

# Dry Eye Signs and Symptoms in Women With Premature Ovarian Failure

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**Objective:** To examine whether women with premature ovarian failure (POF) have abnormal findings in ocular surface or tear parameters and whether they report symptoms of ocular discomfort compared with age-matched controls.

**Methods:** Sixty-five patients with POF and 36 age-matched healthy controls were examined for signs and symptoms of dry eye. The Ocular Surface Disease Index questionnaire and the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) were administered to the participants. Assessments of ocular surface damage (Oxford and van Bijsterveld scores of vital dye staining) and tear status (Schirmer tests 1 [without anesthesia] and 2 [with anesthesia] and tear breakup time) were performed.

**Results:** Women with POF scored significantly worse than controls on all ocular surface damage parameters: Oxford score (3.2 vs 1.7;  $P=.001$ ), conjunctival lissamine green (2.1 vs 1.3;  $P=.02$ ), corneal fluorescein staining (1.2 vs 0.4;  $P=.005$ ), and van Bijsterveld score

(2.1 vs 1.3;  $P=.02$ ). Further, the proportion of patients with POF meeting the dry eye diagnostic criterion of a van Bijsterveld score greater than or equal to 4 was significantly greater among women with POF than among controls (20% vs 3%;  $P=.02$ ). The POF group also tended to have worse scores than controls on self-reported symptoms, as measured by the overall Ocular Surface Disease Index (12.5 vs 2.1;  $P<.001$ ) and the overall NEI-VFQ (94 vs 98;  $P=.001$ ) after adjustment for age and race. Schirmer test scores and tear breakup time did not differ.

**Conclusions:** Women with POF were more likely to exhibit ocular surface damage and symptoms of dry eye than age-matched controls. They were not, however, more likely to have reduced tear production. To our knowledge, this association between ocular surface disease and POF has not been previously reported. These data provide further evidence of the multifaceted role of sex hormones in the health and disease of the ocular surface.

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**P**REMATURE OVARIAN FAILURE (POF) is defined as cessation of normal ovarian function in women younger than 40 years and affects 1% of women as determined by a large cohort study of Minnesota women followed up for date and type of menopause.<sup>1</sup> In addition to amenorrhea, women with POF exhibit hypoandrogenemia, hypoestrogenemia, and elevated gonadotropin levels. Women with POF experience the same symptoms of estrogen deficiency as do postmenopausal women, including hot flashes, night sweats, fatigue, and mood swings and have an increased risk of cardiovascular disease and osteoporosis.<sup>2</sup> Although chemotherapy, irradiation, and chromosomal abnormalities can cause POF, an autoimmune origin is also well recognized. Women with autoimmune POF are at increased risk of potentially fa-

tal autoimmune adrenal insufficiency.<sup>3</sup> In addition, women with POF demonstrate impaired immune regulation, including increased activation and total number of peripheral T cells, increased CD4/CD8 ratio, increased number of B cells,<sup>4</sup> and reduced natural killer cell activity.<sup>5</sup> In most cases, the mechanism of POF is unknown.

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In the United States, it is estimated that 15% of individuals aged 65 to 84 years<sup>6</sup> have keratoconjunctivitis sicca, defined as at least one symptom of dry eye often or all of the time. There are 2 major categories of keratoconjunctivitis sicca: aqueous tear deficiency and evaporative tear deficiency.<sup>7</sup> Aqueous tear deficiency is characterized by the decreased volume of

tear production by the lacrimal glands, chronic ocular surface inflammation, fluctuating visual disturbance, decreased ability to perform activities of daily living, such as reading and using a computer, and ocular discomfort.<sup>8</sup> Evaporative tear deficiency can result from qualitative disturbance in the tear film with resultant instability, leading to increased evaporation and dryness of the ocular surface. It is most often caused by meibomian gland disease. Although dry eye can occur in men or women of any racial group at any age, many studies have found a higher risk of dry eye in women. Dry eye can be associated with autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or Sjögren syndrome.

