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ARTICLE

Retinal and Macular Changes in Pregnant Women of Advanced Maternal Age: A Retrospective Study

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Abstract

Aims/Background Pregnancy may cause physiological and pathological changes in multiple organs in a woman's body, including the heart, liver, and eyes. With rapid advances in societies and economies, the proportion of advanced maternal age (AMA) women has significantly increased. Here, we aimed to investigate the changes in arteriole retinal diameter, venule diameter, macular layer thickness, and arteriole to venule ratio (AVR) in this population.

Methods This retrospective case-control study included 523 pregnant women (1046 eyes) and was performed on both eyes. In total, 318 subjects were included in the AMA group, and 205 subjects were included in the non-AMA group. Nonmydriatic fundus photography and optical coherence tomography (OCT) were performed on the same day, and the results were analyzed for the central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), AVR, and macular thickness (9 subfields) by integrative vessel analysis and automatic OCT software.

Results In both eyes, the CRAE was significantly lower in the AMA group than that in the non-AMA group ($p < 0.05$; respectively). The CRVE in the AMA group was higher than that in the non-AMA group ($p < 0.001$; respectively). Compared to the non-AMA group, the AMA group exhibited a significant reduction in macular thickness within the inner nasal, outer nasal, and inner temporal subfields of both eyes ($p < 0.05$; respectively). Age was significantly correlated with CRVE and AVR in both eyes of pregnant women (CRVE: $p < 0.0001$; AVR: $p < 0.01$).

Conclusion This study reports variations in the diameter of the retinal vasculature and the thickness of the macula in women of AMA. It is important to consider these changes when interpreting the adverse eye outcomes experienced by women of AMA.

Key words: retinal vasculature; advanced maternal age; pregnant women; macular thickness

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Introduction

Pregnancy can cause physiological and pathological changes in multiple organs in a woman's body, including the heart, lungs, liver, and eyes. During pregnancy, increasing levels of estrogen and progesterone are associated with changes in these organs. In the eyes, for instance, the physiological changes are mainly manifested in corneal sensitivity, ocular pressure, ocular blood flow, and vision (Khong et al, 2021; Malkić et al, 2013; Qin et al, 2020; Taradaj et al, 2018). Pathological changes in the eyes documented during pregnancy are associated with the

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development of pregnancy-related diseases, including preeclampsia/eclampsia and gestational diabetes (Chandrasekaran et al, 2021). Furthermore, pregnancy may also alter the course of preexisting ocular conditions leading to more serious eye conditions such as glaucoma (Khong et al, 2021), dry eye (Asiedu et al, 2021), keratoconus (Jani et al, 2021), and central serous retinopathy (Daruich et al, 2015).

Pregnant women of advanced maternal age (AMA) are defined as those aged 35 years or older (Pinheiro et al, 2019). With rapid developments in societies and economies, the proportion of AMA women has significantly increased (Correa-de-Araujo and Yoon, 2021). Numerous studies have consistently demonstrated that, compared to younger women, AMA is associated with an elevated risk of both maternal and fetal complications, including ectopic pregnancy, spontaneous abortion, gestational diabetes, preeclampsia, and cesarean delivery (Attali and Yogev, 2021; Care et al, 2015; Frick, 2021; Pinheiro et al, 2019). This suggests that advanced age may disrupt the function of different organs in pregnant women. However, there is no study about the ocular changes associated with AMA.

Optical coherence tomography (OCT) is a noninvasive tool that can be used to observe subtle alterations in the macula and retinal nerve fiber layer, along with the choroidal thickness in pregnant women (Khong et al, 2021). OCT allows for quasihistological *in vivo* optical sections of the retina to be acquired, quantified, and analyzed. In pregnant women, the retinal microvasculature can be used to detect early structural changes and pathological features. However, no study has focused on the quantification of retinal vessels in pregnant women. Therefore, to obtain objective evidence of the changes in the macular and retinal vessel diameter in pregnant women of AMA and non-AMA, we investigated the correlations among the different regions of the macula, central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), and arteriole to venule ratio (AVR) in both eyes using OCT and Integrative Vessel Analysis software (IVAN, Department of Ophthalmology Visual Science, University of Wisconsin, Madison, WI, USA).

Methods

Subjects

This retrospective case-control study enrolled 523 pregnant women (1046 eyes) who delivered at the Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, from September 2020 to September 2022. We recruited pregnant women aged 18 to 60 in the late stage of pregnancy. The participants were at 37 to 40 weeks of gestation. The pregnant women included in our study exhibited well-controlled blood pressure levels and blood glucose levels during their hospitalization. The body weight of all pregnant women was also maintained within the normal range during their hospitalization. The inclusion criterion for previous pregnancy status in this study was the absence of a current live birth resulting from previous fetal abortion due to various reasons. Each fetus in this study was the mother's first live birth. Demographic details included the patient's age, sex, and eyes. We excluded subjects with any other comorbidities, such as glaucoma, cataract, ocular surgery, high myopia, ocular trauma, or preexisting retinopathy, and patients with preexisting vascular/renal diseases or systemic diseases, such as hypertension, diabetes, eclampsia, and thyroid disease, known to affect the retina. All patients underwent a detailed ophthalmological examination consisting of slit-lamp biomicroscopy, nonmydriatic fundus photography (NMFCS), and OCT. We performed the ocular examination at 1 to 2 weeks before delivery. This study was approved by the Institutional Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University (Approval the Institutional Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University [2023] No. 113) and adhered to the tenets of the Declaration of Helsinki. Upon hospitalization, patients were required to sign the informed consent form, thereby granting permission for data collection. Written informed consent was obtained from all patients.

