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# The Effect of Oral Contraceptive Pills on the Macula, the Retinal Nerve Fiber Layer, and Choroidal Thickness

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDF 1 **Yusuf Madendag**  
AFG 1 **Gokhan Acmaz**  
BCDF 2 **Mustafa Atas**  
BDEF 1 **Erdem Sahin**  
AEG 3 **Ahter Tanay Tayyar**  
ABCE 1 **Ilknur Çol Madendag**  
BDF 4 **Fatma Özdemir**  
ADFG 5 **Vesile Senol**

1 Department of Obstetrics and Gynecology, Health Sciences University Kayseri Education and Research Hospital, Kayseri, Turkey  
2 Department of Ophthalmology, Health Sciences University Kayseri Education and Research Hospital, Kayseri, Turkey  
3 Department of Obstetrics and Gynecology, Health Sciences University Zeynep Kamil Maternity and Children Training and Research Hospital, Istanbul, Turkey  
4 Department of Obstetrics and Gynecology, Nevsehir Government Hospital, Nevsehir, Turkey  
5 Department of Public Health, Erciyes University Faculty of Medicine, Kayseri, Turkey

**Corresponding Author:** Ahter Tanay Tayyar, e-mail: drahtertayyar@yahoo.com  
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**Background:** The aim of this study was to evaluate the effect of oral contraceptive pills (OCP) on the macula, the retinal nerve fiber layer (RNFL), and choroidal thickness (CT).





**Material/Methods:** A total of 24 healthy women taking monophasic OCP (3 mg drospirenone and 0.03 mg ethinylestradiol) for contraception only for at least one year were compared with a control group of 24 healthy women who were not taking an OCP. Optical coherence tomography (OCT) was used to evaluate the posterior ocular segments, and measurements were taken in the follicular phase (day 3) of the cycle in all women.

**Results:** No disparity in terms of age and body mass index between the groups was observed ( $p=0.436$ ,  $p=0.538$ , respectively). In comparison of the macular region and CT between groups, we found that all variables except foveal center thickness and CT were significantly thinner in the OCP group. Nasal and temporal inferior parts of the RNFL and average RNFL were significantly thinner in the study group versus the control group ( $p=0.013$ ,  $p=0.018$ , and  $p<0.001$ , respectively).

**Conclusions:** OCP resulted in several structural changes in the posterior ocular segment. Thus, women using OCP for more than one year may have some eye problems. Therefore, it OCT should be performed for these women. Further clinical trials researching long-period effect of OCP on the eyes are needed.

**MeSH Keywords:** **Choroid • Contraceptives, Oral, Hormonal • Macula Lutea • Retinal Neurons**

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## Background

Oral contraceptive pills (OCP) have some risks and side effects with regard to several organs, one of which is the eye. Estrogen and progesterone receptors have been recently observed in miscellaneous ocular tissues, such as the choroid, retina, lens, conjunctiva, cornea, and the Meibomian gland [1].

Spectral-domain optical coherence tomography (OCT), which is used to both quantitatively and qualitatively evaluate the retina [2], is a non-invasive procedure. In addition, OCT makes it possible to perform retinal examinations repeatedly without eye drops and dilatation [3].

Disorders related to the aging of the retina include functional and structural alterations in the macula [4] and blood flow changes in the macular vessels. Age-related macular degeneration (AMD) is classified as dry (atrophic) and wet (neovascular or exudative) for clinical purposes. Changes in retinal aging include common thickening of the inner membrane of the retina, decrease of nuclei in the external nuclear sheet of the retina, peripheral cystoid degeneration, reduction of neural elements with gliosis in the peripheral retina, peripheral retinal degeneration, reduction in the count of capillaries around the fovea, arteriosclerotic changes in the retinal vessels, and choroidal vascular insufficiency [5,6]. The macula is the central portion of the retina; if there are some degenerative changes in this area, central vision may be affected. Central vision is required for activities such as driving, reading, watching television, and performing activities of daily living. Retinal nerve fiber layer (RNFL) thickness may also decrease with aging or with some degenerative diseases because of responses such as ischemia. These changes cannot only occur with chronic inflammatory processes [7], but these changes may also be multi-factorial, with genetic, environmental, and hormonal factors playing important roles [8]. Sex hormones can affect the retina and choroid, so that OCP use may result in alterations to OCT findings [9]. In addition, a correlation between sex hormones and disorders that can cause loss of vision has been described [10,11]. Thus, OCP containing estrogen and progesterone may influence the eye. Therefore, in the present study, we used OCT to evaluate the effects of OCP on the eyes of women.

