



# The Influence of Estrogen on Dry Eye Prevalence in Women

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## Abstract

**Introduction:** The Dry Eye Disease (DED) is a multifactorial disease of tears and ocular surface. Some of the symptoms include burning, foreign body sensation, decreased vision and lacrimation. It is known that estrogen acts on corneal receptors, so the fluctuation of its serum levels can promote changes in the tear film, causing this disease. Objective: Identifying the influence of estrogen on the prevalence of DED in women.

**Methodology:** This is a non-interventionist, cross-sectional and quantitative study, based on the application of an online questionnaire with the participation of 207 women. The instruments used in the research were the Ocular Surface Disease Index (OSDI) questionnaire validated for the Portuguese language. In addition to that, other questions were added by the researchers regarding the use of oral contraceptives, the date of the last menstruation and whether the menopause has already begun. All the variables used were compared with the interviewee's situation in relation to the severity level of dry eye, estimated by the OSDI.

**Results:** It was possible to verify that women with higher estrogen levels, in the late follicular phase and luteal phase, presented a higher OSDI score compared to women in the menstrual phase, with lower estrogen levels.

**Conclusion:** Further studies on the subject are still needed, with more sensitivity, from a less heterogeneous group and with a daily assessment of symptoms in women at menarche and menopause, in order to achieve more significant data on the influence of estrogen on DED severity.

**Keywords:** Dry eye syndromes; Estrogens; Menstrual cycle; Oral contraceptives; Menopause

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## Introduction

According to the International Consensus Dry Eye Workshop (DEWS), Dry Eye Disease (DED), or Keratoconjunctivitis Sicca (KCS) is a multifactorial disease of tears and the ocular surface [1]. Some of the related eye symptoms include burning, foreign body sensation, decreased vision, dryness, photophobia, tearing, which can affect the people's daily lives [2]. DED has a common prevalence worldwide, with rates between 7% and 33%. The most common cause is the normal aging process, affecting adults over 40, with women being the most affected by discomfort [3].

DED can be classified according to its etiopathogenesis into two main categories: Water deficiency or evaporative state. DED due to water deficiency can be associated with Sjogren's syndrome (primary and secondary) and non-Sjogrens (due to lacrimal gland deficiency, lacrimal gland duct obstruction and reflex hyposecretion). DED due to excess of tear evaporation can derive from intrinsic factors (dysfunction of the Meibomian glands, alteration in the eyelid movement and decreased blink frequency) or extrinsic (vitamin A deficiency, environmental factors, use of contact lenses and other diseases on the eye surface) [1].

The female predominance is defended taking into account the role of sex hormones in DED, with estrogen being the most correlated [4]. Sex hormones act on their receptors present in the cornea, lacrimal gland, palpebral and bulbar conjunctiva meibomian gland [5]. As a result, fluctuation of serum hormone levels can promote a change in tear production, evaporation, drainage and homeostasis of the ocular surface [2].

Estrogen causes less lipid production and a decrease in the size of sebaceous glands, such as the meibomian gland. Therefore, authors assume that high rates of estradiol in pregnancy, ovulation or

hormonal replacement are aggravating in the pathology of dry eye [4-6]. In contrast, studies point to an alteration in the ocular surface due to decreased levels of estrogen during menopause, in the late luteal phase and in the use of oral contraceptives that suppress ovulation, reducing estrogen levels throughout the menstrual cycle [7].

The objective was to identify the influence of estrogen on the prevalence of dry eye in women.

### Methodology

It is a non-interventionist, cross-sectional and quantitative study, based on the application of a questionnaire, online and with an average duration of 5 min for its completion. It was carried out in the second half of 2020 and was attended by 207 women, among them medical students, dentists, nurses, physiotherapy and biomedicine, in addition to employees of the Health Sciences Center (HSC) of a University in Santa Catarina. The study was approved by the Research Ethics Committee of the University, CAAE 33576520.9.0000.5368. The women's consent was obtained after a complete explanation of the research, through the Free and Informed Consent Term (FICT).