Retinal Vessel Diameter Measurements/Retinal Image Analysis

All pregnant women underwent fundus imaging using a fundus camera (Kowa Fundus Camera VX-10α, Aichi, Japan). Two pairs of fundus photos were obtained from the center of the optic disk and macula. The diameters of the six largest retinal arteries and veins within a specified zone (0.5 to 1 disc diameter) from the optic disc margin were measured using a semi-automated system Integrative Vessel Analysis (IVAN). The Atherosclerosis Risk in Communities (ARIC) study protocol was employed for grading retinal vessel characteristics (Wong et al, 2001). The zone of the retinal vascular caliber measurement in the ARIC study was defined as the radial area extending 0.5–1.0-disc diameters from the margin of the optic disc (Rim et al, 2020). The ARIC grid was calibrated to a fixed size according to the resolution of the photograph and was manually centered on the optic disc. Based on the patient characteristics, one experienced grader made manual corrections when necessary. The revised Knudtson-Parr-Hubbard formula was used to standardize and summarize the retinal arteriolar and venular calibers. CRAE and CRVE were determined by calculating the mean diameter of the six largest arterioles and venules, and the AVR were also calculated (Hubbard et al, 1999; Knudtson et al, 2003). The IVAN software interface is depicted in Fig. 1. Two masked graders independently conducted image measurements. In cases where the inter-grader discrepancy exceeded 10%, a third grader was involved to evaluate the images, and subsequently, the average of these three values was used for analysis.

Optical Coherence Tomography Images

The OCT device (Topcon 3D OCT-2000, version 8.42, Tokyo, Japan) was used to acquire images of the macula from all patients. Images were obtained using the 3D macular 512 $\times$ 128 scan mode, which covered an area of 6 $\times$ 6 mm^2. The OCT image assessments of the patients were conducted by an experienced technician. Macular thickness was automatically evaluated using OCT software, and a macular thickness map was used for analysis. During the assessments, the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria were applied to define the 9 subfields within the macula. These ETDRS subfields facilitated measurement of macular thickness across various regions. Circular areas with diameters of 1, 3, and 6 mm were used. The macula was divided into two rings according to

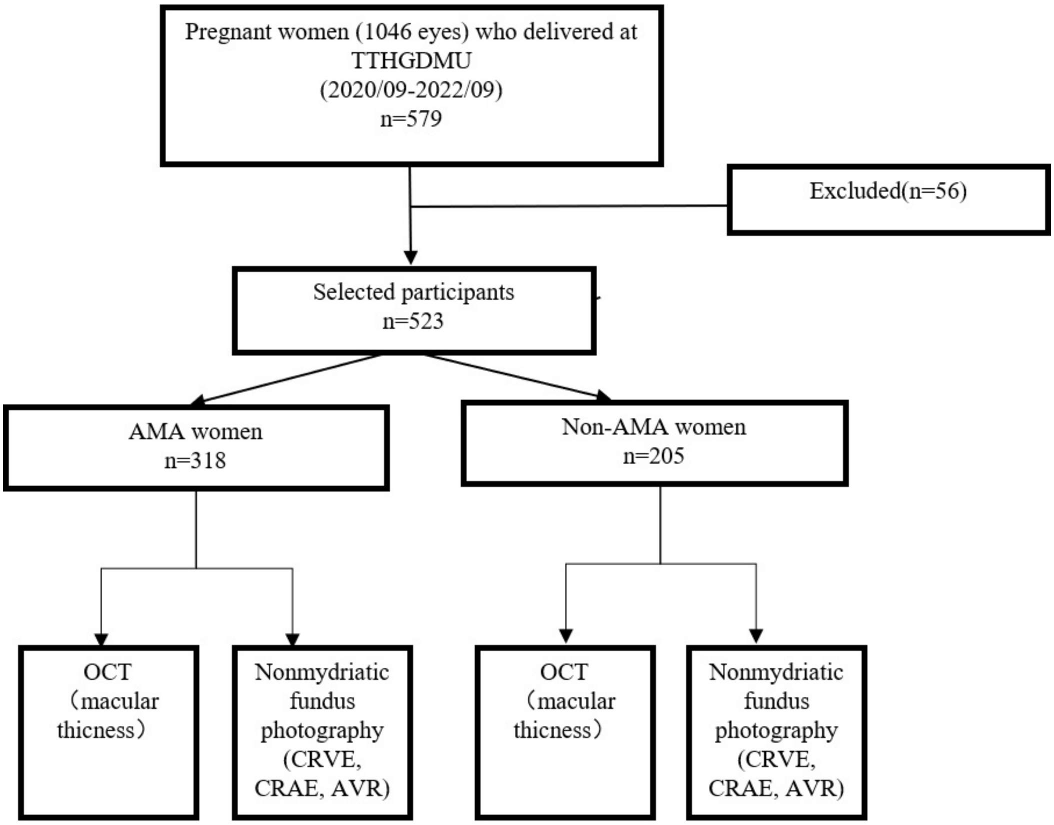

Fig. 1. A screening flow chart of the pregnant women in our study. NMFCS results and OCT observations were the main observation indicators in this study. TTHGDMU, The Third Affiliated Hospital of Guangzhou Medical University; AMA, advanced maternal age; NMFCS, nonmydriatic fundus photography; OCT, optical coherence tomography; AVR, arteriole to venule ratio; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

the ETDRS, which subdivided the macula into four quadrants: superior, inferior, nasal and temporal quadrants. Patients with low-quality scans were excluded. The images are shown in Fig. 2.

