Evaluation of Choroidal Thickness during Pregnancy and Post-partum: A Longitudinal Study

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Abstract

Purpose: This study aimed to assess the longitudinal changes of choroidal thickness using enhanced depth imaging optical coherence tomography (EDI-OCT) during pregnancy and post-partum.

Methods: The study included 23 eyes of 23 healthy pregnant women and 23 eyes of 23 healthy non-pregnant women. Choroidal thickness (CT) was measured manually with EDI-OCT at seven locations: the fovea, 500, 1000 and 1500 μm temporal (T) from the fovea and 500, 1000 and 1500 μm nasal (N) from the fovea. Measurements were obtained at each pregnancy trimester and 6 weeks post-partum and in the follicular phase of the menstrual cycle for the control group.

Results: The mean subfoveal choroidal thickness was 410.2 ± 82.4 μm, 434.8 ± 79.6 μm, 433.5 ± 80.3 μm, and 395.0 ± 71.1 μm in the first, second and third trimesters and 6 weeks post-partum, respectively. In all seven measured locations, statistically significant changes were noted during pregnancy and post-partum in the choroidal thickness ($p<0.001$). Choroidal thickness increased from the first trimester to the second and third trimester, after which it decreased at post-partum. Choroidal thickness was greater in the pregnant group during pregnancy and post-partum compared to the control group ($p<0.001$).

Conclusion: This study indicated significant change in choroidal thickness at seven locations measured with EDI-OCT throughout pregnancy and 6 weeks after delivery. We showed that 6 weeks after delivery, choroidal thickness remains significantly higher than non-pregnant subjects.

Introduction

Pregnancy is a period associated with many physiologic changes throughout the body [1]. The majority of these changes occur in the hormonal, hematologic and cardiovascular systems. As it is well understood the blood volume is increased during pregnancy, reaching 40-45% higher than pre-pregnancy volumes by the 32-34 weeks of gestation [2]. Also, an increase in the cardiac output and reduction of peripheral vascular resistance provide a suitable situation for fetus development.

The impact of these hormonal and hemodynamic alterations on the ocular structure has been studied in literature. Changes in central corneal thickness, corneal curvature and intraocular pressure have been well documented [3, 4]. Since the choroid has the highest blood flow per unit weight in the body and supplies much of the nutritional needs of the retina, choroidal changes may lead to various ophthalmic conditions [5, 6]. Investigating choroidal changes during pregnancy offers insight to ocular pathologies encountered in this period such as central serous chorioretinopathy (CSC) and eclampsia-associated retinopathy [7, 8]. The extent of these choroidal changes and its reversibility after pregnancy is of great clinical significance.

Optical coherence tomography (OCT) is an essential device for diagnosing retinal and choroidal pathologies and evaluating treatment. New generation OCT devices perform scans much faster, hence providing higher resolution imaging with extensive detail. Studies have shown the great reproducibility and repeatability of spectral-domain optical coherence tomography (SD-OCT) in retinal and choroidal thickness assessment [9–11]. The enhanced depth imaging (EDI) technique of SD-OCT is a precise and non-invasive method, ideal for documenting the choroidal morphology [12, 13]. The choroidal thickness is a useful parameter in indicating physiologic and pathologic ocular changes as it is affected by the blood flow and ocular perfusion pressure.

Various studies with controversial results have reported choroidal thickness in pregnancy and pregnancy-associated states [14, 3, 15, 16]. A review of current literature indicated inadequate longitudinal research which determines choroidal thickness during pregnancy and post-partum. Therefore, the purpose of this study was to longitudinally monitor changes in choroidal thickness during each trimester and post-partum, and also compares results with a control group.

Patients And Methods

This prospective longitudinal study included 23 eyes of 23 healthy pregnant women and 23 eyes of 23 healthy non-pregnant women. To ensure unbiased results only one eye (right eye) was included for each study participant. Participants from both groups were recruited from the Gynecology and Obstetrics clinic at the same university hospital between January to August 2018. All participants provided written informed consent and the purpose of the research was fully explained. The research protocol was approved by the local ethics committee (IR.GUMS.REC.1395.282) and adhered to the Declaration of Helsinki principles.