The instruments used in the research were the Ocular Surface Disease Index (OSDI) questionnaire, validated for the Portuguese language, and other questions created by the researchers. The OSDI questionnaire is considered a valid and faithful instrument for measuring the severity of dry eye and its effects on the patient's vision. In total, 12 questions were asked including symptoms of DED and its impact on women's lives in the period of the questionnaire's week, graded on the level of discomfort, from 0 (absence of the symptom) to 4 (all the time). The calculation was made using the formula (sum of the scores × 25)/number of questions answered. The overall OSDI score ranges from 0 to 100, with higher values indicating greater symptoms. From the responses to the OSDI questionnaire, patients were classified into mild, moderate or severe dry eye symptoms.

The formulated questions created by the researchers aimed to estimate estrogen rates in women. They indicated whether they were using oral contraceptives, during menopause, under hormone replacement, or those who were in the reproductive phase and do not use oral contraceptives, regarding the phase of their menstrual cycle, obtained from the Date of Last Menstruation (DUM) and

the questionnaire response date. In order to control differences in cycle length and number of menstrual days, all participants were conditioned for a 28-day cycle. Based on the response, they were classified as menstrual phase (0 to 5) days, follicular phase (6 to 14) days and luteal phase (15 to 28) days. The questions created by the researchers aimed to estimate estrogen rates in women. They indicated whether they use oral contraceptives, whether they are in menopause, hormone replacement, or those who are in the reproductive phase and do not use oral contraceptives, regarding the phase of their menstrual cycle, obtained from the Date of Last Menstruation (DUM) and the questionnaire response date. In order to control differences in cycle length and number of menstrual days, all participants were sized for a 28-day cycle. Based on the response, they were classified as menstrual phase (0 to 5) days, follicular phase (6 to 14) days and luteal phase (15 to 28) days.

In addition to these questions, women were also asked whether they had previous eye surgery and used contact lenses before answering the questionnaire. These factors are already proved to promote DED, which could influence data analysis, and therefore were excluded from the survey.

The variables of menopause, use of oral contraceptives and phases of the menstrual cycle were compared with the situation of the interviewee in relation to her severity level of dry eye. Afterwards, these were estimated by OSDI, with the objective of verifying the influence of estrogen on eye symptoms dry in women. By the obtained results, linear regressions were made between the questions elaborated by the authors and the OSDI table, in order to verify whether estrogen influences the symptoms of dry eye. The experiment was conducted in a complete randomized design, considering a woman as a repetition. Microsoft® Excel 2016 was used to organize the data obtained, and statistical analysis was performed using the SPSS® Statistics Version 26 (IBM®) Software.

### Results

In total, 207 women participated in the study and answered the questionnaire in its entirety. Their age ranged between 18 and 67 years, with an average of approximately 33.4 years old; 174 declared themselves academic and 33 employees. Regarding the menstrual cycle, 199 (96.1%) were at menacme, and 8 (3.9%) at menopause.

**Table 1:** Analysis of linear regression of menopause with the OSDI score.

Model Summary						
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate		
1	0.119 <sup>a</sup>	0.014	0.005	0.98		
ANOVA <sup>a</sup>						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	0.372	1	0.372	1.498	0.224 <sup>b</sup>
	Residual	26.058	105	0.248		
	Total	26.430	106			
Coefficients <sup>a</sup>						
Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	1.311	0.049		26.702	0.000
	Menopausa	-0.311	0.254	-0.119	-1.224	0.224

a. Predictors: (Continuous), Menopause

a. Dependent Variable: Dry eye

b. Predictors: (Constant), Menopause

Source: Elaborated by the researchers

**Table 2:** Analysis of linear regression of the menstrual cycle with the OSDI score.

Model Summary						
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate		
1	0.003 <sup>a</sup>	0.000	-0.10	0.502		
ANOVA <sup>a</sup>						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	0.000	1	0.000	0.001	0.972 <sup>b</sup>
	Residual	26.430	105	0.252		
	Total	26.430	106			
Coefficients <sup>a</sup>						
		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	1.286	0.053		24.584	0.000
	Menstruacao	0.002	0.068	0.003	0.224	0.972