Statistical Analysis

All statistical analyses were performed using SPSS (version 23.0; IBM Corporation, Chicago, IL, USA) and R software (version 3.6.3; University of Auckland, Auckland, New Zealand). The Kolmogorov-Smirnov test was employed to assess the normality of the data, and it was found that the baseline data deviated from a normal distribution. Mann-Whitney U test was used in the analysis of age in the baseline data. Chi-square test was employed in the statistical analysis of the baseline data. The Wilcoxon rank-sum test was performed to compare the parameters of macular thickness in different regions and the diameters of the CRAE, CRVE, and AVR between the AMA group and the non-AMA group. Spearman's correlation coefficient analysis was applied to assess the correlation between age, the parameters of macular thickness per quadrant, CRVE, CRAE, and AVR. $p < 0.05$ was considered to be a statistically significant difference.

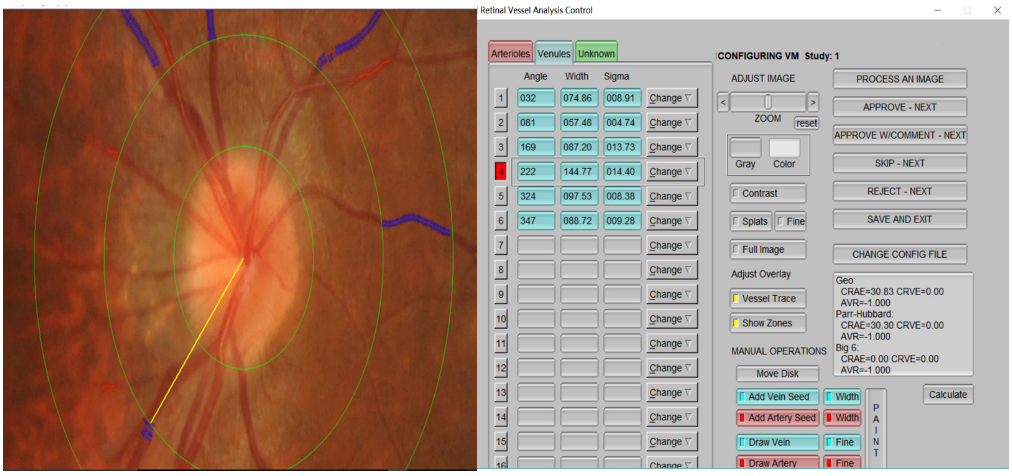

Fig. 2. A screenshot of the IVAN interface. The left image shows a circle precisely centered on the optical disc. The software can automatically detect 4 to 6 of the largest arterioles and venules (veins depicted in blue; arteries depicted in red). In the right image, an interactive interface calculates CRAE, CRVE, and AVR using specific formulas, while also enabling data export and other related functions. IVAN, Integrative Vessel Analysis; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole to venule ratio.

Results

Descriptive Statistics

A total of 523 (1046 eyes) pregnant women were studied: 318 subjects were included in the AMA group and 205 subjects were included in the non-AMA group. The demographic characteristics of the pregnant women and their fetuses are summarized in Table 1. The maternal age ranged from 19 to 50 years, with an average age of 34.5 years among the pregnant women in our study population.

The proportion of pregnant women with different education levels were: AMA group (uneducated: 5.03%; with compulsory education: 61.32%; with advanced education: 33.65%) and non-AMA group (uneducated: 5.37%; with compulsory education: 53.17%; with advanced education: 41.46%). There were 193 patients' (60.69%) husbands aged 35 years and older and 125 (39.31%) patients' husbands aged younger than 35 years in the AMA group; in the non-AMA group, these proportions were 97 (47.32%) and 108 (52.68%). In the AMA group, 215 (67.61%) pregnant women had a history of *in vitro* fertilization and embryo transfer (IVF-ET), while 94 (45.85%) pregnant women in the non-AMA group had a history of IVF-ET.

In total, 17 pregnant women had multiple pregnancies in AMA and non-AMA groups. The proportion of previous pregnancy in the AMA group was 259 (81.45%) and in the non-AMA group was 153 (74.63%). Of the pre-pregnancy obesity patients, 67 (21.07%) were in the AMA group and 47 (22.93%) were in the non-AMA group. For a family history of diabetes or hypertension in the AMA group, 152 (47.80%) had no history, 98 (30.82%) had a history, and 68 (21.38%) did not know if they had a history; in the non-AMA group, these proportions were 134 (65.37%), 55 (26.83%), and 16 (7.80%).

Table 1. Maternal baseline characteristics.

Parameter	Advanced maternal age (n = 318) Median (25th; 75th percentiles)/Number (%)	Non-advanced maternal age group (n = 205) Median (25th; 75th percentiles)/Number (%)	χ^2/Z	*p*
Age	38 (36, 40)	30 (26, 33)	–22.194	0.000
Education level			3.525	0.172
Uneducated	16 (5.03%)	11 (5.37%)		
With compulsory education	195 (61.32%)	109 (53.17%)		
With advanced education	107 (33.65%)	85 (41.46%)		
Husband age			9.026	0.003
≥35	193 (60.69%)	97 (47.32%)		
<35	125 (39.31%)	108 (52.68%)		
Conception			24.405	0.000
Nature conception	103 (32.39%)	111 (54.15%)		
IVF-ET	215 (67.61%)	94 (45.85%)		
Multiple pregnancy			4.797	0.029
With	6 (1.89%)	11 (5.37%)		
Without	312 (98.11%)	194 (94.63%)		
Previous pregnancy			3.460	0.063
With	259 (81.45%)	153 (74.63%)		
Without	59 (18.55%)	52 (25.37%)		
Pre-pregnancy obesity			0.252	0.615
With	67 (21.07%)	47 (22.93%)		
Without	251 (78.93%)	158 (77.07%)		
Family history of diabetes or hypertension			22.021	0.000
No	152 (47.80%)	134 (65.37%)		
Yes	98 (30.82%)	55 (26.83%)		
Unknown	68 (21.38%)	16 (7.80%)		

IVF-ET, *in vitro* fertilization and embryo transfer.

