

# Ocular Surface Disease Severity in Polycystic Ovary Syndrome: Is This Really Significant in Daily Life?

Demet YABANOGLU<sup>1,2</sup>, Funda CIRAK GODE<sup>3,4</sup>

Ankara, Turkey

## ABSTRACT

**OBJECTIVE:** The purpose of this study was to ascertain the extent to which the ocular surface of women with polycystic ovary syndrome is impacted.

**STUDY DESIGN:** Included in this case-control study were 23 eyes of 23 patients (Group I) with polycystic ovary syndrome and 10 eyes of 10 healthy subjects (Group II). Polycystic ovary syndrome was diagnosed when two of the following conditions were met: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and ultrasonographic documentation of polycystic ovaries. Ocular surface disease grading was performed using the Ocular Surface Disease Index questionnaire, slit lamp examination, meibomian gland secretion scoring, tear film breakup time, staining scores of ocular surfaces, the Schirmer's test, and tear osmolarity assessment.

**RESULTS:** The study observed no significant difference in age ( $p=0.896$ ). Group I was found to have a significantly higher median luteinizing hormone level ( $p=0.027$ ). The Ocular Surface Disease Index scores in group I were significantly higher than those in group II ( $p=0.031$ ). The prevalence of anterior blepharitis was significantly greater in group I ( $p=0.05$ ). Tear film breakup time was higher in group I than in group II ( $p=0.026$ ). The ocular surface disease severity was found to be significantly higher in group I ( $p=0.03$ ). In group I, Ocular Surface Disease Index scores were significantly positively correlated with free testosterone, while tear osmolarity was significantly positively correlated with estradiol levels but significantly negatively correlated with dehydroepiandrosterone sulfate levels ( $p<0.05$ ).

**CONCLUSIONS:** Daily activities appear to be slightly impaired in patients with polycystic ovary syndrome due to ocular surface problems. However, environmental factors (humidity, temperature, etc.) contribute to the aggravation of ocular symptoms. Patients with polycystic ovary syndrome may be referred to an ophthalmologist to preserve ocular surface health.

**Keywords:** Meibomian gland, Ocular surface, Polycystic ovary syndrome, Tear osmolarity

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<sup>1</sup> Department of Ophthalmology, Pediatric Ophthalmology and Strabismus Unit, Hacettepe University, Faculty of Medicine Ankara, Turkey.

<sup>2</sup> Formerly, Department of Ophthalmology, The State Hospital of Rize, Rize, Turkey.

<sup>3</sup> Department of Obstetrics and Gynecology, Izmir University of Economics, Faculty of Medicine, Izmir, Turkey


<sup>4</sup> Formerly, Department of Obstetrics and Gynecology, The State Hospital of Rize, Rize, Turkey.

Address of Correspondence: Demet Yabanoglu  
Hacettepe University Hospital, Faculty of  
Medicine, Department of Ophthalmology,  
06230, Ankara, Turkey.  
demet.aban@hacettepe.edu.tr

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ORCID IDs of the authors: DY: 0000-0003-4532-3543,  
FCG: 0000-0002-9371-6942

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## Introduction

Although the term polycystic ovary syndrome (PCOS) refers to the presence of multiple cystic structures in the ovaries, it is actually a multisystemic disorder that encompasses a variety of diseases, including insulin resistance/metabolic syndrome, diabetes mellitus, cardiovascular disease, and endometrial cancer (1-3). The ophthalmological system is one of the systems affected by PCOS (4). It is affected directly by the local and systemic balance of sex steroid hormones, including androgens, estrogens, and progesterone (5). Over the last decade, a growing body of research has established a connection between PCOS and ocular surface diseases (OSDs) such as meibomian gland dysfunction (MGD), tear film instability, and dry eye syndrome (4-8). None of these studies, however, investigated the extent to which PCOS affects the ocular surface. At the moment, it is unclear how severely ocular surface problems impact the daily activities of patients with PCOS. This study endeavored to address this shortcom-

ing. The aim of this study was to assess the severity of OSD in PCOS and lay the groundwork for future research to determine interventions or treatment options to improve the ocular surface health of patients with PCOS.