a. Predictors: (Constant), Menstruation

a. Dependent Variable: Dry eye

b. Predictors: (Constant), Menstruation

Source: Elaborated by the researchers

**Table 3:** Linear regression analysis of the use of oral contraceptives with the OSDI score.

Model Summary						
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate		
1	0.022 <sup>a</sup>	0.000	-0.009	0.502		
ANOVA <sup>a</sup>						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	0.012	1	0.012	0.049	0.825 <sup>b</sup>
	Residual	26.418	105	0.252		
	Total	26,430	106			
Coefficients <sup>a</sup>						
		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	1.286	0.077		16.612	0.000
	Uso_contraceptivo	0.022	0.099	0.022	0.224	0.825

a. Predictors: (Constant), Contraceptive use

a. Dependent Variable: Dry eye

b. Predictors: (Constant), Contraceptive use

Source: Elaborated by the researchers

Regarding the use of oral contraceptives in menacme, 55 reported not using it, while 144 use it.

The OSDI score for menopausal women had a limit of 4.16 to 33.33, with a median of 22.91. According to Table 1, significant results were not obtained ( $p > 0.05$ ) to verify that post-menopause influences dry eye symptoms. These women answered that they use hormone replacement and, therefore, were considered in the calculation under low estrogen levels.

Women with a regular menstrual cycle were also analyzed for this search. It was stipulated from the physiology of the menstrual cycle that the lowest concentration of estrogen occurs during the menstrual phase, followed by an increase in the follicular phase, before ovulation, and then a decline with gradual increase to another smaller peak and more ample during the luteal phase.

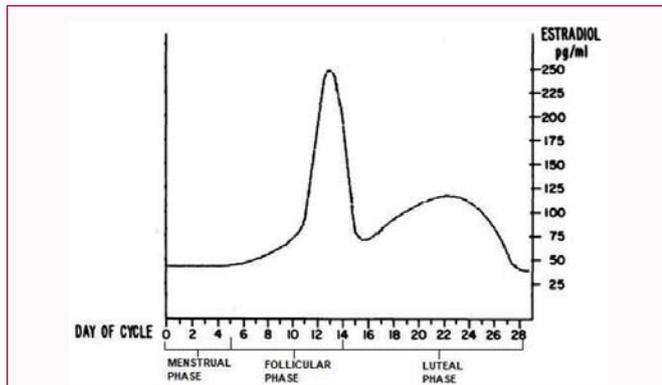
For the women that answered they were under the luteal phase, the OSDI score presented a limit of 2.08 to 75 and a median of 17.7. In the follicular phase, the OSDI score had a limit of 4.16 to 62.5 and a

median of 14.58. In the menstruation phase, the OSDI score limit was 2.08 to 33.33, with a median of 19.7. For the sample used, there was no significant result ( $p > 0.05$ ) in the linear regression between OSDI scores and estrogen levels, Table 2.

In total, 28 types of combined contraceptives were identified, among women who use this contraceptive method, and only four women affirmed the use of progesterone alone. The women under the use of contraceptives had a limit on the OSDI score of 0 to 68.75 and a median of 16.66. The use of oral contraceptives, which represents low estrogen levels, was not statistically significant ( $p > 0.05$ ) in the regression with the OSDI score, Table 3.

