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Maternal Optical Coherence Tomography Angiography Changes Related to Small for Gestational Age Pregnancies

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Purpose: To study maternal retinal changes in pregnancies that resulted in a small for gestational age (SGA) infant.

Methods: Pregnant women with SGA infants at birth and age-matched pregnant women with appropriate for gestational age (AGA) infants at birth (controls) were enrolled. All subjects underwent spectral domain optical coherent tomography angiography (OCTA) imaging using a 10° × 10° scan pattern centered on the fovea. Vessel density (VD) and vessel length density (VLD) of the superficial capillary plexus (SCP), intermediate capillary plexus (ICP), and deep capillary plexus (DCP) were analyzed and compared between the two groups.

Results: Twelve eyes of eight subjects with SGA infants and 64 eyes of 44 age-matched subjects with AGA infants were included in this study. There was no significant difference in chronic hypertension ($P = 1.0$), gestational hypertension ($P = 1.0$), type 1/2 diabetes ($P = 1.0$), gestational diabetes ($P = 0.97$), or preeclampsia ($P = 0.50$) between the SGA group and AGA group. There were significant increases in both VD and VLD in the SCP and ICP layers when comparing the SGA group with the AGA group ($P < 0.05$).

Conclusions: In this pilot study, subjects with SGA infants had increases in selective retinal vasculature layers that may represent systemic perfusion changes compensating for placental insufficiency.

Translational Relevance: Additional assessment of maternal retinal changes in pregnancy using OCTA could prove the technology useful as a biomarker of fetal morbidity.

Introduction

Small for gestational age (SGA) is the failure of a developing fetus to achieve his/her genetically predetermined growth potential and can result from known causes such as smoking, genetic abnormalities, infections, diabetes, or hypertension. SGA is associated with placental insufficiency, where the placenta is unable to sufficiently support the fetus, and is one of the leading causes of perinatal morbidity and death. Additionally, SGA is correlated to future childhood neurodevelopmental disorders.[1–3] There is limited understanding of the pathophysiology of SGA, and searching for effective predictive and preventive measures for SGA remains a challenge.

The quantification of placental perfusion is not currently possible with routine obstetric ultrasound techniques. While magnetic resonance imaging is being used in research, it is costly and limited because of

the risks of contrast dye in pregnancy.[4–6] By contrast, measuring subclinical retinal vasculature changes using optical coherence tomography angiography (OCTA), an important breakthrough imaging technology, can provide depth-resolved quantification of the retinal microvasculature.[7–9] OCTA is noncontact and noninvasive and does not require pharmacologic dilation, which makes it feasible for use in pregnant women.

To date, there have been a limited number of studies exploring retinal vasculature changes in normal and pathologic pregnancy. By using OCTA, our group found that the retinal vascular area increases in the third trimester of a normal pregnancy compared to nonpregnant controls.[10] We hypothesized that increased total body blood volume and high levels of progesterone associated with pregnancy may result in physiological retinal capillary dilation during normal pregnancy. It is unknown, however, whether additional retinal vascular changes can occur in the setting of SGA.

Thus the purpose of this study was to evaluate the retinal vasculature in pregnant subjects with SGA pregnancies and compare them to pregnant subjects with appropriate for gestational age (AGA) pregnancies using OCTA.

Methods

Setting and Participants

This study was a prospective study, which was approved by the Institutional Review Board of the University of California-Los Angeles and was conducted in accordance with the ethical standards stated in the Declaration of Helsinki. Written informed consent was obtained from all subjects before enrollment.

Consecutive subjects meeting eligibility criteria were recruited from the Fetal Diagnostic Unit ultrasonography clinic at the Ronald Reagan Medical Center–UCLA between April 2018 and July 2018. Inclusion criteria for the SGA group included an estimated fetal weight of less than the tenth percentile for gestational age calculated by Fenton growth charts at birth. Subjects were excluded if they had any history of previous ocular diseases, any visual complaints, presence of refractive error greater than −6.0 diopters spherical equivalent (SE), or twin pregnancy. When available, placental weight and percentile was collected.

Image Acquisition and Scanning Protocols

OCTA images were captured without pharmacologic dilation using the spectral-domain OCTA (SD-OCTA) device (Spectralis, Heidelberg Engineering, Heidelberg, Germany). A 10° ×10° (512 × 512 A-scans) OCTA scan was acquired while centered on the fovea. OCTA scans were repeated until a scan of sufficient quality (Q ≥ 30, no evidence of motion artifact) was obtained.

