• Review •

The impact of combined oral contraceptives on ocular tissues: a review of ocular effects

Marilita M. Moschos, Eirini Nitoda

Department of Ophthalmology, Medical School, National & Kapodistrian University of Athens, Greece
Correspondence to: Marilita M. Moschos. Department of Ophthalmology, Medical School, National & Kapodistrian University of Athens, Greece 6, Ikarias street, Ekali 14578, Athens, Greece. moschosmarilita@yahoo.fr

Abstract

● **The aim of this manuscript is to review the action and adverse effects of combined oral contraceptives (COCs) on ocular tissues. The percentage of unwanted pregnancies and the subsequent abortions make contraception crucial worldwide. Over 100 million women around the world use common contraceptive methods, including intrauterine devices, combined estrogen and progestin oral contraceptives, as well as progestin only preparations (oral contraceptives, implants or injections). COCs are widely used for contraception, but they are also indicated in menorrhagia, endometriosis, acne and hirsutism, fibroid uterus and premenstrual syndrome. However, they have been associated with high rates of cardiovascular events, venous thromboembolic disease, ischemic strokes and breast cancer. The incidence of COCs-related ocular complications is estimated to be 1 in 230 000, including dry eye symptoms, corneal edema, lens opacities and retinal neuro-ophthalmologic or vascular complications. We may infer that the serious ocular complications of COCs can be prevented by eliminating the estrogen dosage and choosing third-generation progestins. In any case, doctors should take into consideration the systemic and ocular history of the patients before selecting any method of contraception.**

● **KEYWORDS:** adverse effects; ocular complications; oral contraceptives

INTRODUCTION

The prevalence of unintended pregnancies in the United States approaches the 50% of total pregnancies, being at least four times higher than some countries in Europe and Japan[1]. The correlation of unwanted pregnancies with abortion, especially around adolescence, makes contraception crucial. Common contraceptives methods include intrauterine devices, combined estrogen and progestin hormonal contraception, as well as progestin only preparations (oral contraceptives, implants or injections). Over 100 million women around the world use hormonal contraceptive methods, whereas 93 million of them use combined oral contraceptives (COCs)[2].

The biological actions of progesterone are regulated by its receptors, which belong in a superfamily of almost 50 ligand-activated nuclear transcription factors[1-3]. This steroid receptor family includes the progesterone, estrogen, androgen, glucocorticoid and mineralocorticoid receptors, which are hormone-activated transcription factors, sharing a high level of structural and functional similarity[3]. Progestins suppress ovulation, whereas progesterone is responsible for the embryo implantation, the protection of the myometrium and endometrium, the breast development and differentiation[1-4]. However, selective progesterone receptor modulators have been associated with adverse effects, including liver toxicity, ovarian cysts and elevated prolactin levels[4]. The first generation of synthetic progestins seems to promote vascular inflammation, atherosclerosis and angiogenesis, favoring the production of vascular endothelial growth factor (VEGF)[3]. On the other hand, progesterone and the fourth generation of synthetic progestins display vasodilatory activity *via* nitric oxide (NO) accumulation[3]. Estrogens are composed of two isoforms: the ERa and ERb. The ERa seems to contribute to the negative feedback of estrogens, whereas ERb interferes in luteinizing hormone (LH) surge during ovulation and the transcriptional activity of ERa[5-6]. Estrogens contraceptives primarily serve to regulate bleeding and alter secretions and cellular structures of endometrium, along with inhibiting follicle-stimulating hormone (FSH) and preventing formation of the dominant follicle[1].