## Discussion

The tear film, located above the corneal epithelium, provides protection to the eyes against infections, keeping the eyes moist, nourished and lubricated. It is composed of three main layers. The outermost layer, which is in contact with air, is a lipid layer secreted by the meibomian glands, responsible for delaying the evaporation of



**Figure 1:** Cyclical variations in estradiol levels during a normal menstrual cycle. Between 0 to 5 days there is the menstrual phase, in which estrogen is at its lowest level. In the follicular phase, there is an increase in estradiol between 12 to 14 days, before ovulation. Finally, there is a decline in estrogen, then a gradual, smaller and broader increase in the luteal phase between 15 to 28 days. Retrieved from Daily fluctuations in ocular surface symptoms during the normal menstrual cycle and with the use of oral contraceptives, 2019; 17 (4) pp: 6.

the aqueous layer, altering the surface tension and maintaining the integrity of the tear film. The intermediate aqueous layer, secreted by the lacrimal gland, has the function of supplying oxygen to the corneal epithelium, preventing infections due to having antimicrobial substances (such as lysozyme) and removing residues that come from the cornea, conjunctiva and external environment. The most intern layer of mucin secreted by conjunctival goblet cells maintains hydration of the ocular surface [2].

Estrogen influences the mechanisms mentioned above, as it acts on its receptors present in the cornea, lacrimal gland, meibomian gland and eyelid and bulbar conjunctiva. Therefore, this hormone plays an important role in the pathogenesis of DED [5].

### Menopause

Menopausal women present lower levels of estrogen, this being verified from laboratory tests. Estrogen levels in premenopausal women range from around 30  $\text{pgmL}^{-1}$  to 400  $\text{pgmL}^{-1}$ , which decreases to 0  $\text{pgmL}^{-1}$  to 30  $\text{pgmL}^{-1}$  in postmenopausal [8]. Therefore, it was considered in this search that women in menopause have low levels of estrogen, as they stated that they did not undergo hormone replacement therapy. Studies have found that high estrogen causes a decrease in the production of lipids, which is a risk factor for dry eye, as they affect the mechanism of the meibomius glands and consequently alter the tear film integrity [2].

In the United States of America, epidemiological studies have shown a higher prevalence, almost double, of DED in women over 50 than in men of the same age. The high number of women who use hormone replacement therapy can explain this data. This is because when the therapy is made only with estrogen or high levels of estrogen plus progesterone, the symptoms increase significantly in comparison at lower doses of treatment or other therapies [2].

### Menstrual cycle

According to the study, women with higher estrogen levels, in the late follicular phase and luteal phase, demonstrated a higher OSDI score compared to women in the menstrual phase. Such information is in accordance with studies that reported higher symptoms, with higher scores on the OSDI, on ovulation and on the luteal phase [4-5]. Cyclic estrogen variations are shown in Figure 1.

Research suggests that dry eye can happen in the context of Premenstrual Syndrome (PMS), as some symptoms of dry eye appear in the same period (luteal phase) as other symptoms characteristic of PMS. They also propose that estrogen has a pro-inflammatory role on the ocular surface, so under elevated conditions they predispose to DED [3]. However, other authors identified worse eye symptoms on day two, which corresponds to the menstrual phase; when estrogen levels are lower [7].

### Oral contraceptive

The same study that demonstrated greater ocular symptoms in the menstrual phase, with a lower rate of estrogen, found that the use of oral contraceptives worsens ocular symptoms. Its use makes estrogen levels suppressed, i.e., lower when compared to women who do not take it, which promotes constant hormonal levels and, consequently, prevents ovulation [7]. The regression analysis of the present search did not obtain significant results to prove such a relationship, despite presenting a large number of women with mild, moderate and severe symptoms.

### Multifactorial causes of dry eye

Dry eye disease is multifactorial, caused by environmental factors, climate, pollution, air conditioning, screen use, with estrogen variations being one of the factors proposed and under study [9]. Therefore, there is difficulty in proving the cause and effect, since there are other elements that can contribute significantly to DED.

### Conclusion

This research is relevant, considering that many of the women participating presented high OSDI results. There is a need for further studies on the subject, with more sensitivity, from a less heterogeneous group, and with a daily assessment of symptoms in women at menacme and menopause, in order to have more data that are significant on the influence of estrogen in DED.

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