

Retinal Vascular Changes During Pregnancy Detected With Optical Coherence Tomography Angiography

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PURPOSE. To evaluate retinal vascular status during pregnancy by using optical coherence tomography angiography (OCTA).

METHODS. Women in their third trimester of pregnancy and nonpregnant age-matched women were recruited for this prospective, case-control study. Subjects were imaged with OCTA. Main outcome measures were foveal avascular zone parameters, perfusion density (PD) percentage in the superficial retinal capillary plexus (SCP), PD percentage in the deep retinal capillary plexus (DCP), SCP vessel length density (VLD), DCP-VLD, and choriocapillaris (CC) flow voids (i.e., flow deficits in the CC).

RESULTS. Nineteen eyes of 10 pregnant subjects and 44 eyes of 27 nonpregnant control women were included. Mean ages were 36 ± 7 and 35 ± 8 years (SD), respectively (P value = 0.78). Mean gestational age of pregnant women was 33 weeks (range = 29-39, SD = 3). There was a significant reduction in the SCP-PD in the entire scan and in the nasal Early Treatment Diabetic Retinopathy Study subfield (47.9 vs. 49.7, $P = 0.04$ and 49.3 vs. 51.6, $P = 0.03$, respectively) in the pregnant cohort versus controls. There was a significant increase in the DCP-PD in the parafoveal region and in the temporal and inferior Early Treatment Diabetic Retinopathy Study subfields (58.0 vs. 55.9, $P = 0.03$; 57.9 vs. 55.5, $P = 0.02$; 58.0 vs. 55.9, $P = 0.05$, respectively) in the pregnant cohort. There was no significant difference in foveal avascular zone parameters, SCP-VLD, DCP-VLD, or CC flow voids between the two populations.

CONCLUSIONS. This study detected retinal vasculature changes in the third trimester of pregnancy. Mean SCP-PD was significantly decreased and mean DCP-PD was significantly increased without a difference in VLD.

Keywords: imaging, pregnancy, optical coherence tomography angiography, retina, vasculature

Pregnancy is a transient state that elicits profound physiologic changes in every organ system to support the developing fetus and to prepare the mother and baby for delivery.^{1,2} Adaptations in the reproductive, endocrine, hematologic, cardiac, renal, and respiratory systems interact over the course of 9 months to nourish the developing fetus and prepare for delivery, and most changes are fully reversed in the months after delivery.

Hemodynamic changes in pregnancy are in response to increased circulatory demand in pregnancy.^{3,4} Starting at 6 weeks until 32 weeks of gestation, plasma volume increases by 50%.⁵ Despite this significant increase in plasma volume, there is arterial under-filling because 85% of blood volume resides within the venous circulation. Cardiac output increases by 40% due to increased blood volume, peripheral vasodilation, and a fall in systemic vascular resistance. On a hormonal level, estrogen, progesterone, and renin-angiotensin levels increase considerably in pregnancy, which, in turn, upregulates nitric

oxide and contributes to decreased peripheral resistance.⁶⁻⁸ Endothelial cells throughout the body are thus likely affected, including the systemic and retinal vasculature.

Retinal studies in pregnancy have been limited by the potential risks of eyedrops and fluorescein dye used for pupillary dilation and angiography. Both agents are classified by the US Food and Drug Administration as Category C (i.e. animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).⁹ Optical coherence tomography angiography (OCTA) is an advanced retinal imaging modality that does not require pupillary dilation or intravenous dye injection and is, therefore, an ideal tool to study vascular eye findings in pregnancy.¹⁰⁻¹² In addition, OCTA provides high-contrast depth-resolved visualization of the retinal microvasculature and automated or semiautomated quantitative analysis. OCTA uses decorrelation signals that arise



from the movement of erythrocytes within blood vessels taken from sequential B-scans at the same location and can produce en face images of the retinal microcirculation.

The purpose of this study was to investigate the retinal vascular changes in pregnant women. We hypothesized that the retinal microvasculature may undergo vasodilation during pregnancy, despite the temporary nature of this state, due to increased total body blood volume and hormonal changes.