Table 2. Alteration of retinal vessel diameter in women of advanced maternal age and non-advanced maternal age in both eyes.

		Advanced maternal age (n = 318)	Non-advanced maternal age group (n = 205)	*W*	*p* value
Right eyes	CRAE (μm)	128.43 (114.86, 147.06)	135.39 (121.64, 149.00)	49,993	0.0332
	CRVE (μm)	331.48 (298.64, 355.80)	318.28 (292.50, 343.68)	64,348	0.0003
	AVR	0.40 (0.36, 0.46)	0.43 (0.37, 0.49)	46,763	0.0006
Left eyes	CRAE (μm)	129.73 (115.58, 147.33)	135.80 (119.92, 150.55)	49,984	0.0315
	CRVE (μm)	331.51 (304.44, 356.76)	327.37 (293.12, 342.00)	64,752	0.0002
	AVR	0.39 (0.35, 0.45)	0.42 (0.37, 0.49)	44,730	<0.0001

CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole to venule ratio. Data presented as median (25th; 75th percentiles), and the Wilcoxon rank-sum and test was used for pairwise comparisons.

We observed a significantly higher association of AMA with husband's age, use of various methods of conception (particularly IVF-ET), absence of multiple pregnancies, and greater number of family history cases involving diabetes or hypertension compared to non-AMA ($p < 0.05$).

Alteration of the Retinal Vessel Diameter by IVAN

The quantitative analysis of CRVE, CRAE, and AVR in both eyes of the pregnant women is shown in Table 2 and Fig. 2. We found that the CRAE was significantly lower in the AMA group than in the non-AMA group in both eyes (Right eyes: 128.43 (114.86, 147.06) vs. 135.39 (121.64, 149.00), $p < 0.05$; Left eyes: 129.73 (115.58, 147.33) vs. 135.80 (119.92, 150.55), $p < 0.05$; Table 2). The CRVE in the AMA group was higher than that in the non-AMA group (Right eyes: 331.48 (298.64, 355.80) vs. 318.28 (292.50, 343.68), $p < 0.001$; Left eyes: 331.51 (304.44, 356.76) vs. 327.37 (293.12, 342.00), $p < 0.001$; Table 2). Further comparison revealed that the AVR in the AMA group was lower than that in the non-AMA group (Right eyes: 0.40 (0.36, 0.46) vs. 0.43 (0.37, 0.49), $p < 0.001$; Left eyes: 0.39 (0.35, 0.45) vs. 0.42 (0.37, 0.49), $p < 0.0001$; Table 2).

Macular Thickness in Different Subfields by OCT

The thicknesses of different subfields of the macula in our study are shown in Table 3 and Fig. 3. To our surprise, in the inner and outer nasal subfields of the ETDRS, the macular thickness in the AMA group was thinner than that in the non-AMA group in both eyes (nasal inner macula (NIM) region, Right eyes: 290 (280, 306) vs. 296.00 (286, 312), $p < 0.05$; Left eyes: 295 (285, 304) vs. 297 (287, 306), $p < 0.05$; Table 3; nasal outer macula (NOM) region, Right eyes: 280 (271, 290) vs. 286 (276, 292), $p < 0.05$; Left eyes: 279 (270, 290) vs. 283 (272, 292), $p < 0.05$; Table 3). Furthermore, we also observed a decrease in the macular thickness of the inner temporal subfields of the AMA group compared with the non-AMA group (Right eyes: 270 (260, 282) vs. 280 (270, 289), $p < 0.05$; Left eyes: 273 (267, 283) vs. 276 (267, 285); $p < 0.05$, Table 3). We did not observe significant

Table 3. Alteration of macular thickness in different subfields in women of advanced maternal age and non-advanced maternal age in both eyes.

		Advanced maternal age (n = 318)	Non-advanced maternal age group (n = 205)	*W*	*p* value
Right eyes	SIM (µm)	292 (283, 303)	293 (282, 302)	55,171	0.9408
	SOM (µm)	265 (256, 275)	266 (256, 273)	55,591	0.9255
	IIM (µm)	286 (279, 297)	286 (275, 295)	59,192	0.1246
	IOM (µm)	256 (245, 265)	257 (247, 266)	53,109	0.3679
	NIM (µm)	290 (280, 306)	296 (286, 312)	59,760	0.0479
	NOM (µm)	280 (271, 290)	286 (276, 292)	55,999	0.0474
	TIM (µm)	270 (260, 282)	280 (270, 289)	58,008	0.0385
	TOM (µm)	245 (238, 253)	247 (238, 256)	52,495	0.2516
	CSF (µm)	213 (203, 228)	215 (204, 228)	57,277	0.4420
Left eyes	SIM(µm)	293 (283, 303)	294 (285, 305)	59,062	0.1379
	SOM (µm)	267 (259, 275)	268 (258, 277)	57,067	0.4936
	IIM (µm)	286 (278, 296)	288 (279, 298)	58,314	0.2363
	IOM (µm)	257 (248, 268)	257 (247, 267)	55,514	0.9502
	NIM (µm)	295 (285, 304)	297 (287, 306)	60,954	0.0250
	NOM (µm)	279 (270, 290)	283 (272, 292)	60,537	0.0381
	TIM (µm)	273 (267, 283)	276 (267, 285)	60,708	0.0321
	TOM (µm)	247 (239, 258)	248 (241, 259)	52,608	0.2709
	CSF (µm)	216 (202, 228)	217 (207, 230)	59,582	0.0907