## Material and Method

This case-control analysis adopted the principles of the Helsinki Declaration and was approved by the Rize University Faculty of Medicine Clinical Research Ethics Committee (Ethics approval reference number: 2012/59, date: 20.04.2012). Informed consent was obtained from each subject to participate.

The diagnosis of PCOS was made in accordance with the recommendations of the PCOS consensus workshop community, as approved by the European Society of Human Reproduction and Embryology/American Reproductive Medicine (9). Patients who fulfilled two of the following three requirements were diagnosed with PCOS: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and the evidence of polycystic ovaries on ultrasonography. Subjects with a history of ocular surgery, using topical or systemic medications that may influence the lacrimal system, using contact lenses, having any ocular surface disorders, other hormonal and systemic disorders, and receiving any hormone therapy in the last 6 months were excluded from the study. Subjects for the study and control groups were identified by the Department of Gynecology and Obstetrics. Each ophthalmological analysis was carried out by the same researcher (DY), who was not informed of the study or control groups. To prevent bias, data were obtained only from each participant's right eye (10). All participants underwent the following ophthalmologic procedures in order: assessment of ocular symptoms using Ocular Surface Disease Index (OSDI) (Allergan Inc., Irvine, CA), evaluation of best-corrected visual acuity, slit-lamp examination of the anterior segment, measurement of tear film breakup time (TFBUT), fluorescein, and lissamine green staining of ocular surfaces, Schirmer's test, measurement of tear osmolarity, and examination of the posterior segment.

Prior to the ophthalmic examination, participants were requested to answer the OSDI questionnaire which is validated in Turkish, consisting of 12 questions (11). Morphologic eyelid characteristics, lid margin neovascularization and irregularity, conjunctival vascular congestion, anterior blepharitis, papillary hypertropia, meibomian gland (MG) function, corneal surface changes, and staining patterns were all carefully examined in a thorough anterior segment examination. Corneal fluorescein staining was assessed by using the National Eye Institute/Industry (NEI) Scheme (12). Corneal and conjunctival lissamine green staining were assessed by using the Oxford Grading System (13). The TFBUT test determined the first time the fluorescein dye was broken on the corneal surface after blinking. Breaking time less than 10 sec-

onds was considered pathological. The Schirmer's test was performed with topical anesthesia to evaluate the actual basal tear production of the participants. Osmolarity tests of the tear film were carried out in the same testing room on the same day of the week at the same time of the day in order to reduce factors such as temperature and humidity in the test results. The tear film osmolarity was tested by using the OcuSense TearLab™ Osmometer (TearLab, San Diego, CA, USA) (14). The system was provided with electronic check cards which were used to validate the calibration at the beginning of each practice session. The test cards kept by the test pen were used to assess tear osmolarity in the lower eyelid.

All posterior segment examinations were performed after pupil dilation.

The severity of OSD was determined in patients with PCOS using clinical and patient-reported subjective methods, as well as quantitative testing techniques adapted from the International Meibomian Gland Dysfunction Workshop (MGDW) grading scales (15). Six of the criteria defined in the MGDW were adapted to this study in order to assess the severity of OSD; 1-OSDI questionnaire, 2-NEI/Industry score, 3-Oxford score, 4-TFBUT, 5-Schirmer's test, and 6-tear film osmolarity (15). Each subject's ocular surface test result was rated on a severity scale ranging from 0 to 5, as defined in MGDW (15). The final OSD severity level of each subject was determined based on the mean OSDI score and the median values of NEI/Industry score, Oxford score, TFBUT, Schirmer's test, tear film osmolarity and was graded on a scale of 0 to 5. (Grade 0, asymptomatic; grade 1, occasional; grade 2, precipitated by environmental factors; grade 3, certain activity limitations; grade 4, frequent activity limitations; grade 5, extreme and debilitating symptoms).