METHODS

Subjects were recruited for this prospective, case-control study at the Stein Eye Institute, University of California-Los Angeles. The study was approved by the Institutional Review Board of the University of California-Los Angeles and adhered to the tenets set forth in the Declaration of Helsinki. Informed consent was obtained from all participants.

Inclusion criteria for the pregnancy group included uncomplicated pregnancy in the third trimester (>28 weeks gestational age) in healthy females. Subjects were excluded if they had pre-existing medical conditions, such as diabetes mellitus or hypertension, or complications of pregnancy, such as gestational diabetes or preeclampsia at the time of imaging. A control group of age-matched nonpregnant women without significant past medical or ocular history was included for comparative analysis. Additional exclusion criteria for either the pregnancy or control group included the presence of any ocular disease and refractive error greater than -6 diopters spherical equivalent.

Image Acquisition

Without dilation, subjects underwent OCTA imaging using the RTVue XR Avanti OCT device with AngioVue software (version 2016.1.0.26; Optovue, Inc., Fremont, CA, USA). The device uses a 840-nm light source with a bandwidth of 45 nm, and an A-scan rate of 70,000 scans per second. A 3 × 3-mm cube scan centered on the fovea was acquired containing 304 × 304 A-scans. Instrument-provided projection artifact removal software was used to facilitate analysis of the deep retinal vascular layers.¹³

Image Analysis

Major automated outcomes included foveal avascular zone (FAZ) parameters¹⁴ (Fig. 1) and perfusion density (PD), measured as a percentage, in the superficial retinal capillary plexus (SCP) and deep retinal capillary plexus (DCP). In addition, PD was evaluated within specific regions: fovea (central circle with 1-mm diameter: foveal area, F), parafovea (ring around the fovea with inner and outer radii of 0.5 and 1.25 mm, respectively: parafoveal area; PF), and by Early Treatment Diabetic Retinopathy Study (ETDRS) subfields. (Fig. 2) Only images with a signal strength index greater than 70 and a quality index greater than 5 were included in the analysis. The inner retina was segmented from the internal limiting membrane to the outer portion of the inner plexiform layer and the outer retina from the inner portion of the inner nuclear layer to the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium. This segmentation allowed the software to separately measure the parafoveal thickness of the inner and outer retina.

To quantify vessel length density (VLD), the original en face angiograms of the SCP and DCP were imported into ImageJ (version 1.50; National Institutes of Health, Bethesda, MD, USA) available at <http://rsb.info.nih.gov/ij/index.html> and binarized according to a previously reported method.^{13,15,16}

TABLE 1. Mean Foveal Parameters, SCP-PD, and DCP-PD in Pregnant and Control Subjects

Automated Parameters	Mean (SD)		P Value
	Pregnant (n = 19)	Control (n = 44)	
FAZ area (mm ²)	0.3 (0.1)	0.3 (0.1)	0.99
FAZ perimeter (mm)	2.1 (0.4)	2 (0.5)	0.547
Fractal dimension	51.8 (3.2)	51.9 (3.4)	0.95
Acircularity index	1.1 (0)	1.1 (0)	0.075
SCP-PD (%)			
Whole	47.9 (3.3)	49.7 (3.1)	0.04*
Parafovea	50.8 (3.7)	52.4 (3.5)	0.11
Fovea	19.6 (8.3)	23.6 (5.6)	0.07
Temporal	49.1 (3.5)	50.7 (3.6)	0.11
Nasal	49.3 (3.8)	51.6 (3.8)	0.03*
Superior	52.1 (4.2)	54.1 (3.6)	0.07
Inferior	51.9 (3.3)	52.9 (4.0)	0.33
DCP-PD (%)			
Whole	55.5 (3.9)	53.8 (3.5)	0.09
Parafovea	58.0 (4.0)	55.9 (3.3)	0.03*
Fovea	35.2 (10.1)	35.2 (6.7)	0.99
Temporal	57.9 (3.9)	55.5 (3.3)	0.02*
Nasal	57.5 (3.8)	56.1 (3.5)	0.16
Superior	57.7 (4.6)	55.9 (3.8)	0.12
Inferior	58.0 (4.3)	55.9 (3.5)	0.05*

* Less than or equal to 0.05.