SIM, superior inner macula; SOM, superior outer macula; IIM, inferior inner macula; IOM, inferior outer macula; NIM, nasal inner macula; NOM, nasal outer macula; TIM, temporal inner macula; TOM, temporal outer macula; CSF, central subfield. Data presented as median (25th; 75th percentiles), and the Wilcoxon rank-sum and test was used for pairwise comparisons.

differences in the macular thickness in the central subfield, superior inner and outer macula, inferior inner and outer macula, or temporal outer macula in the different age groups.

Correlation of Age with Retinal Vessel Diameter and Parameters of Macular Thickness

Spearman's correlation coefficient analysis was used to evaluate the correlation among age, retinal vessel diameter and macular thickness. A positive correlation was found between age and the CRVE in both eyes of the pregnant women (Right eyes: rs = 0.13, Left eyes: rs = 0.12, $p < 0.0001$, Tables 4,5; Figs. 4,5). Furthermore, a negative correlation was observed between age and the AVR (Right eyes: rs = –0.14, Left eyes: rs = –0.16; $p < 0.01$; Tables 4,5; Figs. 4,5). However, we did not observe a significant correlation between age and any other parameter of macular thickness ($p > 0.05$; Tables 4,5; Figs. 4,5).

Table 4. ***p*** **value for correlation of the NMFCS and OCT parameters of pregnant women in right eyes.**

	Age	CRAE	CRVE	AVR	SIM	SOM	IIM	IOM	NIM	NOM	TIM	TOM	CSF
Age	–	0.2117	<0.0001	0.0016	0.4493	0.8622	0.8175	0.3628	0.0846	0.3938	0.4959	0.0885	0.8142
CRAE		–	0.0001	0	0.1626	0.8883	0.8905	0.2268	0.8879	0.6311	0.6241	0.1765	0.9524
CRVE			–	0	0.7631	0.6413	0.9116	0.7623	0.5719	0.1520	0.4855	0.4898	0.4872
AVR				–	0.2577	0.8522	0.9348	0.2853	0.8286	0.2864	0.4416	0.5804	0.9168
SIM					–	0.0020	0	0	0.0005	0	0	0	0
SOM						–	0.0023	0.0616	0.6503	0.0031	0.0014	0.0029	0.2919
IIM							–	0	0.0003	0	0	0	0
IOM								–	0.0954	0	0	0	<0.0001
NIM									–	<0.0001	0.0030	0.0026	0.3423
NOM										–	0	0	<0.0001
TIM											–	0	0
TOM												–	<0.0001
CSF													–

Spearman's correlation coefficient analysis was applied to assess the correlation between age, the parameters of macular thickness per quadrant, CRVE, CRAE, and AVR. NMFCS, nonmydriatic fundus photography; OCT, optical coherence tomography.

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Table 5. ***p*** **value for correlation of the NMFCS and OCT parameters of pregnant women in left eyes.**

	Age	CRAE	CRVE	AVR	SIM	SOM	IIM	IOM	NIM	NOM	TIM	TOM	CSF
Age	–	0.2117	<0.0001	0.0015	0.4493	0.8622	0.8175	0.3628	0.0846	0.3938	0.4959	0.0885	0.8142
CRAE		–	0.0001	0	0.1626	0.8883	0.8905	0.2268	0.8879	0.6311	0.6241	0.1765	0.9524
CRVE			–	0	0.7631	0.6413	0.9116	0.7623	0.5716	0.1520	0.4855	0.4898	0.4872
AVR				–	0.2577	0.8522	0.9348	0.2853	0.8286	0.2864	0.4416	0.5804	0.9168
SIM					–	0.0020	0	0	0.0005	0	0	0	0
SOM						–	0.0023	0.06162	0.6503	0.0031	0.0014	0.0029	0.2919
IIM							–	0	0.0003	0	0	0	0
IOM								–	0.0954	0	0	0	<0.0001
NIM									–	<0.0001	0.0030	0.0026	0.3423
NOM										–	0	0	<0.0001
TIM											–	0	0
TOM												–	<0.0001
CSF													–

Spearman's correlation coefficient analysis was applied to assess the correlation between age, the parameters of macular thickness per quadrant, CRVE, CRAE, and AVR. NMFCS, nonmydriatic fundus photography; OCT, optical coherence tomography.