Statistical analysis was carried out using the Windows version 15 statistical package for social sciences (SPSS Inc., Chicago). The normality of numerical data was assessed with the Shapiro Wilks test. The data that confirms normal distribution was summarized with mean  $\pm$  standard deviation (SD), and the data that does not confirm normal distribution was presented with median [minimum-maximum (min-max)] values. The categorical variables were displayed with the number and the percentage. The Chi-square test was used to detect the relationship between the categorical variables. In independent samples t-test was used to detect the difference between groups when parametric test assumptions were met. In the case of a violation of these assumptions, the Mann-Whitney U test was utilized. To evaluate the relationship between the variables, the Spearman correlation test was used. The 2-tailed *p*-value of  $<0.05$  was presumed to be significant.

## Results

23 eyes of 23 PCOS patients with a mean age of  $26.26 \pm 6.916$  years and 10 eyes of 10 healthy women with an

average age of  $25.33\pm 3.428$  years were included in the study as group I and group II, respectively. No statistically significant difference was observed in terms of age between groups ( $p=0.896$ ).

Serum hormonal and biochemical test results of groups included in the study are summarized in table I. The median luteinizing hormone (LH) levels in group I was found to be significantly higher than those in group II ( $p=0.027$ ). The groups demonstrated no significant difference in other hormonal and biochemical characteristics ( $p>0.05$ ).

In both groups, the best-corrected visual acuity was 20/20. The OSDI questionnaire scores in group I were significantly greater than those in group II, with a median of 30 points ( $p=0.031$ ). Outcomes from the anterior segment of groups are summarized in table II. There was a significantly higher prevalence of anterior blepharitis in group I ( $p=0.05$ ). The results of the ophthalmological tests and the overall severity level of the OSD of groups are shown in tables III and IV. The

mean TFBUT values in group I ( $7.74\pm 3.87$ ) significantly declined in comparison to group II ( $13.11\pm 5.798$ ,  $p=0.026$ ). The median severity of OSD was found to be significantly higher in group I (grade 2) than in group II (grade 1). The significance level was 0.03. Correlation analysis is presented in table V. The OSDI questionnaire scores were found to have a significant positive correlation with serum free testosterone levels in group I (Spearman correlation coefficient ( $r^2$ ); 0.447,  $p=0.033$ ). Tear osmolarity in group I was significantly positively correlated with serum estradiol levels ( $r^2$ ; 0.433,  $p=0.01$ ), and was significantly negatively correlated with serum dehydroepiandrosterone sulfate (DHEAS) levels ( $r^2$ ; -0.563,  $p=0.005$ ). Group II demonstrated no significant association of the ocular surface and hormonal and biochemical parameters ( $p>0.05$ ).

The disc, macula, and peripheral retinal areas were found to be normal in all participants during the dilated fundus examination.

**Table I:** Serum hormonal and biochemical test results of groups

	Group I (n=23) Mean SD Median[min-max]	Group II (n=10) Mean SD Median[min-max]	p
Total testosterone (ng/dL)	0.391±0.132	0.294±0.149	0.081
Free testosterone (ng/dL)	1.847±0.72	1.555±0.853	0.336
Sex hormone binding globulin (nmol/L)	39.065±16.995	41.156±13.085	0.743
Follicle-stimulating hormone (mIU/mL)	7.745±1.628 5.65 [3.15-11.15]	5.832±1.228 6.14 [3.7-7.3]	0.483
Luteinizing hormone (mIU/mL)	8.830±6.330 7.04 [3.53-25.52]	4.955±1.510 4.220 [3.31-7.90]	0.027*
Estradiol (pg/mL)	48.596±21.911 45.71 [12.86-101.40]	61.892±41.998 48.7 [29.36-169.10]	0.433
Dehydroepiandrosterone sulfate (µg/dL)	252.780±144.743 226.4 [43.49-682]	281.133±107.438 288.9 [149-450]	0.386
Homocysteine (µmol/L)	12.957±7.219 10.5 [7.16-36.0]	12.535±6.360 10.5 [6.42-25.20]	0.742
Insulin (µIU/mL)	9.336±5.464 8.18 [3.48-24.65]	7.383±2.155 7 [3.75-10.36]	0.458
Fasting blood glucose (mg/dL)	91.26±8.302	90.22±8.422	0.753
HOMA-IR	2.172±1.431 1.84 [0.71-5.903]	1.651±0.529 1.611 [0.814-2.481]	0.564