The instrument software's automatic segmentation boundaries (all B-scans) were inspected, and manual correction was performed on any B-scans demonstrating segmentation errors. The manufacturer's projection artifact removal function was used to remove residual artifact from the overlying retinal circulation. After confirmation of proper segmentation, the en face images from the superficial capillary plexus (SCP), intermediate capillary plexus (ICP), and deep capillary plexus (DCP) were exported from the Spectralis software. The SCP was autosegmented to include the nerve fiber layer and ganglion cell layer. The ICP was autosegmented to include the deep portion of the inner plexiform layer and the superficial portion of the inner nuclear layer. The DCP was autosegmented to include the deep portion of the inner nuclear layer and the outer plexiform layer.

Image Processing

The SCP, ICP, and DCP images were imported into the freely available FIJI software (an expanded version of ImageJ version 1.51a; fiji.sc). Then the SCP, ICP and DCP images were binarized using a modified version of a previously reported method.[11,12] Briefly, the images were duplicated to apply two binarization methods. One image was processed first by a Hessian filter, followed by global thresholding using Huang's fuzzy thresholding method. The other (duplicate) image was binarized using median local thresholding. Finally, the two different binarized images were combined to generate the final binarized image in which only pixels that existed on both binarized images were included.

Vessel density (VD) was assessed on this final resultant image and defined as the ratio of the area occupied by vessels divided by the total assessable (i.e., no overlying superficial large retinal vessels) area. After skeletonization of the image, vessel length density (VLD), which represents the vessel length per unit area, was evaluated as described previously.[11–16] In addition, VD and VLD were evaluated within seven specific regions: (1) total image (entire field of 10° ×10°); (2) fovea (central circle with 0.5 mm radius); (3) parafovea (ring

Table 1. Cohort Demographics and Confounding Factors Showing No Significant Differences Between SGA and AGA Group

	SGA Group	AGA Group	*P*
Eyes	12 eyes (8 subjects)	64 eyes (44 subjects)	/
Age (years)	30.75 ± 6.90	34.75 ± 4.93	0.053
Gestational Age (weeks)	35.27 ± 3.69	36.32 ± 2.55	0.322
Spherical Equivalent (D)	−0.42 ± 1.08	−0.65 ± 1.47	0.989
Hypertension			
Chronic	0/8	5/44	1.000
Gestational	0/8	4/44	1.000
Diabetes			
Type 1/2	0/8	2/44	1.000
Gestational	1/8	9/44	0.970
Smoking	0/8	4/44	1.000
Preeclampsia	1/8	3/44	0.499

around the fovea with inner and outer radii of 0.5 and 1.5 mm, respectively).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY, USA). Pearson χ^2 test, continuity correction or Fisher's exact test were used to access the difference in frequency of chronic hypertension, gestational hypertension, type 2 diabetes or gestational diabetes between the SGA and AGA group. To detect VD and VLD differences in SCP, ICP, and DCP between two groups, a linear mixed model was used to adjust for correlations between two eyes of the same subject. A P value <0.05 was considered statistically significant.

Results

The study cohort consisted of 12 eyes from eight subjects with a SGA pregnancy and 64 eyes from 44 subjects with an AGA pregnancy. All pregnant subjects were singleton pregnancies. All eyes had 20/20 best corrected visual acuity. The demographic data for the two groups in this cohort was shown in Table 1. The mean age was 30.75 ± 6.90 years for the SGA group and 34.75 ± 4.93 years for the AGA group ($P > 0.05$). The mean gestational age at time of imaging was 35.27 ± 3.69 weeks (range, 28 to 38 weeks) for the SGA group and 36.32 ± 2.55 weeks (range, 29 to 40 weeks) for AGA group ($P > 0.05$). There were no significant differences in spherical equivalent between the two groups ($P > 0.05$). There were no significant differences in chronic hypertension, gestational hypertension, type I/II diabetes, gestational diabetes, smoking history or preeclampsia between the SGA and AGA group ($P > 0.05$). Four subjects with SGA pregnancies had placental weight and percentile information available; they were <3%, 5%, 5% to 10%, and 50% to 75%.

