithm of minimal angle resolution (logMAR).

The retinal and choroidal thicknesses, FAZ area, and vessel densities were measured with Swept Source OCT (DRI OCT Triton; Topcon); which uses 1050 nm (nanometer) wavelength, 2.6 µm (micrometer), and 8 µm digital and axial resolution and scanning speed of 100,000 scan/second. Vascular structures were evaluated with 6×6 mm OCT angiogram software and IMAGEnet 6 program (version 1.24.1.15742). FAZ areas were measured manually by two retinal specialists and the average value was used. Vessel Density (VD) values were measured automatically by the device. Fovea-centered 1 mm diameter ring central area; the 3 mm diameter ring surrounding this ring was considered as the parafoveal area. The parafoveal space was divided into 4 quadrants: superior, temporal, inferior, and nasal. RNFL (retinal nerve fiber layer), ganglion cell layer (GCL) thickness, and choroidal thickness (CT) were measured automatically from the zone map (Fig. 1). Measurements were performed between 2 pm and 4 pm to avoid diurnal variation in retinal and choroidal thickness.

The superficial capillary plexus VD measurement was calculated automatically, and the deep capillary plexus and choriocapillaris VD measurements were calculated by the device after manually entering the internal and external limit values (Fig. 1).

**Statistical Analysis**

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov Smirnov test. Mann-Whitney U test was used in the analysis of quantitative independent data. Wilcoxon signed-ranks tests were used in the analysis of dependent quantitative data, the chi-square test was used in the analysis of qualitative independent data, and the Fischer test was used when the chi-square test conditions were not met. SPSS Statistics version 27.0 (IBM Corp., Chicago, IL, USA) was used for the analysis. A p-value less than 0.05 is considered statistically significant.

**Results**

The mean age in the pregnant group was 30.8 ± 5.9 (20–40), and the mean age in the control group was 29.7 ± 5.9 (20–40). There was no statistically significant difference among the groups (p: 0.22). The number of parity and the number of living children did not differ significantly between the pregnant and control groups (p: 0.94, p: 0.98, respectively). Pregnant women were measured at an average of 9.5 ± 2.7 (5–13) weeks in the first trimester, 20.1 ± 2.4 (17–27) weeks in the second trimester, and 31 ± 2 (29–36) weeks in the third trimester.

A decrease in IOP was observed during pregnancy. No significant difference was observed in visual acuity and OPP between trimesters and the control group. The third trimester spherical equivalent (SE) measurement showed a significant increase compared to the first and second trimester measurements (p < 0.001, p: 0.011, respectively) (Table 1).
There was no significant difference in the central and parafoveal retinal thicknesses of the right eye (except for the inferior quadrant) when compared with the control group and between trimesters. The second and third trimester parafoveal inferior retinal thickness measurements showed a significant increase compared to first trimester measurements. (Table 2). The RNFL thickness changes are summarized in the table below (Table 2).

All GCL thickness measurements except for the nasal quadrant, did not differ significantly compared to the control group (p:0.61) and between trimesters (p:0.96)

SFCT (subfoveal choroidal thickness) and CT measurements in all quadrants did not differ significantly compared to the control group (p: 0.16) (Table 3).

There was an increase in central SCP VD in the second trimester and a significant decrease in the third trimester compared to the first trimester (p: 0.16, p: 0.01 respectively). The SCP VD (superior, nasal, inferior quadrants and mean values) increased significantly in the third trimester compared to the first trimester measurements. When compared with the control group, in almost all quadrants, the second and third trimester SCP VD values were significantly higher than the control group (Table 4) (Fig. 2). A significant increase was detected in the SCP FAZ area during the pregnancy period (p: 0.011) (Fig. 3).

During pregnancy, the central DCP VD significantly increased in the second trimester and decreased in the third trimester compared to the first trimester (first-second trimester p: 0.04 ; first- third trimester p: 0.002 respectively). The mean VD measurement of DCP in all trimesters in both eyes was significantly higher than in the control group. The DCP mean VD increased significantly towards the second trimester (p: 0.02) (Table 4)) (Fig. 2).