\* Mann-Whitney U test,  $p<0.05$  was considered as statistically significant

**Table II:** Anterior segment examination findings of groups

	Group I n (%)	Group II n (%)	p
Anterior blepharitis	11 (47.8 %)	1 (9%)	0.007*
Bulbar injection	8 (34.7%)	2 (20%)	0.472
Tarsal injection	5 (21.7%)	1 (9%)	0.714
Meibomitis	6 (26.0%)	1 (9%)	0.483

\* Chi-square test,  $p<0.05$  was considered as statistically significant

**Table III:** Ocular surface parameters test results and Ocular Surface Disease Index scores of groups

	Group I (n=23) Mean±SD Median[ <i>min-max</i> ]	Group II (n=10) Mean±SD Median[ <i>min-max</i> ]	<i>p</i>
OSDI score	32.976±15.568 30 [10-66.67]	20.391±17.628 9.09 [5.50-52.27]	0.031*
TFBUT (sec)	7.74±3.781	13.11±5.798	0.026**
Schirmer's test (mm)	14.83±7.114	18.33±8.689	0.248
Osmolarity (mOsm/L)	300.35±9.485 299 [286-320]	287.0±33.604 295 [200-311]	0.301
OSD severity level	Grade 2	Grade 1	0.03*

\* Mann Whitney U test,  $p < 0.05$  was considered as statistically significant. \*\*Independent samples t-test,  $p < 0.05$  was considered as statistically significant. OSDI: Ocular surface disease index. TFBUT: tear film breakup time. OSD: Ocular surface disease

**Table IV:** Ocular surface staining scores of groups

Ocular surface staining tests	NEI/Industry Scheme		Oxford Grading System		
	Grade 0 n (%)	Grade 1 n (%)	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)
Group I	18 (78.3%)	5 (21.7%)	16 (69.6%)	5 (21.7%)	2 (8.7%)
Group II	9 (100%)	0 (0%)	8 (88.9%)	1 (11.1%)	0 (0%)

Corneal fluorescein staining was graded on a scale of 0 to 3 according to the National Eye Institute/Industry Scheme. When no staining is present, a grade of 0 is stated; when advanced staining is present, a grade of 3 is specified. There was no evidence of a grade 3 staining pattern in any of the subjects. The degree of lissamine green staining on the cornea and conjunctiva was graded using the Oxford grading system of 0 to 5. When there was no staining, level 0 was given. The advanced staining pattern indicates level 5. No individual exhibited staining patterns at level 3 or higher.

**Table V:** Spearman correlation coefficients ( $r^2$ ) for the relation of serum biochemical test parameters and ocular surface assessment parameters in patients with polycystic ovary syndrome

		OSDI	TFBUT	Osmolarity	Schirmer's test
Total testosterone (ng/dL)	$r^2$	0.173	0.129	-0.168	0.238
	$p$	0.430	0.558	0.443	0.273
Free testosterone (ng/dL)	$r^2$	0.447	-0.210	-0.274	-0.004
	$p$	0.033*	0.337	0.205	0.986
Sex hormone binding globulin (nmol/L)	$r^2$	-0.095	0.304	0.212	-0.038
	$p$	0.666	0.159	0.332	0.864
Follicle-stimulating hormone (mIU/mL)	$r^2$	0.406	0.039	0.154	-0.132
	$p$	0.055	0.860	0.482	0.550
Luteinizing hormone (mIU/mL)	$r^2$	-0.119	0.265	0.351	0.124
	$p$	0.589	0.223	0.101	0.574
Estradiol (pg/mL)	$r^2$	-0.078	0.016	0.433	-0.004
	$p$	0.723	0.941	0.039*	0.984
Dehydroepiandrosterone sulfate ( $\mu$ g/dL)	$r^2$	0.249	0.266	-0.563	0.077
	$p$	0.252	0.220	0.005*	0.726
Homocysteine ( $\mu$ mol/L)	$r^2$	0.079	0.055	0.120	0.133
	$p$	0.721	0.802	0.585	0.546
Insulin ( $\mu$ mol/L)	$r^2$	-0.33	-0.064	0.086	-0.018
	$p$	0.124	0.773	0.698	0.934
Fasting blood glucose (mg/dL)	$r^2$	-0.185	-0.169	0.140	-0.124
	$p$	0.397	0.440	0.524	0.573
HOMA-IR	$r^2$	-0.310	-0.089	0.076	-0.03
	$p$	0.149	0.688	0.731	0.891