The role of sex hormones in dry eye has been investigated in several studies.<sup>9-12</sup> Most recently, Schaumberg et al<sup>13</sup> found an increased prevalence of dry eye in women who had received hormone therapy (9.1% in those treated with estrogen alone and 6.7% in those treated with estrogen plus progesterone/progestin); the prevalence was lowest in women who had never used hormone therapy (5.9%). It remains unclear, however, what role estrogen excess, androgen deficiency, and/or estrogen-androgen imbalance play in association with dry eye. Androgen deficiency, as seen in congenital androgen insensitivity syndrome and antiandrogen therapy, has been associated with dry eye.<sup>14,15</sup> Androgen deficiency is also seen in Sjögren syndrome, and it has been proposed to lead to evaporative tear deficiency in affected women.<sup>16</sup> Since women with POF also suffer from androgen deficiency, we hypothesized that they would exhibit signs or symptoms of dry eye more frequently than age-matched controls with normal ovarian status.

## METHODS

Sixty-five consecutive women with POF and 36 age-matched normal control women were evaluated for subjective evidence of dry eye symptoms and objective signs of ocular surface disease. Premature ovarian failure was diagnosed as follows: amenorrhea for at least 4 months and 2 consecutive instances of elevated FSH concentrations ( $\geq 40$  IU/dL) obtained at least 1 month apart. Women were excluded from the control group if they had any of the following: abnormal menstruation, eye disease (except refractive error), contact lens use, or use of prescription medications, including oral contraceptives. The protocol was approved by the institutional review board for the National Institutes of Child Health and Human Development (Bethesda, Md), and all participants signed an informed consent.

No controls had ever received hormone therapy at the time of the screening examination. Patients with POF who were currently using hormone therapy were asked to discontinue it for at least 2 weeks prior to the visit. Control women were seen at any time during the menstrual cycle. All participants underwent ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity assessment, masked slitlamp biomicroscopy, including a standardized grading of eyelid margin thickness and hyperemia, conjunctival erythema, chemosis, tear film debris and mucus, and extent of meibomian gland plugging. Grading of external eyelid disease was accomplished as follows. For meibomian gland disease, 5 meibomian glands were selected in the central lower eyelid, and the number of glands from which meibum could be readily expressed was graded as none (0), mild (+1) if 1 to 2 glands were plugged, moderate (+2) if 3 to 4 glands were plugged, or severe (+3) if all 5 glands were plugged. Eye-

lid margin erythema was graded as none (0) if there was no erythema, mild (+1) if redness was localized to a small region of the eyelid(s) margin, moderate (+2) if redness affected most or all of the eyelid(s) margin, severe (+3) if redness affected most or all of the eyelid(s) margin and skin, or very severe (+4) if there was marked diffuse redness of the eyelid(s) margin and the skin. Eyelid margin swelling was graded as none (0), mild (+1) if localized to a small region of the eyelid(s), moderate (+2) if it affected most or all of the eyelid(s) but was not prominent, severe (+3) if most or all of the eyelid(s) was affected and prominent, or very severe (+4) if the swelling was prominent, with eversion of the eyelid(s).

In addition, we performed tests of tear production (Schirmer test 1 [without anesthesia] and 2 [with anesthesia]) and an assessment of ocular surface damage using vital dye staining with 5  $\mu$ L of 2% sodium fluorescein or 10  $\mu$ L of 0.5% lissamine green instilled using capillary tubes. The van Bijsterveld grading method assessed lissamine green staining of the cornea and the temporal and nasal bulbar conjunctiva. The cornea and conjunctiva were graded separately (0-3 for each zone) and then combined for the total van Bijsterveld score.<sup>17</sup> The Oxford method assessed sodium fluorescein staining of the cornea and lissamine green staining of the nasal and temporal bulbar conjunctiva, graded separately (0-5 for each zone) and then combined for the total Oxford score.<sup>18</sup> Determination of tear film stability was assessed by fluorescein tear breakup time. If the tear breakup time was less than 10 seconds, the test was repeated for a total of 3 values, and the average was determined. The tests were performed according to standard operating procedures and in the following order: Schirmer 1, slitlamp examination, vital dye staining, tear breakup time, and Schirmer 2.