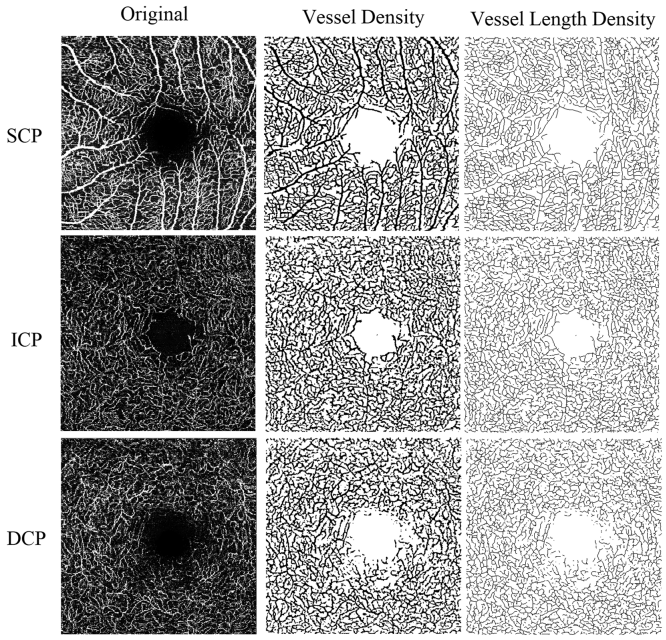

Figure. Example of raw images and processed images for VD and VLD analysis in SCP, ICP and DCP.

Representative raw and processed images for VD and VLD analysis are shown in the Figure. The mean VD and VLD of the SCP, ICP, and DCP is shown in Tables 2 through 4. Although most subfields trended in the direction of increased vascularity in the SGA group, only six reached statistical significance.

Table 2. VD and VLD of SCP in SGA and AGA Group

SCP	SAG Group	AGA Group	*P*
VD			
Total	32.77 ± 1.11	32.15 ± 1.27	0.234
Fovea	9.02 ± 4.94	7.53 ± 3.75	0.293
Parafovea	35.25 ± 1.24	34.71 ± 1.37	0.354
Superior	35.32 ± 1.77	34.86 ± 1.90	0.534
Nasal	35.86 ± 2.00	34.48 ± 1.92	**0.004**
Temporal	34.47 ± 2.06	34.80 ± 1.93	0.419
Inferior	35.37 ± 1.32	34.71 ± 1.51	0.169
VLD			
Total	8.66 ± 0.45	8.30 ± 0.40	**0.045**
Fovea	2.17 ± 1.20	1.81 ± 0.88	0.272
Parafovea	9.17 ± 0.50	8.82 ± 0.44	0.074
Superior	9.28 ± 0.54	8.91 ± 0.51	0.062
Nasal	9.47 ± 0.75	8.78 ± 0.65	**0.000**
Temporal	8.75 ± 0.77	8.72 ± 0.61	0.950
Inferior	9.20 ± 0.51	8.86 ± 0.49	0.116

Bold denotes *P* values <0.05.

Table 3. VD and VLD of ICP in SGA and AGA Group

ICP	SGA Group	AGA Group	*P*
VD			
Total	32.42 ± 1.30	32.17 ± 0.86	0.817
Fovea	15.55 ± 6.24	16.90 ± 3.41	0.621
Parafovea	34.21 ± 1.20	33.80 ± 0.97	0.360
Superior	33.84 ± 2.16	33.03 ± 1.52	0.254
Nasal	35.82 ± 1.76	34.46 ± 1.61	**0.004**
Temporal	33.88 ± 1.86	34.64 ± 1.76	0.180
Inferior	33.29 ± 2.11	33.06 ± 1.53	0.496
VLD			
Total	8.77 ± 0.39	8.56 ± 0.29	0.214
Fovea	3.88 ± 1.48	4.09 ± 0.86	0.999
Parafovea	9.11 ± 0.37	8.85 ± 0.32	0.095
Superior	9.14 ± 0.59	8.76 ± 0.40	**0.023**
Nasal	9.49 ± 0.59	8.93 ± 0.53	**0.001**
Temporal	8.86 ± 0.67	8.98 ± 0.56	0.563
Inferior	8.96 ± 0.53	8.74 ± 0.40	0.358

Bold denotes *P* values <0.05.

Neither the VD or VLD of the SCP, ICP or DCP in the total, foveal, or parafoveal showed significant differences between the SGA and AGA groups ($P > 0.05$).

Discussion

In this study, we observed that of the 42 retinal subfield measurements, 32 (76%) trended higher in the SGA pregnancy group compared with the AGA control group, with six (14%) reaching statistical significance. To our knowledge, the present study was the first in which the relation between SGA and maternal retinal microvascular parameters was assessed by OCTA.