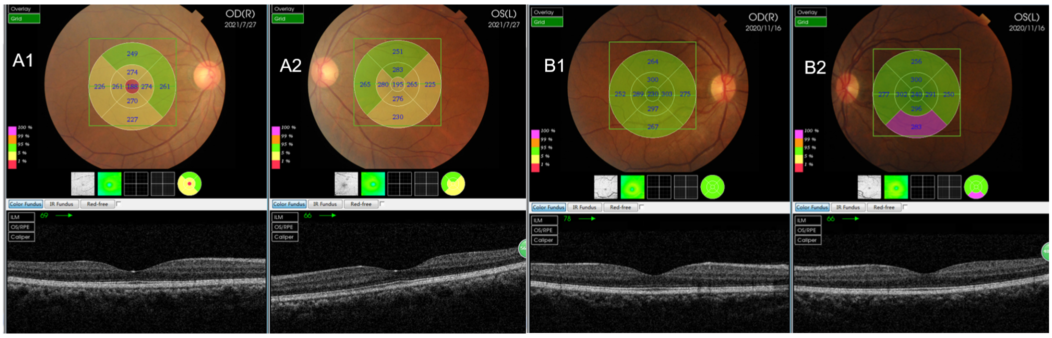

Fig. 3. A ETDRS subfield template used to derive macular thickness measurements from different regions of a high-density volume scan of the macula. Circles are 1, 3, and 6 mm in diameter. These images depict the central and peripheral retinal thicknesses of the macula in various zones, including CSF, SIM, SOM, IIM, IOM NIM, NOM, TIM, and TOM, accompanied by fundus color and ETDRS. The subsequent image illustrates the morphology of the macular central region on a tomography scan. OCT images of the AMA group with both eyes (A1,A2). OCT images of the non-AMA group with both eyes (B1,B2). SIM, superior inner macula; SOM, superior outer macula; IIM, inferior inner macula; IOM, inferior outer macula; NIM, nasal inner macula; NOM, nasal outer macula; TIM, temporal inner macula; TOM, temporal outer macula; CSF, central subfield; ETDRS, Early Treatment of Diabetic Retinopathy Study.

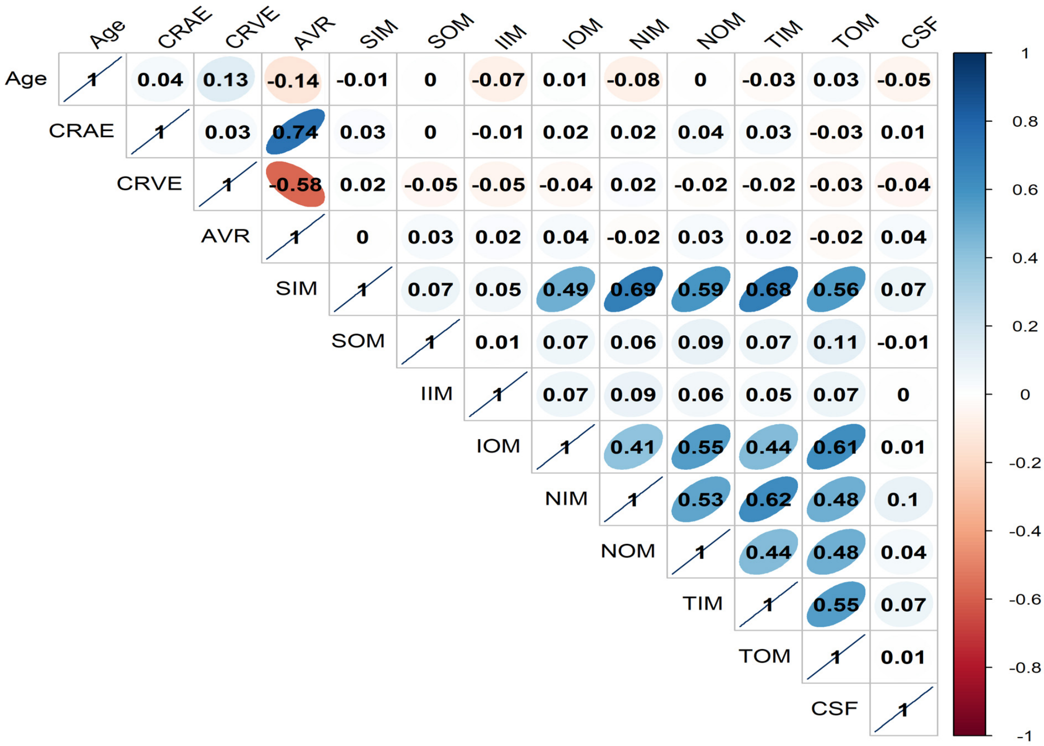

Fig. 4. Statistically significant correlations of age with retinal vessel diameter and macular thickness in right eyes. Age was significantly correlated with CRVE and AVR in the right eyes of the pregnant women. $p < 0.05$ was considered a statistically significant difference.