COCs are widely indicted for contraception, menorrhagia, endometriosis, acne and hirsutism, fibroid uterus and premenstrual syndrome[7]. However, the incidence of venous

thromboembolic disease in healthy women of reproductive age receiving COCs is increased from 4-5/10 000 women to 9-10/10 000, being aggravated by the presence of obesity, smoking, alcohol consumption and positive family or personal history[8]. The anti-estrogenic activity of progestins was estimated to be responsible for COCs-induced modifications of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimers as well as protein S, favoring a hypercoagulative state[9]. Although the risk for venous thromboembolic disease is approximately three-fold higher in COCs users, compared to controls, it is eliminated along with the duration of use[10]. Beaber *et al*[11] highlighted that COCs are associated with high breast cancer risk (predominantly in ER+ than ER− breast cancer) among women of 20-49 years old. Visual disturbances in women receiving COCs also seem to have cardiovascular background, being related to of the expression of the progesterone receptors in ocular tissues. The review aims at summarizing the ocular effects of COCs.

OCULAR EFFECTS OF ORAL CONTRACEPTIVES

The incidence of ocular complications, among women who receive birth control pills, is estimated to be 1 in 230 000, including dry eye symptoms, corneal disturbances, lens opacities and retinal neuro-ophthalmologic or vascular complications (Table 1)[12].

Alterationss in Ocular Surface Oral contraceptives have been related to corneal edema, which is usually asymptomatic[13]. However, contact lenses users may manifest discomfort and intolerance, which are possibly attributed to increased permeability of the lens and vascular dilatation[13-15]. Although intolerance has been described in contact lens users, recent studies revealed that oral contraceptives do not affect tear physiology. The latter is influenced by pituitary hormones, estrogens, androgens, which increase tears volume and protein levels, and progestins, which have been found to inhibit androgen activity[16]. Moreover, estrogens have been related to decreased lipid production and size of sebaceous glands, resulting in low tear secretion[16-17]. The impact of gonadal hormones is more prominent on goblet cells, resulting in mucus secretion alterations[16].

Tomlinson *et al*'s[16] study observed no differences in ocular discomfort level, tear film structure, evaporation and tear turnover rate, non-invasive tear thinning time, tear volume and tear protein levels, between controls and young women receiving oral contraceptives treatment. Contrariwise, topical estrogens have been found to ameliorate the symptoms of post menopausal women with keratoconjunctivitis sicca. This beneficial effect of estrogens on lacrimal gland has been related to nitric oxide synthase (NOS) stimulation and the subsequent vasodilation[16]. Recently, Chen *et al*[17] also noted that no differences in tear osmolarity were measured neither between the follicular and luteal phases of the menstrual

cycle nor between controls and young women receiving oral contraceptives. Although, tear osmolarity was not affected in women using oral contraception along with contact lens, the dry eye symptoms, as assessed by Ocular Surface Disease Index (OSDI) and Symptom Assessment iN Dry Eye (SANDE) questionnaires, were more intense in this group[17]. Moreover, Rahimi Darabad *et al*[18] noted that even the complete absence of estrogens did not result in inflammation of lacrimal gland or tear deficiency. On the other hand, Mostafa *et al*[19] observed that, when genetically predisposed to Sjögren's syndrome mice were ovariectomized, the symptoms of the disease were accelerated. However, the use of hormone replacement therapy (HRT) eliminated these symptoms. Sacchetti *et al*[20] suggested that both estrogens and androgens levels were elevated in males with vernal keratoconjunctivitis. Furthermore, estrogens have been associated with alterations in corneal thickness and biomechanics, due to the stimulation of matrix metalloproteinases, collagenases and glycosaminoglycans[21]. The subsequent accumulation of water results in weakening of the collagen network, increase of the corneal interfibrillar space and mechanical expansion of the crosslinks between the collagen[21]. Moreover, the interfibrillar cohesion induced by proteoglycans seems to be eliminated by estrogens activity[21]. Their corneal stiffness-reducing effect is minimal under normal conditions, but it is enhanced after weakening procedures, such as photorefractive keratectomy (PRK) and laser-assisted *in situ* keratomileusis (LASIK). The risk of keratectasia after LASIK is ninefold higher in women[21].