Inclusion criteria for the study group were healthy pregnant women in the first trimester, who attended prenatal care and completed pregnancy without any complications (including gestational diabetes, pre-eclampsia or eclampsia). All the pregnancies were singleton and all participant were primigravid with no history of abortion. The control group consisted of healthy nulligravid women with regular menstrual cycles. All participants were between 18 to 40 years old and had refractive errors less than ±1.0 diopters with a best corrected visual acuity (BCVA) of ≥20/20 (Snellen chart), and intraocular pressure (IOP) below 21 mmHg at the time of enrollment. Subjects with a history of anemia, diabetes, hypertension, polycystic ovarian syndrome, thyroid dysfunction, collagen vascular, renal, or cardiovascular diseases and smoking and those with any ocular pathology including any previous ocular intervention were excluded from the study.

Demographic and previous medical history of participants were obtained. A complete ophthalmic examination was performed, including refraction (Topcon KR-8000 autorefractor) and visual acuity testing, slit-lamp biomicroscopy, IOP measurement by Goldmann applanation tonometry and dilated fundus examination. Axial length measurement was performed using an optical biometer (Lenstar 900, Haag-Streit AG, Switzerland). Data regarding patients systolic and diastolic blood pressure (BP), anthropometric data, and fasting blood sugar (FBS), BUN, creatinine and ferritin were also obtained. Ocular perfusion pressure (OPP) was calculated based on the following formula: mean blood pressure - intraocular pressure.

For the pregnant group choroidal thickness was measured at the first trimester (at 6-12 GA weeks), second trimester (at 16-22 GA weeks) and third trimester (at 28-34 GA weeks) and 6 weeks post-partum and for the control group in the follicular phase of the menstrual cycle. Participants were asked to avoid any caffeine containing diet, such as coffee, tea and chocolate, for 24 hours before image acquisition. Measurements were acquired in the morning between 9 to 11 A.M. to avoid diurnal variations and after 15 minutes of rest in the sitting position. Choroidal thickness (CT) was measured using spectral-domain OCT (SD-OCT) with the EDI technique (Spectralis; Heidelberg Engineering, Heidelberg, Germany). The macular region was scanned using a horizontal 1-line raster scan (30°×5°) centered on the fovea, generated from 7 B-scans with 100 frames averaged per scan. The choroidal thickness was measured as the vertical distance from Bruch's membrane to the choroid-sclera interface (hyperreflective line of the inner surface of the sclera) using the manual caliper in the Heidelberg software. All OCT imaging were separately assessed by two ophthalmologists.

Choroidal thickness measurements were obtained at seven locations: at the fovea, 500, 1000 and 1500 μm temporal (T) from the fovea and 500, 1000 and 1500 μm nasal (N) from the fovea.

Statistical analyses were performed using SPSS Statistics version 21 (IBM-SPSS, Chicago, USA). Variables are presented as mean ± standard deviation were appropriate. To compare variables between groups student t-test and Mann-Whitney test was used for normally and non-normally distributed data, respectively. Changes in choroidal thickness were analyzed using Repeated Measures ANOVA. Also, pairwise comparisons were performed using a paired sample t-test. A linear regression analysis with choroidal thickness as a dependent parameter and ocular and general parameters as independent parameters was performed. All P values were 2-sided and a P value <0.05 was considered statistically significant.

Results

The study enrolled 23 eyes of pregnant women and 23 eyes of age-matched women for the control group. Two participants in the pregnant group did not complete follow-up for the third trimester and post-partum imaging, and thus analyzed as missing data. One patient who had premature delivery was excluded from the study and another healthy pregnant woman was recruited for replacement. All other participants in the pregnant group had normal vaginal delivery.

The mean age was 26.1±3.6 years (range, 22-34) at the time of the first examination in the pregnant group and 26.7±4.0 (range, 21-34) in the control group. Intraocular pressures (IOP) were within the normal range in both groups. The BCVA was 20/20 or better for all participants. Baseline clinical evaluations were not statistically different between the two groups, except for the body mass index (BMI), which was higher in the pregnant group. This difference in BMI was probably due to the weight gain which occurs in pregnancy. Hemoglobulin (Hb) was also in the normal range for all subjects of both groups, although significantly lower in the pregnant group. Table 1 shows demographic and baseline clinical data in the two groups.