Briefly, each image was first processed with a top-hat filter (window size, 12 pixels) and then duplicated to obtain two distinct binarized images; one was processed with a Hessian filter, followed by global thresholding using Huang's fuzzy thresholding method, and the other (duplicate) image was binarized through median local thresholding. Last, the two binarized images were combined, generating the final image in which only those pixels that existed on both binarized images were included. The resulting binary image was skeletonized, and VLD, which was expressed as vessel length per unit area, was computed as described previously (Fig. 3).¹⁷⁻¹⁹

The choriocapillaris (CC) was sampled as a 10- μ m-thick slab starting 31 μ m posterior to the retinal pigment epithelium-Bruch membrane complex. The resulting en face angiogram was extracted and imported into ImageJ to quantify the CC flow voids (lack of minute vessels) as previously described.¹⁸ Briefly, each image was binarized using an automatic local thresholding with the Phansalkar method (radius, 15 pixels). The thresholded images were then analyzed with the "Analyze Particles" command, which measured and counted all thresholded areas greater than or equal to 1 pixel where there was a lack of flow information (Fig. 4). The resulting outcomes considered for the analysis were total number of flow voids, percentage of flow voids in the total area, and average size.

Statistical analysis was performed using Statistical Package for Social Sciences (version 23; SPSS Inc., Chicago, IL, USA). Mean values (FAZ area, percentage of SCP and DCP-PD, percentage of SCP and DCP-VLD, and CC flow voids) of all variable were compared by independent Student's *t*-test, and statistical significance was defined by *P* value of ≤ 0.05 .

RESULTS

Nineteen eyes of 10 pregnant subjects and 44 eyes of 27 nonpregnant, female controls were included. One subject was excluded for myopia of -10 D spherical equivalent in both eyes. Mean ages of the two groups were 36 (SD = 7) years for

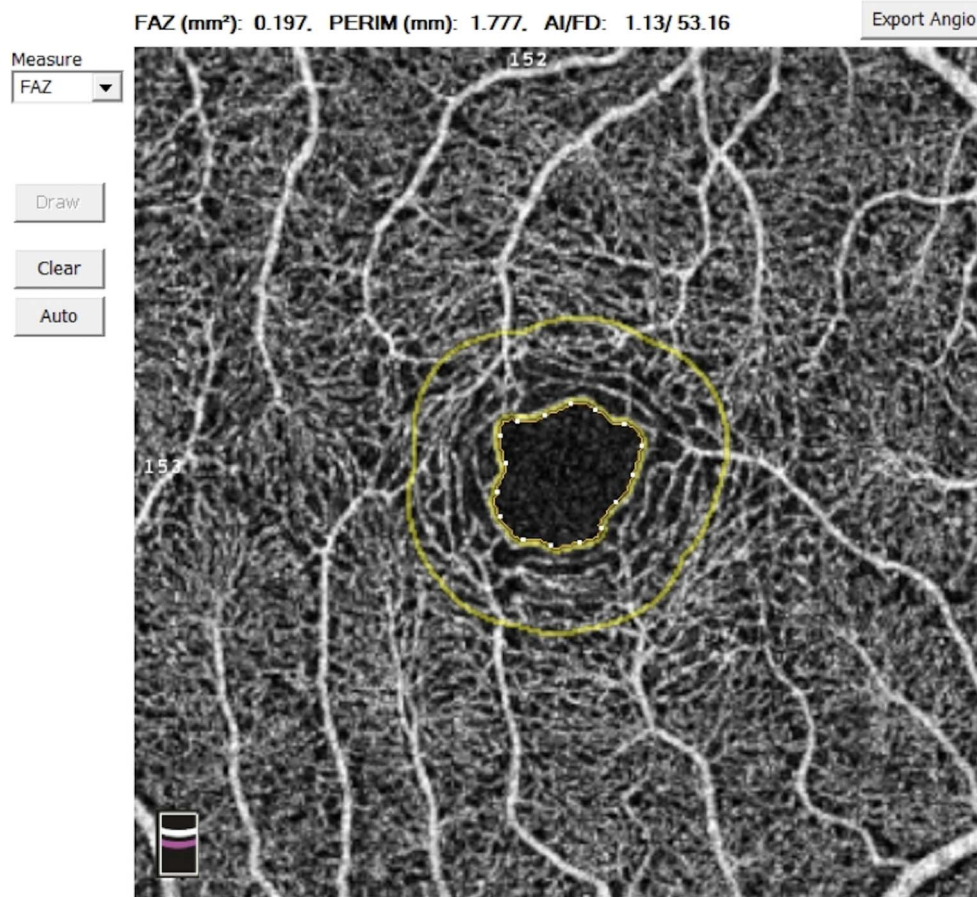


FIGURE 1. Automated FAZ parameters (area, perimeter, acircularity index, and fractal dimension).