Disturbances of the Anterior Segment of the Eye Faust and Tyler[22] noted that there was no difference in prevalence of glaucoma between patients receiving oral contraceptives and control group, whereas lens pathology was observed at 4% of control individuals compared to 1.5% of patients under contraception. A more recent study of Abramov *et al*[23] revealed no differences in intraocular pressure (IOP), vertical and horizontal cup-to-disc (C/D) ratios, or glaucoma between controls and women receiving HRT. Drill *et al*[24] observed equal corneal and lenticular opacities frequency between control group and women treated with COCs. Two cases of hypercupremia, which led to copper corneal deposits at Descemet's membrane, have been reported among women who received estrogen-based oral contraceptives[25]. Gong *et al*[26] found that the spherical and cylindrical lens, the axis, the interpupillary distance and the vision exhibited statistically significant differences during the menstrual cycle, according to the serum estradiol (E2) levels. The visual acuity was higher during the 14th and 28th day, where E2 levels were maximum, compared to those on the 2nd or 3rd days, where E2 levels were eliminated[26].

Table 1 Ocular effects of contraceptives

	Symptoms and signs	Mechanisms
Ocular surface		
Alterations	Discomfort and reduced tear secretion	Decreased lipid production and size of sebaceous glands Alterations in mucus secretion Alterations in corneal thickness and biomechanics by stimulating the production of matrix metalloproteinases, collagenases and glycosaminoglycans and enriching of water
	Discomfort and intolerance in contact lenses wearers	Increased permeability of the lens and vascular dilatation
Beneficial action	Amelioration of the symptoms in post menopausal women with keratoconjunctivitis sicca	Vaso-dilatory action of estrogens on lacrimal gland No differences in tear osmolarity
Anterior segment		
Alterations	Spherical and cylindrical lens, axis, interpupillary distance and vision exhibited statistically significant differences during the menstrual cycle	Modified by serum E2 levels
Beneficial action	Decreased IOP and risk for primary open angle glaucoma No differences in mean IOP, C/D ratios, and in prevalence of increased IOP, C/D ratio	Neuroprotective action through the RGCs estrogen receptors Increase in retinal blood flow
	Prevention of cataractogenesis	17-β-estradiol prevents oxidative stress by neutralizing H_2O_2 and eliminating catalase activity through ERa, ERb and G protein-coupled estrogen receptors
	Protection of corneal collagen from degradation	17-β-estradiol suspends IL-6, IL-1, TNF-α and metalloproteinases expression
Neuroophthalmologic effects		
Alterations	6th cranial nerve paralysis Parietal syndrome Hemianopsia Retrobulbarneuritis Papillary edema Benign intracranial hypertension	Thrombosis of the cerebral or retinal vessels
Retinal effects		
Alterations	Central retinal artery or vein occlusion Intraocular hemorrhages Aneurisms Macular or papillary edema Ischemic papillopathy Acute ischemic optic neuropathy	Thrombosis of the cerebral or retinal vessels and angiogenesis VEGF-D stimulation along with the consequential vascular remodeling and vasodilation Vascular fragility due to reduction of αSMA and the over expression of endometrial tissue factor Decreased antithrombin III and HDL cholesterol levels Shorten heparin-thrombin coagulation time Elevated fibrinogen and thromboxan A2 concentrations Proliferation of human arterial smooth muscle cells Increased PDGF concentrations NOS and cyclooxygenase endothelial dysfunction
	A case of woman with unilateral proptosis, haemorrhagic retinopathy and increased IOP	
Beneficial action	Treatment of neurodegenerative eye diseases (age-related macular degeneration) Treatment of diabetic retinopathy Treatment of oxygen-induced retinopathy	Antioxidant activity of estrogens by stimulating SOD2, reducing ROS and DNA replication and diminishing VEGF, MDA and NADPH oxidase 17β-estradiol eliminates apoptosis of RGCs, by stabilizing the mitochondrial membrane potential, decreasing intracellular ROS and cytochrome C concentrations, enhancing Bcl-2 expression and inhibiting Bax expression 17β-estradiol regulates of SOD, glutathione peroxidase and catalase, as well as the antioxidant proteins thioredoxin and nuclear factor erythroid 2-related factor 2 Increase in retinal blood flow