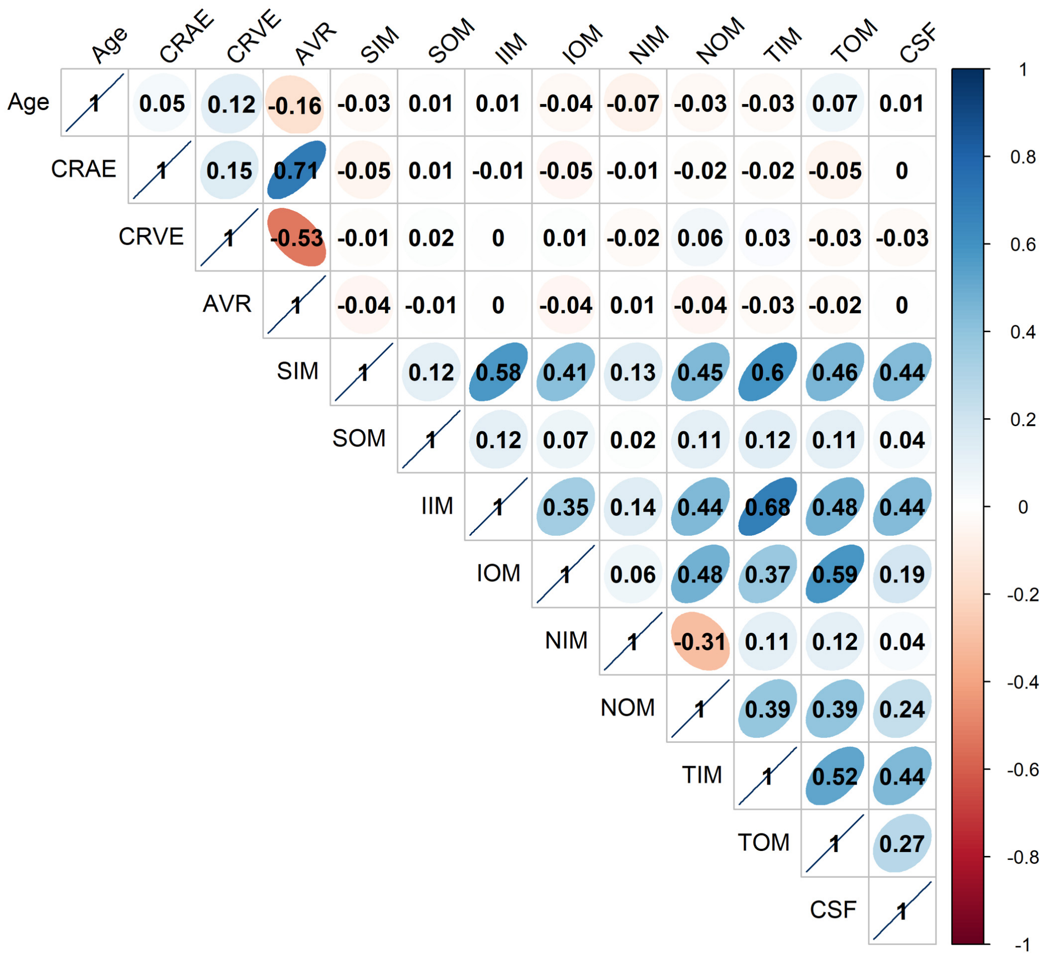

Fig. 5. Statistically significant correlations of age with retinal vessel diameter and macular thickness in left eyes. Age was significantly correlated with CRVE and AVR in the left eyes of the pregnant women. $p < 0.05$ was considered a statistically significant difference.

Discussion

Previous studies related to changes in retinal vessels in pregnant women have primarily focused on pregnancy-induced hypertension (Ge et al, 2021; Soullane et al, 2024; Uma et al, 2022). To our best knowledge, this is the first study to address the effect of advanced age on retinal vascularization and macular thickness in pregnant women. A strength of the present study is that we quantitatively analyzed the diameter of the retinal vessels in pregnant women without pregnancy-induced hypertension syndrome (PIH) using IVAN software. Furthermore, we also found that age was significantly correlated with the CRVE and AVR in both eyes of the enrolled pregnant women. Our results also showed that pregnant women of AMA have a thinner macular layer than pregnant women of non-AMA.

Many studies have reported complications associated with AMA, including obesity, preeclampsia, gestational diabetes, preterm delivery, cardiovascular disease, conditions related to placental dysfunction, and even stillbirth (Care et al, 2015; Frick, 2021; Pinheiro et al, 2019). However, there are no studies about vascular changes in the retinas of patients of AMA. In our study, we found that the

CRVE was wider in both eyes in the AMA group than in the non-AMA group. A study by Care et al (2015), demonstrated that aging is associated with impairments in uterine and systemic arteries during pregnancy, including the uterine and mesenteric arteries in aged dams exhibiting enhanced active myogenic responses. These augmented myogenic responses are likely attributed to elevated vascular oxidative stress and nitric oxide (NO) synthesis. Furthermore, NO is a rapid endothelial relaxant that regulates retinal blood flow under normal conditions (Gericke and Buonfiglio, 2024). Excessive NO production and dysregulated oxidative stress have been implicated in increased thickness of the retinal capillary basement membrane and gliosis, potentially leading to constriction of the retinal arterioles. This phenomenon is consistent with our results, which showed that the CRAE was narrower in the AMA group than in the non-AMA group.

Furthermore, we proved that there was a significant positive correlation between age and CRVE in pregnant women. Several factors have been shown to be potent vasodilators in retinal venular dilatation, such as inflammatory cytokines, serum high-density lipoprotein cholesterol, and high-sensitivity C reactive protein (Newman et al, 2018). The increased level of interleukin (IL)-6 and transforming growth factor (TGF)-β have been reported to be significantly associated with maternal age (Ferrari et al, 2020; Shivani et al, 2023). As mentioned above, we can infer that women of AMA may have higher levels of inflammatory cytokines than women of non-AMA, which causes the retinal venules to widen. These results showed age-related changes in the microvasculature of the retinas in women of AMA, with a decreasing tendency in the ratio of arterioles to venules. In addition, Gila-Díaz et al (2020), proved that there is a significant association between maternal age and oxidative stress markers. Therefore, the widening retinal venular diameter is thought to be due to the increase in NO synthase activity caused by inflammatory cytokines (Newman et al, 2018). Our findings suggest that AMA can cause extensive changes in the function of the retinal vasculature, which may be related to increased systemic inflammation and enhanced oxidative stress responses. Previous study has shown an increase in the average wall-to-lumen ratio of the retinal artery in twin pregnancies, but also a decrease in this ratio at 37 weeks of gestation (Dathan-Stumpf et al, 2024). Therefore, as our study population consisted of patients enrolled after 37 weeks and included a relatively small number of twin pregnancies, these observations had minimal impact on our results.