pregnancy group and 35 (SD = 8) years for control group (*P* value = 0.78). All pregnant subjects were singleton pregnancies. Median gestational age of pregnant women was 33 weeks (range = 29–39, SD = 3). All eyes had 20/20 visual acuity. One person in the pregnancy group had been imaged before pregnancy as well and was included in both groups (Supplementary Fig. S1).

Foveal Avascular Zone

There was no significant difference in FAZ parameters between the pregnancy and control groups (Table 1).

SCP and DCP

For the SCP, mean PD values were consistently lower in the pregnancy group versus the control cohort for all quadrants and were significantly decreased in the entire scanned region and in the nasal ETDRS subfield. Conversely, for the DCP, the PD was consistently higher in the pregnancy group versus the control group for all quadrants tested and was significantly increased in the parafovea and in the temporal and inferior ETDRS subfields (Table 1). Mean SCP- and DCP-VLD in the pregnant cohort and control cohorts were not significantly different (Table 2).

CC Flow Voids

Mean CC flow voids in the pregnant cohort and control cohorts were not significantly different (Table 3).

DISCUSSION

There is relatively little information about retinal and choroidal vascular changes in normal pregnancy due to the potential risks of dilating eyedrops and fluorescein dye injection on the developing fetus. In this study, we used nonmydriatic, noninvasive OCTA to compare retinal vascular measurements of women in their third trimester of pregnancy versus age-matched nonpregnant controls. A prior study of healthy pregnant women found increased total macular volume and total retinal thickness toward the end of pregnancy, which was presumably due to increased body fluid and increased capillary hydrostatic pressure.^{20,21} Therefore, a priori, we hypothesized that increased total body blood volume and high levels of progesterone associated with pregnancy may result in retinal capillary dilation.

The study did find that DCP-PD was greater in all quadrants during pregnancy, especially in the parafoveal, temporal, and

TABLE 2. Mean SCP-VLD and DCP-VLD in Pregnant and Control Subjects

Calculated Parameters	Mean (SD)		<i>P</i> Value
	Pregnant (<i>n</i> = 19)	Control (<i>n</i> = 44)	
SCP-VLD	12.8 (1.5)	12.9 (1.4)	0.75
DCP-VLD	15.8 (0.8)	15.6 (1.0)	0.38