## Material and Methods

This observational cross-section study was conducted at the Department of Obstetrics and Gynecology, Health Sciences University Kayseri Education and Research Hospital, Kayseri, Turkey between January 2014 and April 2016, and was approved by the Ethical Committee of Erciyes University (2013/65). A total of 24 healthy women taking monophasic OCP (3 mg drospirenone and 0.03 mg ethinylestradiol) for contraception only

for at least one year (the OCP group) were compared with 24 healthy women who were not using an OCP (the control group). All participants were in the reproductive age period and were aged 25–40 years. Women who were pregnant or had any medical problems such as diabetes mellitus, cardiovascular events, thyroid disorders, hypertension, thrombo-embolic disease, cancer, or chronic liver disease were excluded, as were smokers. In addition, women who had eye problems such as previous surgery, glaucoma, cataract, eye trauma, intraocular pressure >20 mm Hg, macular degeneration, and uveitis were also excluded before OCT examination. All participants were evaluated in the follicular phase (day 3) of their last menstrual cycle. A third-generation OCT device (version 5.6.3.0; Spectralis OCT Heidelberg Engineering, Dossenheim, Germany) was then used for the examination. The procedure was carried out under the intensity of dim room lighting and without pupillary dilatation. All OCT examinations were conducted by the same person and using the same OCT instrument.

The fast macular thickness map option and OCT software were used to make macular evaluations, such as macular thickness and volume analysis. We chose the macular map analysis protocol in order to assess each of the nine sub-domains as defined by the Early Treatment Diabetic Retinopathy Study [12].

RNFL thickness was automatically computed by the fast RNFL mode and partitioned into several fields. The diagnostic procedure of enhanced depth imaging OCT has been previously described [12]. All measurements of sub-foveal choroid thickness (CT) were obtained by the same specialized technician who had no information regarding the participants.

## Power analysis

A sample size analysis was conducted for the two dependent groups (matched pairs), which were evaluated with regard to CT. We assumed that power=0.80 and alpha=0.05. Sample-size determination was carried out for a double comparison (the mean of the CT in the OCP group versus the mean of the CT in the control group). While determining sample size, reference values (means, standard deviations, and reference sample sizes) were obtained. Considering all of these results, we required a total sample size of 19 for the comparison [13]. The analysis was made by G-Power 3.0.10.

## Statistics

The Shapiro-Wilk test was used to resolve the normality guess of the data, and the Levene's test was used to test the variance homogeneity assumption. Values are expressed as mean  $\pm$  standard deviation or median (25–75%). Parametric comparisons were made using a *t*-test, and non-parametric comparisons were made using the Mann-Whitney U test. The PASW

**Table 1.** Comparison of macular and choroidal thickness in women using oral contraceptive pills and the control group.

Variables (µm)	OCP group (n=48)	Control group (n=48)	p Value
Central subfield	248 (238.50–265.75)	256.50 (249.25–273.50)	0.007
Superior inner macula	339.45±13.66	352.80±13.47	<0.001
Temporal inner macula	325 (314.25–334)	335 (328–343.75)	<0.001
Inferior inner macula	334.13±12.75	347.80±10.39	<0.001
Nasal inner macula	337.48±13.04	349.10±9.74	<0.001
Superior outer macula	298.27±12.18	305.58±12.87	0.011
Temporal outer macula	281.33±11.83	288.90±15.27	0.015
Inferior outer macula	285±11.30	297.20±13.29	<0.001
Nasal outer macula	317 (307.25–323.75)	326 (314–337.50)	0.001
Foveal center	210 (203.25–217.75)	215 (208.50–232.75)	0.072
Choroid	327.50 (290.75–371)	318 (292–405)	0.859

Values are expressed as mean ±SD.