αSMA: Perivascular α-smooth muscle actin; Bax: Apoptosis regulator BAX or bcl-2-like protein; Bcl-2: B-cell lymphoma 2; C/D ratio: Cup-to-disc ratio; E2: Estradiol; ER: Estrogen; H_2O_2: Hydrogen peroxide; HDL: High density lipoprotein; IL: Interleukin; IOP: Intraocular pressure; MDA: Malondiadehyde; NADPH: Nicotinamide adenine dinucleotide phosphate; NOS: Nitric oxide synthase; PDGF: Platelet-derived growth factor; RGCs: Retinal ganglion cells; ROS: Reactive oxygen species; SOD2: Superoxide dismutase 2; TNF-α: Tumor necrosis factor-alpha; VEGF-D: Vascular endothelial growth factor D.

Severe Ocular Complications Related to Combined Oral Contraceptives The severe ocular complications induced by oral contraceptives can be neuroophthalmologic or vascular. Neuroophthalmologic complications include 6th cranial nerve paralysis, parietal syndrome, hemianopsia, and retrobulbar neuritis[27]. Papillary edema, due to unilateral optic neuritis or benign intracranial hypertension, occurs in several reports[27-28]. Central retinal artery or vein occlusion, intraocular hemorrhages, aneurysms, macular or papillary edema and acute ischemic optic neuropathy, are vascular complications, which may be associated with thrombosis of the cerebral vessels or limited to the retinal vessels[27-30]. The consequences can be temporary or permanent. Color vision disturbances have been also described in women receiving oral contraceptives, especially when diabetes mellitus coexists[28].

A case of woman with unilateral proptosis, haemorrhagic retinopathy and increased IOP was described by Jaais and Habib[31]. During the examination, right lid edema, injection with chemosis and dilated conjunctival and episcleral vessels were found, whereas the visual acuity was 6/6. Non-filling of the right superior ophthalmic vein and collaterals were detected during the right orbital venogram. The proptosis and the elevated IOP were retreated with timolol 0.5% drops, after the cessation of COCs[31]. Retinal hemorrhages observed in COCs users may be associated with VEGF-D stimulation and consequential vascular remodeling and vasodilation[32]. The observed vascular fragility and angiogenesis have been attributed to the reduction of perivascular α-smooth muscle actin (αSMA) and the over expression of endometrial tissue factor at the bleeding sites. The αSMA is responsible for the loss of perivascular support cells, including pericytes and vascular smooth muscle cells[32].

Li and Fu[33] described a bilateral ischemic papillopathy and optic atrophy in a woman who received COCs. Vastag and Tornóczky[34] reported a case of unilateral arterial retinal occlusion in a woman who received COCs (1.0 mg ethinodiole-diacetate and 0.05 mg aethynyloestradiole) for 4.5y. The lesions were correlated with vasoconstriction and thrombocyte aggregation, due to decreased antithrombin III and high density lipoprotein (HDL) cholesterol levels, shorten heparin-thrombin coagulation time, and elevated fibrinogen and thromboxan A2 concentrations[34]. Two cases of unilateral arterial retinal occlusions in women taking COCs were also delineated by Leff[12]. The first woman manifested flashing lights, dull frontal headache and poor perfusion of the inferior temporal branch artery with ipsilateral inferior retinal edema. The ipsilateral decreased visual acuity was rehabilitated and the symptoms were disappeared after the discontinuation of the COCs. The second woman had normal visual acuity although the vision was diminished in the superior visual field of the left eye[12].