Table 4. VD and VLD of DCP in SGA and AGA Group

DCP	SGA Group	AGA Group	*P*
VD			
Total	32.77 ± 1.53	32.93 ± 1.42	0.881
Fovea	8.31 ± 5.90	7.07 ± 3.20	0.552
Parafovea	35.11 ± 1.62	35.52 ± 1.45	0.539
Superior	35.32 ± 1.84	35.01 ± 2.55	0.877
Nasal	37.08 ± 1.63	37.07 ± 1.82	0.884
Temporal	34.59 ± 1.87	35.30 ± 1.99	0.207
Inferior	34.37 ± 2.30	34.74 ± 2.27	0.355
VLD			
Total	9.00 ± 0.61	8.89 ± 0.44	0.678
Fovea	2.09 ± 1.47	1.79 ± 0.82	0.582
Parafovea	9.49 ± 0.65	9.42 ± 0.44	0.701
Superior	9.71 ± 0.72	9.41 ± 0.75	0.245
Nasal	9.97 ± 0.75	9.79 ± 0.63	0.406
Temporal	8.91 ± 0.90	9.20 ± 0.58	0.187
Inferior	9.36 ± 0.76	9.27 ± 0.66	0.984

The diagnosis of SGA is based on gestational age at birth as opposed to low birthweight, which is an absolute weight cutoff of 2500 g. An SGA fetus exists in a state of chronic hypoxia, which has been demonstrated using fetal blood sampling and is correlated with abnormal umbilical artery Doppler waveforms.[17,18] Although there was only placental pathology sent on four subjects with SGA pregnancies, three of these placentas were <10% percentile weight, supporting the role of placental insufficiency associated with SGA. Furthermore, SGA is associated with future childhood neurodevelopmental impairments. SGA also affects the mother, causing hypertension, which can remain mild and treatable or may progress insidiously to preeclampsia.[19]

Physiological changes of hematologic, vascular, endocrine, metabolic, and immunological systems occur during pregnancy to accommodate the developing fetus and prepare the mother for labor and delivery.[20,21] The significant systemic changes during pregnancy also affect the retinal circulation. Our previous study found that in the third trimester of normal pregnancy, mean perfusion density of the SCP significantly decreased and mean perfusion density of the DCP significantly increased without a difference in vessel length density compared with nonpregnant controls using the RTVue XR Avanti OCT device with AngioVue software.[10] The present study demonstrated that both VD and VDL in the nasal subfield of the

SCP and ICP layers was significantly higher in the SGA group compared with the AGA group.

We hypothesize that these compensatory increases in retinal vascular measurements were related to placental insufficiency associated with SGA. Retinal blood flow is autoregulated through the release of vasoactive substances by the vascular endothelium and retinal tissue surrounding the arteriolar wall. Autoregulation is achieved by adaptation of the vascular tone of the arterioles and capillaries to changes in the perfusion pressure or metabolic needs of the tissue.[22,23] Cerebral blood flow regulation, which is also highly autoregulated, is physiologically increased in pregnancy and is further increased by hypertensive disorders of pregnancy including preeclampsia.[24] Therefore we speculate placental insufficiency associated with SGA could upregulate the release of circulating bioactive factors and link the uteroplacental and systemic circulation in pathological conditions during pregnancy resulting in increased VD and VLD in SGA pregnancy observed in our study.[25]

In our study, the most significant difference between the SGA and AGA group was an increase of VLD in both SCP and ICP. A higher VLD with a relatively steady VD in the SGA pregnancy may reflect an increase in vessel tortuosity accompanied by vasoconstriction of the SCP and ICP. We speculate that the increase in retinal microvascular tortuosity in SCP and ICP may be associated with other systemic cardiovascular alteration, which may warrant further evaluation in future studies. In contrast, there were no statistically significant changes detected in the DCP, although nine of the 14 DCP measurements were on average higher in the SGA group compared with AGA pregnancies. Our study may have been underpowered, however, to detect smaller differences in the DCP between the groups.

Our study does have additional limitations that should be considered in assessing our results. First, this is a cross-sectional study with only one point in time per subject, and thus we are not able to assess longitudinal changes in the retinal microvasculature through the course of SGA pregnancy. Second, we were not able to specifically correlate the retinal microvasculature with uteroplacental or systemic circulation changes. This may be addressed by future longitudinal studies collecting more systemic maternal data including placental pathology on all subjects. Last, by definition SGA is $<10\%$ of the population resulting in a small cohort size in this study; therefore, we included both eyes for analysis and there were significantly more AGA subjects which could lead to confounders. Our study also has several strengths including its prospective design, standardized image acquisition and processing, and the use of certified image reading center graders.

In summary, using OCTA we observed retinal microvascular network alterations in SGA pregnancy eyes compared to AGA pregnancy eyes during the third trimester. The utility of detecting retinal microvascular network alterations earlier in pregnancy for diagnosis and prevention warrants further study.

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