**Table 2.** Average macular volume in women using oral contraceptive pills and the control group.

Variables (mm <sup>3</sup> )	OCP group (n=48)	Control group (n=48)	p Value
Central subfield	0.19 (0.19–0.21)	0.20 (0.20–0.22)	0.002
Superior inner macula	0.534±0.022	0.553±0.020	<0.001
Temporal inner macula	0.510 (0.500–0.527)	0.530 (0.510–0.540)	0.001
Inferior inner macula	0.525 (0.510–0.540)	0.550 (0.540–0.560)	<0.001
Nasal inner macula	0.525 (0.520–0.550)	0.550 (0.540–0.570)	<0.001
Superior outer macula	1.58±0.07	1.62±0.07	0.039
Temporal outer macula	1.49±0.07	1.54±0.08	0.008
Inferior outer macula	1.51±0.06	1.57±0.07	<0.001
Nasal outer macula	1.67±0.06	1.71±0.08	0.004
Total volume	8.56±0.30	8.83±0.32	<0.001

Values are expressed as mean ±SD.

Statistics 18 program was used to analyze all comparisons and  $p < 0.05$  was considered statistically significant. Values are expressed as n (%). Comparisons were made using a *t*-test because  $n < 30$  (the difference of two proportions).

## Results

The study group consisted of 48 eyes of 24 women taking OCP, and the control group consisted of 48 eyes of 24 healthy women in their reproductive period. The mean age of the OCP group was 31.85±8.86 years and the mean age of the control group was 33.30±7.88 years. The mean body mass index (BMI) was 21.34 in the OCP group and 22.01 in the control group. Both

groups were homogenous in terms of age and BMI ( $p=0.436$  and  $p=0.538$ , respectively). The CT, the macular analysis, and the RNFL thickness analysis acquired by the OCT, are shown in Tables 1–3, respectively.

We found that all measurements of posterior ocular segments, except foveal center thickness and CT, were considerably slimmer in the OCT group versus to the control group. All macular volume variable values were considerably lower in the OCP group versus the control group. We detected that the average of the RNFL, the nasal-inferior (NI), and the temporal-inferior (TI) parts of the RNFL were considerably slimmer in the OCP group versus the control group ( $p=0.013$ ,  $p=0.018$ , and  $p < 0.001$ , respectively).

**Table 3.** Average peripapillary retinal nerve fiber layer thickness in women using oral contraceptive pills and the control group.

Variables ( $\mu\text{m}$ )	OCP group (n=48)	Control group (n=48)	p Value
Temporal (T)	73.30 $\pm$ 10.12	72.93 $\pm$ 8.51	0.858
Temporal superior (TS)	139.73 $\pm$ 16.81	143.60 $\pm$ 14.43	0.272
Nasal superior (NS)	114.50 (99.25–127.50)	119.50 (100.75–129.75)	0.476
Nasal (N)	76 (64.25–82)	75.50 (71–84.50)	0.242
Nasal inferior (NI)	110.30 $\pm$ 22.08	122.25 $\pm$ 22.22	0.018
Temporal inferior (TI)	140.90 $\pm$ 16.28	155.38 $\pm$ 17.31	<0.001
Average (G)	102.30 (94–106)	106 (99.25–109.75)	0.013

Values are expressed as mean  $\pm$ SD.