Schmidt and Kramer-Zucker[35] presented a 22-year-old woman who used COCs (0.03 mg ethinylestradiol and 2 mg chlormadinonacetate) for several months before experiencing monocular visual disturbances. Unilateral hemicentral (superior) retinal artery obstruction combined with elevated thrombin-antithrombin complex and low free protein S were the causes of sudden visual loss observed in this young woman[35]. Tortuosity of venules around the macular area and alteration of the pigment epithelium were the fundoscopic lesions described by Gombos et al[36] in a woman with unilateral retinal vascular occlusion, secondary to the use of oral contraceptives. Combined central retinal artery and vein occlusion was observed in a 40-year-old woman who received oral contraceptives for a period of four years. The occlusion was complicated with neovascular glaucoma and one year later the eye was enucleated[37].

COCs have been found to be implicated in atherogenesis, accelerating the proliferation of human arterial smooth muscle cells. This mitogenicity has been related to the increase of platelet-derived growth factor (PDGF) concentrations[38]. Asymmetric dimethylarginine (ADMA), which is a risk marker of atherosclerosis and endothelial dysfunction, has also been found to be eliminated by estrogens, COCs and HRT[39]. Both ADMA and its stereoisomer symmetric dimethylarginine (SDMA) represent endogenous competitive inhibitors of NOS and vasodilation. Interestingly, ADMA levels varied at different phases of menstrual cycle, according to the estrogens levels, but they are stable in women receiving COCs[39].

Moreover, progesterone induces NOS and cyclooxygenase (COX) stimulation, interfering in mitogen-activated protein kinases (MAPK) and phosphatidylinositol-3-kinase (PI3K) signaling pathways. NOS and COX systems also seem to interact[40]. Progestin levonorgestrel has been found to antagonize ethinyl estradiol induced-vasodilation, ameliorating the vasoconstrictor sensitivity to α1- and α2-receptor agonists[41]. In addition, medroxyprogesterone acetate has been implicated in endothelial dysfunction, modifying estrogens action[42]. Estrogens modify the concentrations of haemostasis proteins in blood, whereas eserogen receptor 1 (ER1) haplotype has been related to an increased risk of myocardial infarction and ischaemic heart disease in postmenopausal women. However, ER1 does not affect haemostasis and inflammation risk markers of arterial and venous thrombosis[43].

Contrary to the previous studies, Drill et al[44] observed no retinal damage, including papilledema, venous dilatation, and venous or arterial retinal thrombosis, in animals (dogs and monkeys) treated with COCs. However, permanent retinal damage due to COCs-induced hypertension has been also reported[45]. We may infer that the serious ocular complications of COCs can be prevented by eliminating the estrogen dosage and choosing third-generation progestins. Furthermore, post-

menopausal HRT seems to act as protective factor for retinal vascular complications[46]. Before deciding the method of contraception, doctors should have in mind that a history of migraine or intraocular vascular disease is considered as contraindication for oral contraceptive therapy[47]. Besides retinal vascular complications, COCs have been associated with the development of pigmentary retinopathy in a 20-year-old woman. The woman complained of sudden blurring of vision in the right eye with ipsilateral macular pigmentary mottling, which was prominent in fluorescein angiography. The cessation of treatment resulted in recession of ocular symptoms, without affecting the ophthalmoscopic and fluorescein angiographic findings[48].

Beneficial Effects of Estrogens and Progesterone in the Eye
It has been found that 17-β-estradiol suspends the expression of interleukin (IL)-6, IL-1, tumor necrosis factor-alpha (TNF-α), and metalloproteinases, protecting corneal collagen from degradation[49-50]. In addition, 17-β-estradiol seems to neutralize H_2O_2 and eliminate catalase activity, preventing oxidative stress and cataractogenesis[51]. However, Aina *et al*[52] supported that estrogens only or combined estrogen-progestogen HRT exhibited small protective effect against cataract development. The detection of ERa, ERb and G protein-coupled estrogen receptor (GPER) as well as estradiol binding sites in the human lens indicates the possible effect of estrogens on lens responses and a protective role against cataract[53].