Table 1
Demographic and baseline clinical parameters in the pregnant and control groups

	Pregnant group *(n=23)*	**Control group** *(n=23)*	**p-value**
Age	26.1±3.6	26.7±4.0	0.723 †
RE (Diopters)	-0.21±0.3	-0.17±0.3	0.560 †
AL (mm)	23.5±1.4	23.4±0.3	0.195 †
IOP (mmHg)	12.9 ± 1.9	13.5 ± 2.7	0.750 [a]
Systolic BP (mmHg)	114.1±7.3	112.6±6.9	0.402 †
Diastolic BP (mmHg)	74.1±3.9	74.5±4.2	0.787 †
MABP (mmHg)	87.3±4.4	87.0±4.0	0.721 †
OPP (mmHg)	47.7±3.8	49.3±3.1	0.129 [a]
Hb	12.2 ± 0.3	13.3 ± 0.4	0.001 [a]
Ferritin	31.4±5.9	29.5±6.2	0.291 [a]
BUN	13.6±3.1	14.3±2.0	0.342 [a]
Cr	0.6±0.1	0.6±0.1	0.062 †
BMI (kg/m^2)	23.2 ± 1.5	22.1 ± 2.3	0.050 [a]
[a] Independent samples t-test			
† Mann Whitney-U			
RE: Refractive Error, AL: Axial Length, IOP: Intraocular pressure BP: Blood pressure, OPP: Ocular Perfusion Pressure, MABP: Mean Arterial blood pressure, BMI: Body mass index			

Table 2 shows the mean choroidal thickness in the pregnancy and control group in each measured location. The mean subfoveal choroidal thickness was 410.2 ± 82.4 μm, 434.8 ± 79.6 μm, 433.5 ± 80.3 μm, and 395.0 ± 71.1 μm in the first, second and third trimesters and 6 weeks post-partum, respectively. The temporal choroid was thicker compared to the nasal choroid in all pregnancy time points and also the control group.

Table 2
Choroidal thickness in different locations in the pregnant group at study time-points and control group

Location (µm from fovea)	Time points in pregnant group				Control *(n=23)*	*p-value*	
	1st Trimester (n=23)	2nd Trimester (n=23)	3rd Trimester (n=21)	Post-partum (n=21)		Pregnancy group †	Vs. control ‡
Sub-fovea	410.2±82.4	434.8±79.6	433.5±80.3	395.0±71.1	304.5±52.6	0.001	< 0.001
N 500	402.7±79.8	420.6±80.9	421.8±80.2	379.9±71.5	296.0±60.5	0.001	< 0.001
N 1000	384.5±74.3	391.2±79.6	393.0±77.5	351.8±70.2	285.2±50.9	< 0.001	< 0.001
N 1500	352.9±74.8	340.4±106.0	350.4±72.0	314.6±68.0	253.8±49.8	< 0.001	< 0.001
T 500	415.8±73.4	433.2±74.6	430.1±77.0	375.0±96.0	304.6±52.5	0.001	< 0.001
T 1000	405.9±70.7	418.8±69.3	416.2±72.0	381.3±71.7	306.5±53.1	0.001	< 0.001
T 1500	387.2±67.9	396.9±64.2	396.6±67.6	365.2±63.2	288.0±49.3	0.004	< 0.001
N: Nasal, T: Temporal							
† Repeated measures ANOVA (In the pregnant group time points)							
‡ Dunnett t-test (values in pregnancy time points compared against control).							

Based on the repeated measures ANOVA there was statistically significant change during pregnancy and post-partum in the choroidal thickness in all seven locations (Table 2) (Figure 1). We noted an increase in mean choroidal thickness from the first trimester to the second trimester, which was statistically significant in most choroidal locations (Table 3). In the 3rd trimester the thickness remained nearly the same as the 2nd trimester, with no significant difference in pairwise comparison of 2nd and 3rd trimesters (Table 3). The mean choroidal thickness decreased significantly after delivery. Table 3 shows p-values for pairwise comparisons of mean choroidal thickness in pregnancy trimesters and post-partum.

Table 3
Pairwise comparison of choroidal thickness between pregnancy trimesters and post-partum

Location (µm from fovea)	P-value in Pairwise Comparisons †					
	1st vs. 2nd Trimester	1st vs. 3rd Trimester	2nd vs. 3rd Trimester	1st vs. Post-partum	2nd vs. Post-partum	3rd vs. Post-partum
Sub-fovea	0.020	0.051	0.794	0.227	0.000	0.000
N 500	0.032	0.050	0.793	0.031	0.000	0.000
N 1000	0.265	0.258	0.736	0.001	0.000	0.002
N 1500	0.572	0.725	0.339	0.001	0.001	0.002
T 500	0.006	0.099	0.577	0.050	0.000	0.001
T 1000	0.021	0.188	0.661	0.037	0.000	0.002
T 1500	0.090	0.206	0.962	0.063	0.003	0.003
N: Nasal, T: Temporal						
† Paired sample t test between pregnant group time points						

Choroidal thickness was greater in all 7 locations during pregnancy and post-partum compared to the control group (p-value<0.001 for all time points). Mean subfoveal, nasal and temporal (500-1500 µm from fovea) choroidal thickness is shown in box plots in the pregnant women and control groups (Figure 1).