## Discussion

Just as in many organ systems in the female body, many hormone receptors are present in the eye [1,9]. There have been various studies published in the literature about these receptors and hormones, and their role in changing eye structures. Estrogen receptors have been shown to be present in various eye structures, such as the conjunctiva, cornea, Meibomian gland, choroid, retina, and lens [1]. Eye complications in users of OCP include retinal vascular occlusion, optic neuritis, and proptosis; in addition, retinal edema, glaucoma, and hemorrhagic retinopathy have also been reported [14]. Because of extensive evidence that OCP cause vascular events elsewhere in the body [15], this is of particular interest for closer analysis. Furthermore, these effects have been shown to change depending on the type of progesterone used. A number of studies have looked at the effect of sex steroid hormone fluctuations in the menstrual cycle on eye [16–19]; and some researchers have shown that these hormone fluctuations exhibited correlations with changes in ocular tissue [16,17]. On the other hand, some researchers advocate that these fluctuations do not affect ocular variability significantly. There may also be some modifications in the ocular tissues due to hormonal changes as age-related alterations. The best known age-related changes are thickening due to edema or slimming due to atrophy in the macula [5,6] and atrophy in the RNFL [7]. OCT is a current imaging method that allows us to better understand these changes [20].

In this study, we aimed to detect ocular tissues changes in women who received hormonal contraception. We observed that the thickness of all the macular areas significantly decreased; similarly, we noted that the average macular volume decreased in the OCP group. Although macular slimming is an acceptable result of aging or degeneration, sometimes it has no clinical significance [21]. In our study we also found that the average RNFL thickness, particularly the NI and TI parts, was significantly decreased in women using OCP. However,

this decrease was not clinically significant (normal range 90–110  $\mu\text{m}$  [22]). It is obvious that this slimming effect is not related to age when we consider that the average age was 31.85 $\pm$ 8.86 in our study group. These two findings suggest that the use of OCP mimics age-related changes. On the other hand, some studies have questioned the physiological effects of sex steroids on endometrium tissue, and today we know that progesterone receptors are present on the arterial smooth-muscle walls, and that the role of progesterone is to counteract estrogen by reducing endothelial nitric oxide production [23–26]. As a result of these mechanisms, flow-mediated vasodilatation can be antagonized when progesterone is added to the structure with estrogen [27]. Thus, it may be that by the same mechanism, OCP may also have an effect on eye structure, as progestogenic activity of OCP dominates [28] and it is well known that drospirenone, which was the progesterone derivate used in this study, has anti-mineralocorticoid and anti-edema effect [29]. However, there are no blood vessels in the fovea [30], which was in accordance with our study results that found there was no significant difference for foveal thickness between the two groups.

We suggest that physiological variables should be studied in the future in order to understand the basis of these changes. In our study, there was no statistically significant difference between two groups in terms of CT. Conversely, Acmaz et al. showed that CT was significantly increased in women with polycystic ovary syndrome (PCOS) compared to healthy women, and they speculated that this was due to increased estrogen-dependent vasodilatory action in the ophthalmic artery, related to high estrogen levels or unopposed estrogen, in the women with PCOS [31]. Based on our study results, we speculated that using a combined oral contraceptive could be the cause of unaffected CT, because there was no unopposed estrogen in the women using OCP, while there was unopposed estrogen in the women with PCOS.

In another similar study, Acmaz et al. found that RNFL thickness, especially the nasal part, was significantly decreased in pregnant women with gestational diabetes more than in the healthy pregnant women [32]. They speculated in a similar way to ours that deterioration of the blood supply to nerves may lead to thinning of RNFL in pregnant women with gestational diabetes.

Limitations of this study include unknown clinical importance, as well as the long-term consequences of these changes, for example, are these changes reversible or irreversible?

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## Conclusions

It is obvious that the use of OCP changes eye structures; but these changes should be further explored in clinical trials which involve clinically significant variables and long-term outcomes. Women using OCP for more than one year may have some eye problems; therefore, we suggest that OCT be routinely performed for these women.

## Conflicts of interest

None.