A significant increase was observed in the third trimester in all quadrants of choriocapillaris VD when compared to the second and third trimesters (p < 0.001). First and second trimester values were significantly lower than the control, and third-trimester values were higher than the control (p < 0.003) (Table 5) (Fig. 3).

**Discussion**

In this study, using OCT and OCTA, we determined an increase in the FAZ area of SCP and VD of SCP, DCP and choriocapillaris during the pregnancy period when compared to the first trimester. The FAZ area significantly increased in the third trimester when compared with the first trimester. A significant decrease was detected in central SCP and DCP VD in the third trimester. As the gestational week progressed, there
was a significant increase in SCP VD in the 2nd trimester, except for the nasal quadrant, and a significant decrease in the 3rd trimester. The VD measurement in nearly all quadrants of SCP and DCP was found to be higher than the control in all trimesters. Choriocapillaris VD was found to be significantly lower in the first and second trimesters and higher in the third trimester compared to the control group. We observed an increase in CT and OPP during pregnancy however this increase was not statistically significant.

The most important feature that makes this study different from other studies is that, the measurements were taken from the same individuals during the pregnancy period. In other studies, measurements were generally taken from different individuals, in different trimesters. In this study, healthy pregnant women with a gestational age of less than 14 weeks were included, and their follow-up was continued in the second and third trimesters. In addition, this is the first study conducted with Topcon DRI Triton device in healthy pregnant women.

As it is well known, cardiovascular, hematological, and hormonal changes during pregnancy affect many systems. While cardiac output, blood volume, and heart rate increase; peripheral vascular resistance decreases and vasodilation occurs [4]. Peripheral vasodilation is seen in the early stages of the first trimester and decreases towards the third trimester. Plasma and blood volume starts to increase in the first trimester and reaches the maximum level in the third trimester. Changes in retinal and choroidal thickness and blood flow are observed due to changes in ocular blood flow and microcirculation [4]. Since OCTA is a non-invasive method that doesn’t require the use of fluorescein, it can easily visualize the retinal and choroidal circulation during pregnancy. In recent years, the use of OCTA has enabled the examination of retinal findings in pregnant women.

It is seen that progesterone and estrogen increase during pregnancy, and blood levels at 36 weeks of gestation are 10 times higher when compared to blood levels at 6 weeks [5, 6]. Estrogen, which causes vasodilation in an endothelium-dependent and independent manner, regulates ocular blood flow [7]. Depending on estrogen, the synthesis of Endothelin-1 decreases, and the synthesis of nitric oxide increases. This leads to vasodilation and a reduction in vascular resistance [8]. All these changes suggest that this may lead to changes in choroidal thickness and retinal blood flow. We consider that the vascular changes seen in our study may also be related to these hormonal changes.

In the previous years, many studies have been conducted on choroidal thickness in pregnant women. In previous studies comparing choroidal thicknesses, Takahashi et al. [9] and Rothwell et al. [10] observed no statistically significant difference, unlike this study. However, Kara et al. [11] observed significant difference in pregnancy compared to the control group, similar to our study. Dadaci et al. [12] demonstrated a decrease in choroidal thickness in the last trimester compared to the first trimester measurement. Goktas et al. [13] observed a significant choroidal thickness difference between the second trimester and control groups. Demir et al. [14] observed a statistically significant increase in retinal thickness only in the superior, temporal, and inferior parafoveal quadrants. The differences in these studies may be due to the difference in the number of patients included in the study, patients’ age, race,
week of gestation, time of measurement, and included refraction intervals. In addition, the usage of the different devices may have had an effect.

It has been shown that choroidal thickness shows diurnal variation, in previous studies [15]. In our study, choroidal thickness measurements of the participants were performed between 2 p.m. and 4 p.m. to avoid diurnal variation in retinal and choroidal thickness. Apart from diurnal variation, values such as ocular perfusion pressure that may affect choroidal thickness were evaluated and no significant difference was found between the groups. Similar to our study, Goktaş et al. [13] did not find a significant difference in OPP when they compared the pregnant and control groups.