\*  $p < 0.05$  was considered as statistically significant. OSDI: Ocular surface disease index. TFBUT: tear film breakup time.

## Discussion

The severity of OSD and its effect on daily activities were evaluated in women with PCOS in this research. This study was the first of its kind in this area. To assess the severity of OSD, the MGDW protocols were adapted for this study (15). The MGDW is a workshop organized by the Tear Film and Ocular Surface Society with the aim of achieving global consensus on MGD diagnosis, classification, severity grading, and treatment (16). The MGDW guidelines were followed in this study due to prior research suggesting that MGD is a frequent cause of ocular surface problems in patients with PCOS. Each participant was evaluated in three ways: through symptom interrogation, qualitative MG function assessment, and quantitative ocular surface impairment diagnostic tests.

In ophthalmology clinics, a variety of questionnaires are used to determine the symptomatology of ocular surface disorders (17). OSDI was chosen for this study because multiple psychometric tests have demonstrated its ability to evaluate the seriousness and functional effects of ocular surface diseases, and a Turkish validated version is available. The OSDI score ranges from 0 to 100, with a higher score indicating a greater degree of ocular surface impairment. The OSDI score ranges from 0-12 for normal, 13-22 for mild dry eye, 23-32 for moderate dry eye, and 33-100 for severe dry eye (18). The fact that patients with PCOS had a higher median OSDI score (30) than healthy controls (9.09) supports the claim that PCOS may affect ocular surface homeostasis. Additionally, the strong positive association between the OSDI score and free testosterone suggests that androgen levels might affect ocular surface symptoms in PCOS.

The expressibility of meibum, an MG secretion, was used to assess the role of the MGs. By applying digital pressure to the lower lid, we assessed the MGs' ability to express the secretion found inside, as well as the volume, viscosity, and quality of the expressed meibum. The presence of fluid, clear, but 2-3 times greater meibum expression from all MGs in patients with PCOS supports the theory that MGD might lead to deteriorating ocular surface homeostasis. This method is not recommended for evaluating MG activity, as the amount of expressed meibum can vary depending on the physical force and duration of application (19). Rather than that, imaging techniques such as meiboscopy and meibography are recommended for determining the MGs' function and anatomy (15). No research in the literature evaluates MG function in women with PCOS using meiboscopy or meibography. The absence of these techniques raised a limitation.

Staining of the conjunctiva and cornea with specific dyes is associated with epithelial defects. Both the NEI/Industry Scheme and the Oxford Grading System are based on the pattern of staining of the cornea and conjunctiva with particular dyes (20). In this analysis, both approaches were used to determine ocular surface damage using two separate dyes. The

NEI/Industry Scheme used fluorescein dye, while the Oxford Grading System used lissamine green dye. The cornea and conjunctiva were divided into zones and given a staining level ranging from 0 to 3 and 0 to 5, respectively. Although the cases in the research had symptoms consistent with impaired ocular surface homeostasis, neither technique detected any advanced ocular surface damage. This discrepancy was interpreted as an effort by ocular compensation systems to control ocular surface dysfunction in the early years following PCOS diagnosis.