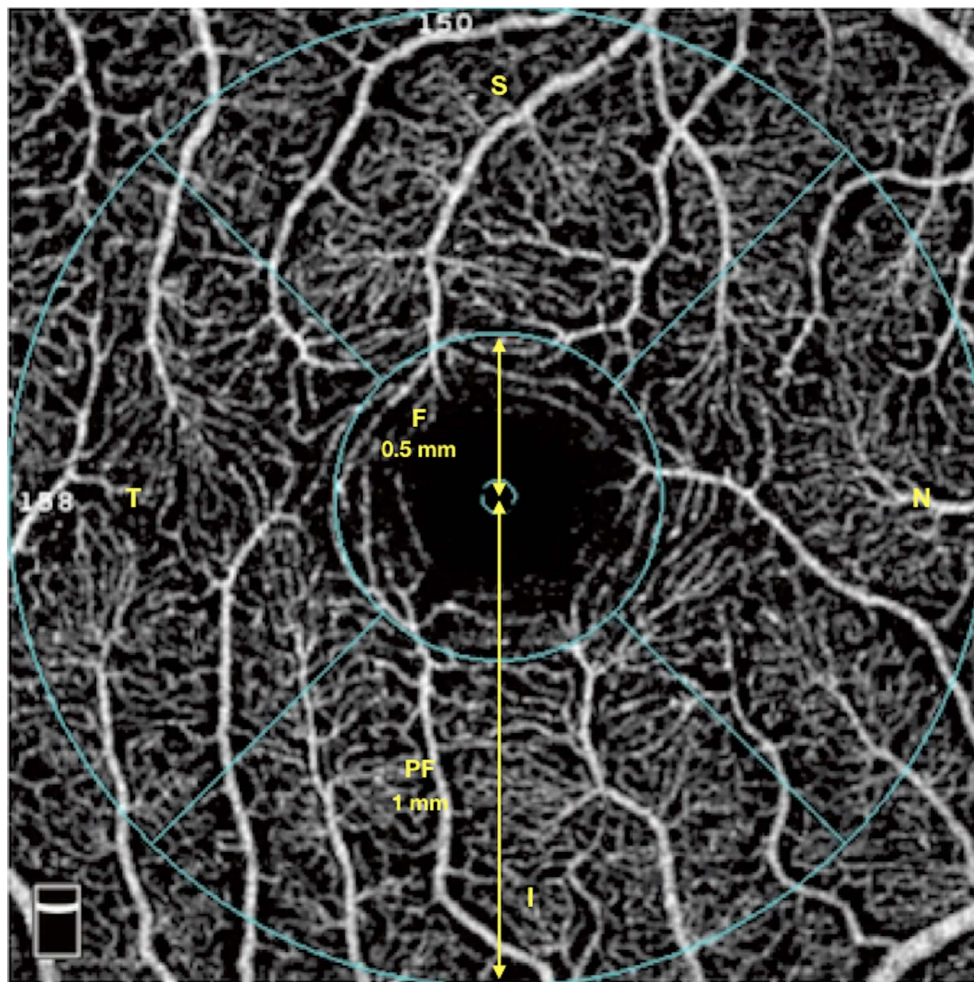


FIGURE 2. Automated superficial capillary plexus PD with overlay of ETDRS subfields. S, superior; I, inferior area; N, nasal; T, temporal.

inferior subfields. However, pregnant women also exhibited a consistently lower SCP-PD in all quadrants that was statistically significant in the entire central macula and in the nasal subfield region specifically. Although the second finding is not what we expected, primary and compensatory circulatory changes are known to occur in pregnancy. Most obviously, during pregnancy peripheral arteries constrict and veins dilate in response to increased blood volume and higher levels of nitrous oxide.¹ In addition, physiologic differences in hydrostatic pressure and structure and function between the SCP and DCP make it plausible that they would be affected differently in pregnancy.^{22,23}

To our knowledge there is no prior OCTA study of pregnant women, but physiologic changes found in pregnancy can be induced. For example, in pregnancy, there is up to a 50%

increase in ventilation, and Hagag et al.²⁴ induced hyperoxia in healthy volunteers and found a significant reduction of flow index and PD in the DCP and trend toward reduction of PD in SCP. OCTA images were taken before and after supplemental oxygen (15 liters per minute) was given for 10 minutes via a facemask. The methodology of this study used the same device as our study and a projection-resolved algorithm similar to ours. Discrepancies between the hyperventilation study and ours could be that hematologic and hormonal changes outweigh the respiratory changes of pregnancy or that the short duration of the nonpregnancy experiment did not allow compensatory changes that pregnancy does.

Although our cohort consisted of healthy pregnant subjects, hypertension is an important complication of pregnancy that predisposes to preeclampsia. An OCTA study of subjects with chronic or acute hypertension showed constriction of retinal vessels compared to healthy controls.²⁵ Therefore, once normative, physiologic pregnancy changes are established, OCTA may be useful to monitor complications of pregnancy such as hypertension.