In a previous study, the AVR has been commonly used as an indicator of the severity of pregnancy-induced hypertension and preeclampsia (Sharifizad et al, 2021). Interestingly, we found a significant negative correlation between the AVR and the age of the pregnant women without pregnancy-induced hypertension. Moreover, the AVR in the AMA group was lower than that in the non-AMA group. As mentioned above, we demonstrated that the retinal artery diameter decreased and the venous diameter increased with increasing maternal age, which may lead to a decrease in the AVR. However, we did not find a significant correlation between CRAE and age. Therefore, the AVR can assist us in assessing retinal vascular changes in women of AMA.

OCT, as a routine part of an ocular examination, is used to detect abnormalities of the retina, especially in the macula (Khong et al, 2021). The differences in the macular thickness in the AMA and non-AMA groups were found in the nasal (both inner and outer) and inner temporal subfields of both eyes, and we observed macular thinning in older pregnant women. A previous study reported modest thinning of the nasal parafoveal retina in early and intermediate age-related macular degeneration (Richer et al, 2012). These investigators proved that the thinning of the macula was associated with the macular pigment optical density, which tends to decrease with age.

Furthermore, it has been observed that the thinning of the macular area is indirectly linked to diminished antioxidant defense in both retinal and choroidal vascular beds (Richer et al, 2012). This finding is also consistent with the retinal microvascular alterations observed in AMA women in our study. In study of pediatric and adult patients with diabetes mellitus, the thickness of the inner retinal layers was changed at an early stage of the disease (Prakasam et al, 2020). At the same time, other studies of pregnant women indicated that the macular retina becomes thinner (Acmaz et al, 2015; Kuo et al, 2020; Ulusoy et al, 2015). Furthermore, in a recent study, specific retinal layer thinning was proposed as a novel biomarker for adverse outcomes in high-risk pregnant women (Hanhart et al, 2022). Therefore, we speculated that age, as an independent risk factor, may exacerbate the extent of the thinning of the macula in older pregnant women compared with younger pregnant women. Although OCT study has shown that twin pregnancies can increase choroidal thickness (Alim and Ozsoy, 2019), our findings were minimally affected due to the focus on macular thickness and the small proportion of twin pregnancies in our subject population. Our findings also suggest that optical coherence tomography angiography (OCTA) can be utilized in future studies to investigate the correlation between alterations in microvascular changes and retinal thickness across different layers in women of AMA. Based on the findings of our study, OCTA observational studies and prospective/follow-up studies should be conducted in the future to offer clinical guidance.

The differences in the thickness of the macula between the AMA group and the non-AMA group may be due to the changes in the microcirculation of the central retinal artery (Herman et al, 2023). Some studies have shown that a high systolic blood pressure in the retinal artery may lead to macular thinning during pregnancy (Lee et al, 2020; Marshall et al, 2021). According to our study, the CRAE was narrower in the AMA group than in the non-AMA group, while the reduction in the CRAE may cause an increase in the blood pressure of the central retinal artery, leading to macular thinning. Specifically, hyperperfusion injury of the retinal artery due to the reduction in the CRAE may destroy the autoregulatory function, which may cause thinning of the macula (Ge et al, 2021). Moreover, another reason that may lead to this difference in our study is cytokines. Upregulated cytokine levels in women of AMA have been demonstrated to interfere with the metabolism of retinal ganglion cells, resulting in retinal thinning (Wang et al, 2020). Thus, we can infer that a reduction in the CRAE may lead to damage of the retinal layer in women of AMA. These research findings also suggest that we should conduct prospective and follow-up studies to investigate longitudinal changes in the correlation coefficient among AMA women, thereby offering valuable insights for informing clinical practice.

Several limitations of this study need to be highlighted. First, additional studies are needed to investigate retinal vascular changes and OCT-related coefficient changes in women of AMA before and after delivery to evaluate whether these indicators may lead to permanent damage. Second, our study was limited by the available equipment. Studies of the choroidal correlation coefficient by OCT are needed to confirm these findings, which may help enhance our understanding of the mechanisms involved in the changes in the fundus vascular microenvironment of patients of AMA.

Conclusion

In conclusion, we found changes in the retinal microvascular diameter, ratio, and macular thickness in women of AMA, and there was a significant correlation among age, CRVE, and AVR in these patients. These findings may provide new insights into adverse eye outcomes due to the advanced age of pregnant women. At the same time, it also suggests that we should extend the retinal examination of women of AMA to other diseases.

Key Points

- This study shows that, in pregnant women, there were significant variations in the diameter of the retinal vasculature in AMA women and non-AMA women.
- In this study, we also showed a significant decrease in the macular thickness in pregnant women.
- This is the first study to focus on the effect of advanced age on retinal vascularization and macular thickness in pregnant women.
- We proposed a novel approach for assessing microvascular alterations in AMA women, providing a foundation for clinical investigations into microcirculatory changes in ocular and other organ systems, thereby facilitating early intervention strategies.

Availability of Data and Materials

Data and materials are available on request from the first author.

Author Contributions

XTL and SYW designed the study. XTL, YYW, HQZ, SYW performed the literature research, data acquisition, data analysis, and manuscript editing. XTL, SYW conducted the clinical studies. XTL drafted the manuscript. XTL and SYW reviewed the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final version of the manuscript.

All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the institutional ethics committee of The Third Affiliated Hospital of Guangzhou Medical University (approval number [2023] No. 113). Written informed consent was obtained from all of the subjects.

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Conflict of Interest

The authors declare no conflict of interest.

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