For statistical analysis, the maximum (worse) score for the 2 eyes of each individual was used for Oxford, lissamine green, and van Bijsterveld, and the minimum (worse) score for the 2 eyes was used for Schirmer 1, Schirmer 2, and tear breakup time. Tear breakup time values greater than or equal to 10 seconds<sup>19</sup> were coded as 10 (normal), and those less than 10 seconds were defined as abnormal. A score of 5 mm or less on Schirmer 1 or a van Bijsterveld score greater than or equal to 4 were used as objective evidence of dry eye, following the past and current European Community Study Group on Classification Criteria for the diagnosis of dry eye for Sjögren Syndrome.<sup>20</sup> Grading of the extent of external disease was performed using a standardized scheme.

The Ocular Surface Disease Index (OSDI)<sup>21</sup> (Allergan Inc, Irvine, Calif) was used to quantify the effect of dry eye on quality of life, including gritty or painful eyes, limitation in performance of common activities, such as reading and working on a computer, and the effect of environmental triggers, such as wind, on dry eye symptoms during a 1-week recall period. The effect of dry eye on activities of daily living and visual functioning was determined using the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25).<sup>22,23</sup> Responses to the questionnaires were scored using the methods described by the authors of these instruments.<sup>21,24</sup> For the NEI-VFQ, subscale scores for general vision, ocular pain, near vision, distance vision, social functioning, mental functioning, role functioning, dependency, driving, color vision, and peripheral vision, as well as an overall score, were computed. The NEI-VFQ scores can range from 0 to 100, with lower scores indicating more problems or symptoms. For the OSDI, 3 subscales for ocular discomfort, visual functioning, and environmental triggers were computed, as well as an overall score. The OSDI scores can range from 0 to 100, with higher scores indicating more problems or symptoms.

Preliminary analyses were performed, adjusting for age and race. Because of a racial imbalance between the controls and

the other 2 groups, we retained race (grouped as black/Hispanic/other vs white) as a potential confounder in all subsequent analyses. Logistic regression models (SAS version 8.02; SAS Institute, Cary, NC) were used to perform comparisons between controls and patients.  $\chi^2$  or Fisher exact tests were used to compare proportions in  $2 \times \kappa$  contingency tables. Spearman correlation coefficients were computed to assess the strength of the linear relationship between pairs of variables. All participants answered that they had "no difficulty at all" with the single color vision item on the NEI-VFQ, so this subscale was not included in the analyses.

## RESULTS

The basic demographic and visual acuity characteristics of participants in the 2 groups are presented in **Table 1**. As expected, the age distributions did not differ between the 2 groups. However, the controls had markedly more black (39%) and other (22%) participants compared with the POF group. Ninety-one percent of women with POF had a visual acuity of 20/20 or better in the better eye compared with 94% of controls. Visual acuity in the worse eye was somewhat worse in patients than in controls: 22% had a visual acuity worse than 20/20 vs 14% of controls ( $P = .41$ ).

### PHYSICAL EVIDENCE OF DRY EYE

Mean values for ocular surface and tear film parameters are presented in **Table 2**. Women with POF had worse mean scores than controls on all measures of ocular surface damage: total Oxford score ( $P = .001$ ), conjunctival lissamine green ( $P = .02$ ), corneal fluorescein staining ( $P < .001$ ), and total van Bijsterveld score ( $P = .02$ ). The percentages of patients with abnormal ocular surface and tear parameters are presented in **Table 3**. Thirteen (20%) of 65 women with POF had a van Bijsterveld score greater than or equal to 4 compared with 1 (3%) of 36 controls ( $P = .02$ ). Furthermore, significantly more POF patients (38%) showed abnormal corneal fluorescein staining (score  $> 1$ ) than did controls (8%) ( $P < .001$  after adjustment for race and age). In addition, significantly more women with POF (30/45 [67%]) demonstrated eyelid margin erythema than controls (11 [31%] of 36;  $P = .03$ ). The proportion of women with any meibomian gland plugging was similar in each group (controls: 36%, POF: 40%). The mean tear breakup time, Schirmer 1, and Schirmer 2 did not differ between women with POF and controls. Although women with POF were roughly twice as likely to have a Schirmer 1 score less than or equal to 5 mm (23% vs 11%), this difference was not statistically significant. The proportion of women with POF that met the past and current European Community Study Group on Classification Criteria for Sjögren syndrome dry eye<sup>25</sup> (van Bijsterveld  $\geq 4$  and/or Schirmer 1 score  $\leq 5$  mm) was greater than that of controls (37% vs 22%), although this difference was not statistically significant ( $P = .19$ ). No significant differences in the percentage with tear film debris were observed.