The use of postmenopausal hormone, acting through the retinal ganglion cells (RGCs) estrogen receptors, has been related to decreased IOP and risk for primary open angle glaucoma. The single use of estrogens resulted in 0.4% per month reduction in primary open angle glaucoma risk, while the combination of estrogen and progesterone exhibited a 0.6% per month reduction[54]. The daily treatment of rats with 17β-estradiol eye drops revealed its neuroprotective action. The sequential reduce in the number of apoptotic RGCs prevented the deterioration of vision in these animals[55]. Additionally, Hao *et al*[56] suggested that 17β-estradiol could be used in the treatment of diabetic retinopathy, due to its properties against oxidative stress. They noted that 17β-estradiol reduced the apoptosis of RGCs, by stabilizing the mitochondrial membrane potential, decreasing intracellular reactive oxygen species (ROS) and cytochrome C concentrations, enhancing B-cell lymphoma 2 (Bcl-2) expression and inhibiting Bax (apoptosis regulator BAX or bcl-2-like protein) expression.

Moreover, non feminizing estrogens have been proposed for the treatment of neurodegenerative eye diseases, such as age-related macular degeneration (AMD)[57]. The anti-inflammatory effects of 17β-estradiol against toll-like receptors (TLRs) and IL-6 stimulation have been associated with the impeding of NF-κB DNA-binding activity and AMD[58]. The

presence of ERb in mitochondrial network of human RGCs and the unmyelinated portion of their axons in the retinal nerve fibre layer, even in patients with Leber's hereditary optic neuropathy, explains the antioxidant activity of estrogens. The latter stimulate superoxide dismutase 2 (SOD2), eliminate ROS, and favor DNA replication[59-60]. Estrogens could be used in the treatment of Leber's hereditary optic neuropathy, preventing oxidative stress and enhancing mitochondrial biogenesis and respiration[59-60].

Furthermore, estrogens have been found to promote VEGF secretion and diminish both malondiadehyde (MDA), an end-product of oxidative stress, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is responsible for the production of free radicals[61]. Both MDA and NADPH are implicated in the early hyperoxic phase of oxygen-induced retinopathy and the late neovascularization. These findings favor the use of estrogens for the treatment of the early phase of oxygen-induced retinopathy[61]. The antioxidant properties of 17β-estradiol against light-induced retinal damage have been associated with the regulation of the enzymes SOD, glutathione peroxidase, and catalase, as well as the antioxidant proteins thioredoxin and nuclear factor erythroid 2-related factor 2[62]. Besides the neuroprotective effects of estrogens on the RGCs and retinal fibre layer, they also seem to increase the retinal blood flow, cooperating to the diminution of AMD and glaucoma risk[63].

CONCLUSION
The expression of estrogen and progesterone receptors in the eye is responsible for their ocular effects. The incidence of ocular complications is estimated to be 1 in 230 000, including dry eye symptoms, corneal edema, lens opacities and retinal neuro-ophthalmologic or vascular complications. The severe neuro-ophthalmologic complications involve the 6th cranial nerve paralysis, parietal syndrome, hemianopsia, papillary edema and retrobulbar neuritis. Central retinal artery or vein occlusion, intraocular hemorrhages, aneurysms, macular or papillary edema and acute ischemic optic neuropathy represent the vascular complications of oral contraceptives. On the other hand, estrogens seem to ameliorate the symptoms of keratoconjunctivitis sicca and exhibit protective effect against glaucoma, cataractogenesis and degradation of corneal collagen. Moreover, the antioxidant and neuroprotective action of estrogens indicates their possible therapeutic use in neurodegenerative eye diseases, including AMD and diabetic retinopathy. However, physicians should take into consideration patients' systemic and ocular history, before selecting any method of contraception.

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