Correlation between the choroidal thickness in different locations and baseline BMI, BP, OPP (the first trimester for pregnant group) was evaluated using Pearson's correlation. No significant correlation was found between the choroidal thickness and BP and OPP, whereas choroidal thickness in all seven locations was positively correlated with BMI (Table 4).

Table 4
Pearson's Correlation Coefficient for Choroidal Thickness and body mass index (BMI)

Location (µm from fovea)	Pearson's correlation coefficient	*p-value*
Sub-fovea	0.371	0.011
N 500	0.382	0.009
N 1000	0.363	0.013
N 1500	0.353	0.016
T 500	0.389	0.007
T 1000	0.313	0.034
T 1500	0.340	0.021

Discussion

Pregnancy related hormonal, hemodynamic and cardiovascular changes can affect the ocular structures [17]. The complex vascular structure of the choroid makes it vulnerable to pregnancy related alterations, either the physiologic or pathologic events. Choroidal thickness changes can be expected due to the increased blood volume and water retention during pregnancy [18, 19]. Certain ocular conditions such as central serous chorioretinopathy (CSC), serous retinal detachment and retinal vascular events have an increased prevalence during pregnancy [20, 21].

There is no definite consensus on whether pregnancy can change choroidal structure and thickness and whether these changes are reversible. Previous studies have shown controversial results regarding choroidal thickness in pregnant women. Studies by Rothwell *et al.*, Kara *et al.*, Atas *et al.*, Sayin *et al.* and Acmez *et al.* have shown increased choroidal thickness in the third trimester of pregnancy compared to controls [14, 22–25]. Whilst Takahashi *et al.*, Benfica *et al.*, Su *et al.* and Kim *et al.* found no significant difference between choroidal thickness of healthy pregnant women in the third trimester and the control group [26–29]. A recent meta-analysis concluded that choroidal thickness is significantly higher in healthy pregnant patients over 24 weeks of GA compared to controls [30].

The case-control and cross-sectional design of most of these previous studies has limited the achievement of definite results due to individual bias. The choroidal thickness is affected by various factors including age, sex, systemic or local diseases, diurnal variation, IOP, axial length, menstrual cycle and pregnancy trimester [31–33]. In our study, we considered these confounding variables and their effect was eliminated to a great extent. Other factors such as previous pregnancy was regarded in our study. We only included nulligravid women (no prior pregnancy) for the control group and primigravid women for our pregnant group. Whereas, most aforementioned studies have not accounted for this factor [26, 23, 24, 34].

To date, very few studies have investigated choroid thickness changes in different trimesters and post-partum. Goktas *et al.* investigated choroidal thickness in the three trimesters but in different sets of pregnant patients at 3 points (subfoveal and 3mm nasal and temporal to the fovea) [35]. Their results showed significantly greater choroidal thickness in the 2nd trimester group in comparison with the 1st and 3rd trimester and control groups. They did not find any statistical difference between the 2nd and 3rd trimester groups and the control. Green *et al.* also conducted a study with a similar design but used the average measurement of subfoveal, 500μm nasal and temporal choroidal thickness [15]. The choroidal thickness was significantly lower in the 3rd trimester compared to the 1st and 2nd trimester and also compared to the control group. They did not find any statistical difference between the 1nd and 2rd trimester groups and the control. In our study, on the other hand, we observed significantly thicker choroids in all three pregnancy trimesters compared to control. We also demonstrated increasing choroidal thickness from the first trimester into the second and third trimesters. The fact that Goktas *et al.* and Green *et al.* included different patients for each trimester may have caused the dissimilar results [35, 15]. Moreover, as choroidal thickness is affected by the menstrual cycle, we measured the choroidal thickness of the control group in the follicular phase. This issue was not addressed in neither of the two mentioned studies.