### SELF-REPORTED SYMPTOMS

Comparisons of the OSDI and NEI-VFQ subscales were done for patients vs controls (**Table 4**). After adjusting

**Table 1. Characteristics of Participants\***

	Controls (n = 36)	POF Patients (n = 65)
Age, mean (range), y	33 (21-41)	34 (17-43)
Race		
Black	14 (39)	11 (17)
White	14 (39)	49 (75)
Other	8 (22)	5 (8)
Visual acuity		
Worse eye		
20/20+	31 (86)	41 (78)
20/25 and worse	5 (14)	14 (22)
Better eye		
20/20+	34 (94)	59 (91)
20/25 and worse	2 (6)	6 (9)

Abbreviation: POF, premature ovarian failure.

\*Data are given as number (percentage) of patients unless otherwise indicated.

for age and race, OSDI scores for all 3 subscales and the overall scale were significantly higher (worse) for patients than for controls. These significant differences in OSDI scores did not change when adjustment was made for any of the ocular surface or tear parameters (Oxford, lissamine green, corneal fluorescein staining, van Bijsterveld, Schirmer 1 or 2, and tear breakup time) (data not shown). For the NEI-VFQ overall scale and subscales, general vision, ocular pain, near vision, distance vision, mental functioning, and driving, POF patients had significantly lower (worse) scores than did controls. Scores on the NEI-VFQ subscales remained significantly worse for patients than for controls after adjustment for the ocular surface and tear parameters that differed significantly between patients and controls (total Oxford, conjunctival lissamine green, corneal fluorescein staining, and total van Bijsterveld scores) (data not shown). Compared with controls, patients ( $n = 22$ ) had significantly worse mean responses to both of the visual analog questions, "how dry do your eyes feel most of the time?" (29 vs 3;  $P = .004$ ), with responses ranging from 0 = not dry at all to 100 = very dry, and "how often do you experience burning, stinging, or grittiness of your eyes?" (18 vs 2;  $P = .003$ ), with responses ranging from 100 = most of the time to 0 = never, even after adjustment for age and race.

### CONDITIONS ASSOCIATED WITH DRY EYE

Of those patients who ever used contact lenses, the proportion who discontinued use did not statistically significantly differ between the groups (control: 3/7 [43%]; POF: 12/31 [39%]). In addition, the proportion who discontinued contact lens use because of dryness did not differ between the groups (1 [33%] of 3 controls vs 5 [42%] of 12 patients). Use of tear substitutes or lubricating ointments was, however, statistically significantly more common among patients (21/65 [32%]) than among controls (1/36 [3%];  $P = .001$ ). This association did not change after adjustment for age and race ( $P = .007$ ). The women with evidence of ocular surface damage (van Bijsterveld  $\geq 4$ ) compared with those without were sig-

**Table 2. Ocular Surface and Tear Film Characteristics**

Outcome Measure	Controls (n = 36), Mean (Range)	POF Patients (n = 65), Mean (Range)	Control vs POF Patients, OR* (95% CI)	P Value†
Oxford‡ score				
Total	1.7 (0-6)	3.2 (0-8)	0.62 (0.46-0.83)	.001
Conjunctiva	1.3 (0-5)	2.1 (0-6)	0.70 (0.52-0.95)	.02
Cornea	0.42 (0-2)	1.17 (0-4)	0.37 (0.21-0.65)	<.001
Total van Bijsterveld‡	1.3 (0-4)	2.1 (0-7)	0.67 (0.48-0.95)	.02
Schirmer 1, mm§	13.2 (0-35)	16.0 (0-35)	0.99 (0.95-1.03)	.6
Schirmer 2, mm§	9.6 (1-28)	10.4 (0-35)	1.00 (0.95-1.06)	.99
TBUT§, s	7.0 (2.3-10)	6.3 (2.0-10)	1.13 (0.96-1.33)	.14

Abbreviations: CI, confidence interval; OR, odds ratio; POF, premature ovarian failure; TBUT, tear breakup time.