In previous OCTA studies, Yildirim et al. [16] observed no statistical difference in SCP VD, unlike our study. VD in DCP was found to be statistically significantly higher only in the parafoveal region. As a result, VD in the parafovea region, FAZ area of SCP, and foveal density in SCP in pregnant women were found to be higher than the control group, similar to our study. They didn't observe a significant difference in SFCT between pregnant women and the control group also similar to our study. Chanwimol et al. [17] observed a statistically significant decrease in the mean of the whole area of SCP and the perfusion density in the nasal quadrant in pregnant women compared to the control group. A statistically significant increase was found in the perfusion density in the parafoveal area, inferior and temporal areas in DCP in pregnant women compared to controls. They consider that this difference in SCP and DCP could be due to the compensatory vascular changes during pregnancy and could be affected differently because of the structural and functional differences in SCP and DCP [17]. They didn't observe a statistically significant difference between the two groups in the FAZ area. Kiziltunc et al. [18] found the parafoveal and perifoveal SCP VD in all areas statistically significantly higher in the pregnant group than the control group, similar to our study; however, foveal VD was found to be significantly lower in contrast to our study. There was no significant difference in VD between the trimester, unlike our study. Hepokur et al. [19] didn't observe any difference in the VD of SCP, DCP, and peripapillary capillaries between trimesters and compared with the control group. Su et al. [20] didn't observe a statistically significant difference between pregnant women in the last trimester and healthy controls. As we mentioned before, the inclusion of different individuals in the study and the lack of prospective studies may have caused the differences in the OCTA results. The reason for these changes has not been clearly explained in these studies. To reveal this difference, further molecular and structural studies are needed.

Our study has certain limitations. Estrogen and progesterone levels in the blood were not measured in pregnant and control groups. Therefore, we don't have any information about whether there is a relationship between hormonal and vascular changes. The other one is the follow-up period is longer compared to the other studies. Postpartum measurements could not be taken due to difficulties in follow-up.

One of the difficulties we encountered in our study was the exclusion of patients who could not be measured in the third trimester due to the termination of pregnancy (such as abortion or premature birth) during their follow-up and developed a systemic disease related to pregnancy (gestational diabetes and
preeclampsia) during pregnancy. Despite all these difficulties and limitations, it was concluded that there are significant changes in retinal and choroidal vascular structures during pregnancy.

In conclusion, to the best of our knowledge, our study is the first study examining retinal and choroidal thickness and microvasculature changes with OCT and OCTA prospectively in all trimesters in the same pregnant woman; and it supports the opinion that there are changes in all vascular structures. An important contribution of our study is the evaluation of OCTA parameters, especially GCL thickness and choriocapillaris vessel density prospectively in the same pregnant women during pregnancy.

**Declarations**

**Data availability**

All data and material are available from supplementary material.

**Author contributions:** Conception and design of the study (ÇEP), acquisition of data (ÇEP), analysis and interpretation of data (ÇEP,KCA); drafting the article or making critical revisions related to relevant intellectual content of the manuscript (ÇEP,KCA); supervision (KCA) validation and final approval of the version of the article to be published (ÇEP,KCA).

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**Ethical approval** This study was approved by the Ethics Committee of the University of Health Sciences, Antalya Training and Research Hospital (Approval Number KAEK-221). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent to participate and publish**

Informed consent for publication of their clinical details and/or clinical images was obtained from all individual participants included in the study. A copy of the consent form is available for review by the Editor of this journal.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Acknowledgements and Funding**
This study was supported by Akdeniz University Scientific Research Projects Coordination Unit (Project ID: 5462).

References


Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures
Figure 1

A representative illustration of OCT and OCTA measurements. (A) OCT layers, (B) FAZ: green circle represent the fovea avascular zone, (C) OCTA measurements
Figure 2

Comparison of the superficial and deep capillary plexus central ad mean vessel density. The bars represent the distribution of data, center lines represent the mean ± standard deviation of the values.

Figure 3

Comparison of FAZ area, choriocapillaris central and mean vessel density. The bars represent the distribution of data, center lines represent the mean ± standard deviation of the values.

Supplementary Files

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- Table1.....docx