Dadaci *et al.* compared choroidal thickness of pregnant women in the first trimester (6–8 GA weeks) with the third trimester (32–37 GA weeks) [36]. Similar to our findings, they reported thicker choroids during pregnancy

compared to control. However, choroidal thickness decreased significantly in the third trimester compared to the first trimester. As we noted in our study, the choroidal thickness in the 3rd trimester was similar to that of the 2nd trimester and greater than the 1st trimester. We believe different sampling time points in the 3rd trimester may have caused this disagreement, as our measurements were taken between 28-34 weeks GA and theirs was between 32-37 GA weeks. Reasons for this finding may be that towards the end of pregnancy, blood flow is redistributed to vital organs and increase in adrenoreceptor activity leads to vasoconstriction [37, 38].

It has been proposed that increased blood flow, enhanced arterial compliance, and decreased vascular resistance during pregnancy leads to an increase in choroidal thickness [16]. Also, fluid retention in the choroidal layer may affect the thickness [39]. Kim *et al.*, Benfica *et al.* and Sharudin *etal.* noted significantly greater choroidal thickness in patients with pre-eclampsia compared to the healthy pregnancy group [40, 41, 27]. This may suggest a correlation between choroidal thickness and ocular perfusion pressure; rather than pregnancy itself. However, other studies in line with ours did not find a correlation between OPP and choroidal thickness [35, 23, 34]. This issue may highlight the influence of hormones, particularly estrogen, progesterone and cortisol, on choroidal thickness [5, 33].

In the present longitudinal study, we also measured choroidal thickness after delivery. Previous studies on choroidal thickness before and after delivery have displayed conflicting results. Ulusoy *et al.* examined subfoveal choroidal thickness in third trimester (36 weeks GA) pregnant woman and prospectively 3 months after delivery [34]. They reported significant decrease in the thickness 3 months after delivery. In contrast Taradaj *et al.*, which assessed choroidal thickness at 36 weeks GA and at 6th week after delivery, reported greater choroidal thickness at 6th week postpartum compared to 36 weeks GA [42]. Additionally, they evaluated choroidal thickness changes depending on mode of delivery and reported more noticeable changes in the cesarean section group compared to normal labour. Therefore, mode of delivery is presumed to affect the choroidal thickness post-partum. As mentioned, all our participants had normal vaginal delivery.

Takahashi *et al.* were the first to evaluate choroidal thickness from early pregnancy until after delivery in the same group of patients [43]. They measured the subfoveal CT of 25 eyes of pregnant women in the 1st and 3rd trimesters, shortly after delivery, and 1 month postpartum. Their results indicated that the choroidal thickness increases in the first trimester and decreases in the third trimester and remains subsequently unchanged until the first month after delivery. In comparison to our study, in which we measured choroidal thickness in seven locations, Takahashi *et al.* only measured the subfoveal choroidal thickness; moreover, their study did not include measurements at the 2nd trimester of pregnancy [43].

In contrast to Takahashi *et al.*, we showed that the choroidal thickness changed significantly during pregnancy and post-partum, with increased thickness until the 3rd trimester and subsequent reduction at 6 weeks post-partum in all seven measured locations. Takahashi *et al.* post-partum measurements was done at 4 weeks after delivery, this issue is of clinical relevance as the regression of pregnancy-related physiological changes takes place at 6-7 weeks post-partum [1]. In our study we also noted that post-partum choroidal thickness was still greater than control, Takahashi *et al.* however, did not include a control group.

To the best of our knowledge, the present study is the first longitudinal design to evaluate the changes in choroidal thickness at several locations throughout pregnancy and post-partum and in comparison with non-pregnant healthy women. As there are considerable choroidal thickness variations between individuals, the

longitudinal design of our study is of great value. To add to the strength of our study we included a group of healthy non-pregnant women, to compensate for the absent pre-pregnancy measurements. Although a study including pre-pregnancy choroidal measurements of the same group of patients would be the ideal and optimal design. Another advantage of our study was that all pregnant participants were primigravid, as it is debated whether previous pregnancy-related choroidal changes are reversible, this matter may act as a confounding factor [44].

Our study also had some limitation. The first was the relatively small number of subjects and also the drop-outs. Although previous studies also had similar sample size and drop-out is an inevitable part of longitudinal studies of this kind. Another limitation was the lack of patients' pre-pregnancy choroidal measurements and data. Further studies including pre-pregnancy choroidal thickness and longer post-partum follow-up measurements are needed to determine precise choroidal changes and reversal. Moreover, evaluating choroidal thickness in patients with pregnancy-related ocular complications can provide guidance for clinical practice.