Despite significant changes in PD, there was no difference in SCP- or DCP-VLD in pregnancy, suggesting that the diameter of blood vessels was altered in pregnancy but not total vessel length. This is perhaps not surprising, as pregnancy spans a relatively short period of time, and vessel diameter can change rapidly, whereas a significant increase in vessel length may require a proliferation of cells and a longer period to develop. In contrast, with diabetic retinopathy, it has been shown that

TABLE 3. Mean CC Flow Voids in Pregnant and Control Subjects

Calculated Parameters	Mean (SD)		P Value
	Pregnant (n = 19)	Control (n = 44)	
CC flow voids %	41.1 (2.2)	40.8 (2.8)	0.65
CC flow voids count	1,459.84 (259.47)	1,459.14 (285.72)	0.99
CC flow voids average size	41.14 (2.23)	40.81 (2.80)	0.62

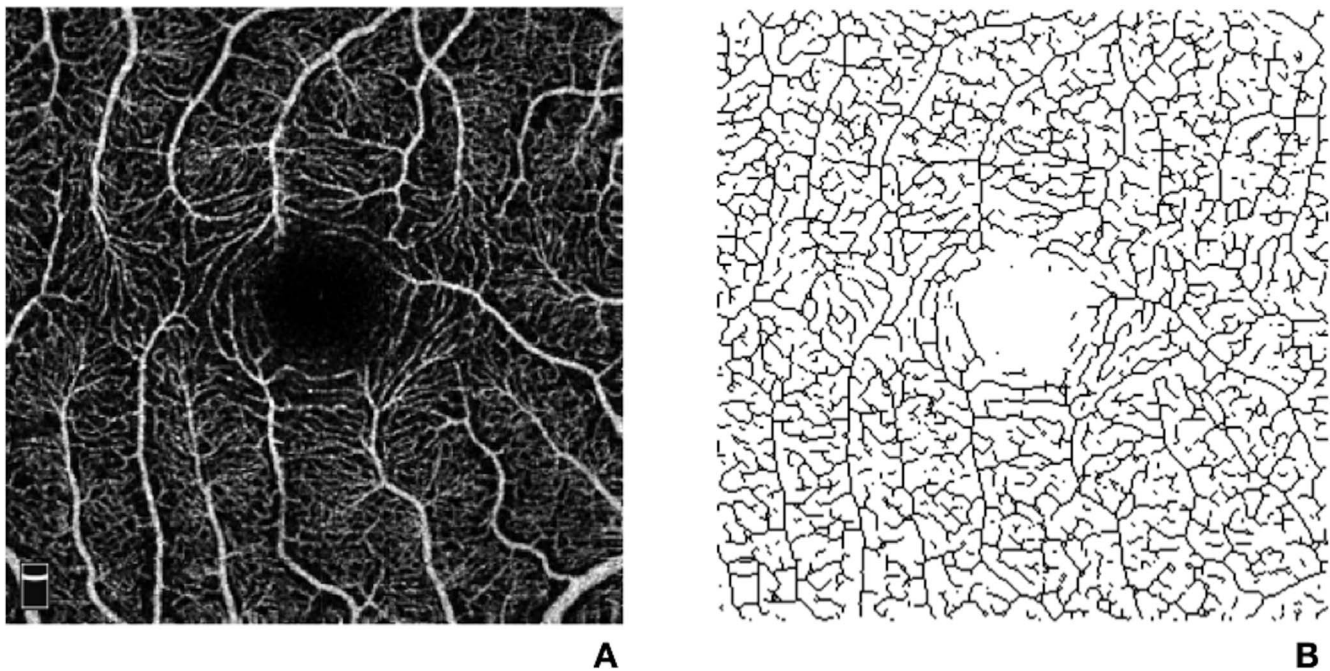


FIGURE 3. Image analysis of superficial capillary VLD. (A) Raw image and (B) processed image.

both PD and VLD can be affected compared to nondiabetic controls.²⁶ The difference may be that diabetes is a chronic disease compared to pregnancy. In addition, diabetic retinopathy is an ischemia-driven process that damages endothelial cells and occludes vessels, thereby impacting both vessel diameter and length.