Tear film breakup time provides clinicians with critical information about the stability of the tear film when evaluating ocular surface diseases. It is a non-invasive procedure that is relatively straightforward to perform. This partly subjective test, on the other hand, needs standardization and has a low correlation with other ocular surface health tests (21). Less than ten seconds indicates reduced stability, and less than three seconds indicates severe dry eye. TFBUT was less than ten seconds in women with PCOS, implying that the tear film's stability might be impaired in this disease.

Schirmer's test is used to determine the tear fluid supply. It can be studied either without anesthetic or with anesthetic assistance. The overall tear secretion potential is calculated using the anesthetic-free process (22). However, in individuals with high corneal-conjunctival sensitivity, reflex tear fluid secretion may become excessive, completely wetting the strip. In this analysis, the Schirmer's test with anesthetic was preferred to evaluate only basal tear production and rule out excessive reflex production. Schirmer's test value greater than 10 mm means that the basal tear fluid production of women with PCOS is sufficient. However, the TFBUT test showed that, despite the formation of sufficient tear fluid, it was unable to remain on the eye surface for a prolonged period due to abnormal evaporation. Additionally, we used the tear film osmolarity test to validate this evaporative state in PCOS. While the tear osmolarity test was only recently introduced into clinical practice in ophthalmology, it has rapidly gained popularity (23). There are several methods for calculating the osmolarity of the tear film. This study employed the OcuSense TearLab™ Osmometer (TearLab, San Diego, CA, USA) procedure, which is based on electrical impedance (14). It is a straightforward test to conduct, and it has been shown to have a high sensitivity for detecting OSDs whether used alone or in combination with other tests. The diagnostic threshold for osmolarity in dry eye diseases has been identified at 321 mOsm/L (24). The study presumed that women with PCOS would have a higher tear film osmolarity, consistent with the TFBUT test findings. However, the results did not adhere to this expectation. The authors concluded that, while tear fluid production is normal in PCOS, ocular homeostasis may deteriorate as a result of the tear film's unusual evaporation proclivity.

This study established a significant correlation between

grade 2 OSD and PCOS. According to the MGDW study, grade 2 OSD is described as mild symptomatic OSD that is exacerbated by environmental factors such as humidity, temperature, wind, and working conditions (15). There are a few possible explanations for why this result falls short of expectations. A potential reason is that short-term follow-ups were conducted. Patients who had recently been diagnosed with PCOS or who had been followed for less than a year were included in this study. Bonini et al (4) confirmed that ocular signs and symptoms manifest approximately three years after the initial ultrasonographic observation of polycystic ovaries. Another factor to remember is preserving the integrity of the ocular surface not only with androgens but also with sex hormone balance and metabolic regulation. Mantelli and colleagues (5) recently published a paper highlighting the effect of a hormonal imbalance on the ocular surface in PCOS. Although this study investigated the effect of insulin resistance, it has a drawback in that it did not consider the lipid profile or body mass index, both of which are measures of metabolic control. Another possibility is that the number of participants was insufficient. Long-term follow-ups with extensive participation are expected to show a more aggressive ocular surface involvement in PCOS. Additionally, the study lacks MG imaging techniques such as meiboscopy and meibography, as well as an assessment of the tear film composition.

## Conclusion

It seems as if PCOS has a negative impact on the ocular surface's health from the moment it is diagnosed. This effect is mild in the first years and may become more serious during the day as a result of environmental factors. Ocular surface problems can have a detrimental effect on an individual's daily life. Environmental control alone may be sufficient to maintain ocular surface integrity in the first years following PCOS diagnosis. The authors recommend that clinics dealing with PCOS refer these patients to an ophthalmologist for an ophthalmologic examination to ensure ocular surface safety.

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*Competing Interest: The authors declare that they have no competing interests.*

*All participants signed informed written consent before being enrolled in the study.*

*All procedures were performed according to the Declaration of Helsinki.*

*Availability of data and materials*

*The datasets and code used and/or analyzed during the current study are available from the corresponding author on reasonable request.*

*Authors' Contribution: DY and FCG raised the presented idea. DY and FCG designed the study. DY and FCG conducted the analyses. DY developed the first draft of the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.*

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