In conclusion, our study showed significant change in choroidal thickness at seven locations measured with EDI-OCT throughout pregnancy and 6 weeks after delivery. We showed that 6 weeks after delivery, choroidal thickness remains significantly higher than non-pregnant subjects.

Declarations

Funding: No funding was received

Ethical approval: All procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figures

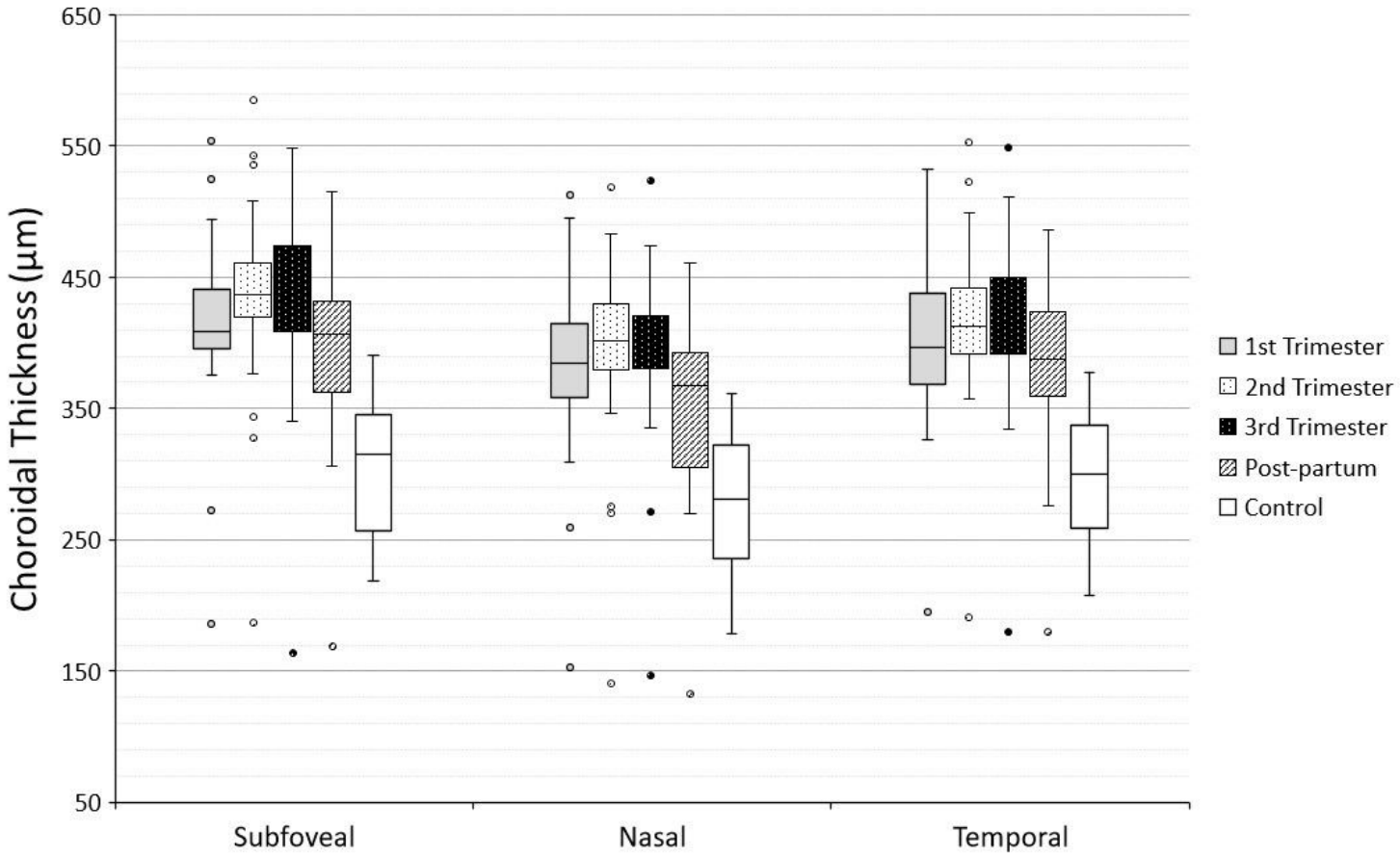

Figure 1

Subfoveal, temporal, and nasal choroidal thickness distribution in the pregnant group at different study time-points and the control group.