There are more than a dozen studies on choroidal thickness changes in pregnancy using enhanced depth imaging OCT, which have provided inconsistent results.²⁷⁻⁴² Some studies have found thickening of the choroid in specific subfields during the second and third trimester of pregnancy, whereas

other studies have observed no difference in choroidal thickness during pregnancy. The discrepancy in these studies could be due to variation in inclusion criteria, confounding factors (i.e. refraction, age, and race), and/or differences in image acquisition and image analysis. One study comparing pregnant women in their third trimester of pregnancy found increased choroidal thickness in the inferior subfield. It is unclear if this is connected to our finding of increased DCP vessel density in the inferior subfield.³⁵ We speculate that these both could represent gravity-dependent changes. Unfortunately, in our study we did not acquire enhanced depth imaging

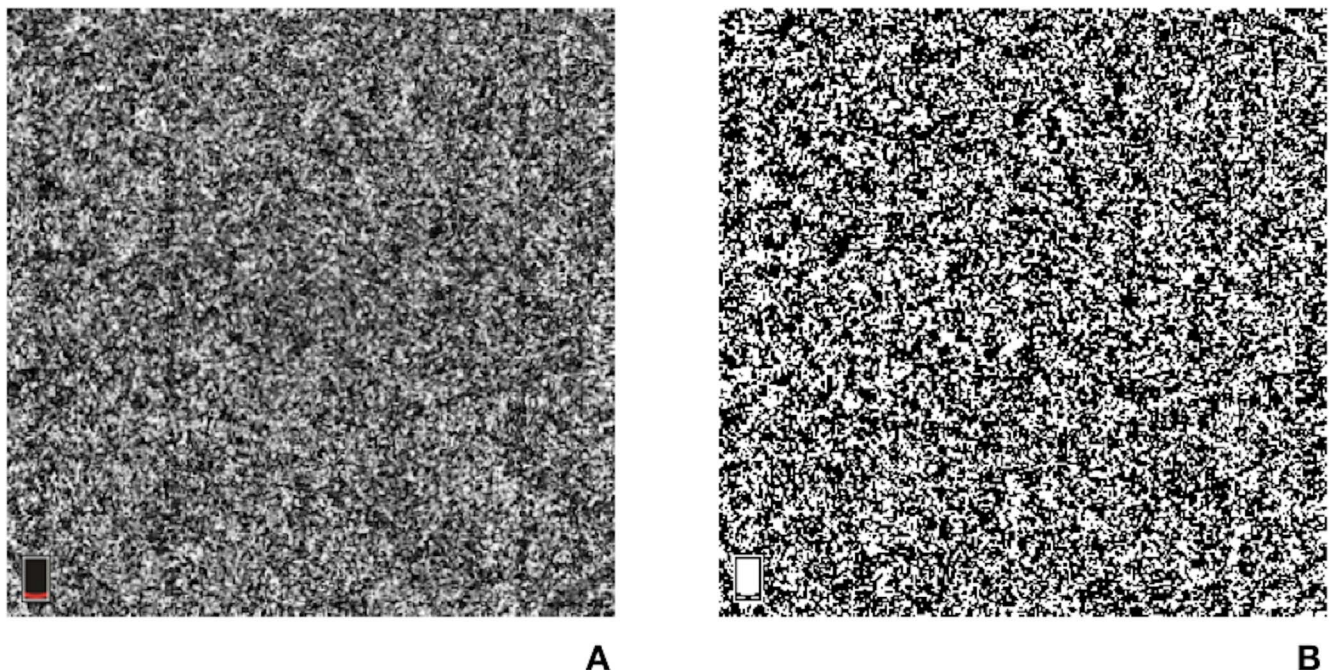


FIGURE 4. Image analysis of CC flow voids. (A) Raw image and (B) processed image.

OCT to measure choroidal thickness. Interestingly, despite the alterations in the DCP and the known changes in choroidal thickness, no differences were evident in measuring CC flow voids on OCTA. This is consistent with prior studies that hypothesize that the retinal vascular autoregulatory process may be more complex than the uniform, relatively constant homeostatic response of the choroid.²⁴

Limitations of our study include a relatively small sample size and the cross-sectional nature of data collection. Nonetheless, the inclusion criteria created a homogenous group of healthy pregnant women and the control group was well-matched. Second, projection artifact may confound analysis of the DCP. Although the new projection artifact removal software was used in this study, it is unlikely to completely eliminate this problem. Despite these shortcomings, our findings make sense in the clinical context given known changes in pregnancy that occur in other organ systems.

In summary, this study demonstrated apparent constriction of SCP-PD with concurrent dilation of DCP-PD in the third trimester of healthy pregnancy. Future longitudinal studies throughout pregnancy and into the postpartum period may provide further insights into the physiology of this complex process.

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