\*The OR of 0.62 indicates that every 1-step increase on the Oxford scale reduces the odds of being normal by 38%; ie, that POF patients tend to have higher Oxford scores. A 95% CI that includes 1.0 indicates that the OR does not differ significantly from 1.0; ie, that scores do not differ between the comparison groups.

†Logistic regression model adjusted for age and race.

‡Maximum (worse) score for the 2 eyes of an individual.

§Minimum (worse) score for the 2 eyes of an individual.

**Table 3. Participants With Abnormal Ocular Surface and Tear Film Parameters\***

	Controls	POF Patients	P Value
Tear breakup time <5 s	11/36 (31)	22/62 (35)	.78
Tear breakup time <10 s	24/36 (67)	49/62 (79)	.26
Schirmer 1 ≤5 mm	7/36 (19)	15/65 (23)	.86
van Bijsterveld score ≥4	1/36 (3)	13/65 (20)	.02†
Meets Sjögren syndrome dry eye criteria <sup>26</sup>	8/36 (22)	24/65 (37)	.19
Oxford score ≥5	2/36 (6)	19/65 (29)	.01
Meibomian gland plugging >0	13/36 (36)	26/65 (40)	.86
Eyelid margin erythema >0	11/36 (31)	36/65 (55)	.03
Tear film debris >0	5/36 (14)	19/64 (30)	.12
Conjunctival erythema >0	27/36 (75)	42/62 (68)	.60
Conjunctival chemosis >0	5/36 (14)	9/62 (15)	.83

\*Values are given as number (percentage) of participants.

†Fisher exact test, 2-tailed.

nificantly more likely to demonstrate positive anti-nuclear (6/13 vs 9/51;  $P=.04$ ) and antiadrenal (2/13 vs 0/50;  $P=.04$ ) autoantibodies but not thyroid peroxidase or parietal autoantibodies. The frequency of clinically apparent autoimmune disease was low and did not differ between the 2 groups.

### SELF-REPORTED SYMPTOMS AND CLINICAL SIGNS

We examined the associations between the objectively measured ocular surface and tear parameters and the subjective OSDI and NEI-VFQ scores using various analytic methods, including Spearman correlation coefficients for the continuous variables and Kruskal-Wallis tests for differences in the median OSDI (or NEI-VFQ) score among groups defined according to severity of ocular surface disease (eg, none, mild, severe). Within the POF group, the following showed significant association: worse near vision with lower (more abnormal) tear breakup time ( $r=0.33$ ;  $P=.01$ ) and worse peripheral vision with lower Schirmer 1 score ( $r=0.31$ ;  $P=.02$ ). Within

the control group, there were no associations between any of the objective parameters (Oxford, Lissamine green, corneal fluorescein staining, van Bijsterveld, Schirmer 1 or 2, or tear breakup time) and OSDI scores (nearly all  $r$  values were  $<0.2$ ). Although there was a consistently significant association of lower (more normal) Oxford score with better driving scores among the controls, it should be noted that only 2 controls had abnormal Oxford scores.

### COMMENT

The women with POF showed significantly more severe ocular surface damage than controls on all grading scales and scored significantly worse on all of the dry eye symptom assessments and the visual function questionnaire. Further, a larger proportion of POF patients met a diagnostic criterion for dry eye by the severity of ocular surface vital dye staining (van Bijsterveld score  $\geq 4$ ) than did controls; however, aqueous tear production, as measured by the Schirmer test, was not significantly different between the groups.

Sex hormone messenger RNAs, proteins, and receptors have been found in ocular tissues, including the cornea, conjunctiva, meibomian glands, lacrimal gland acinar cells, and retinal pigment epithelium.<sup>26-33</sup> Estrogens in general are immune response stimulators, and androgens act as immunosuppressors.<sup>34</sup> Sullivan et al<sup>35</sup> have proposed that androgen insufficiency contributes to meibomian gland dysfunction, tear film instability, and evaporative dry eye in menopause, aging, Sjögren syndrome, complete androgen insensitivity syndrome, and antiandrogen use. Hykin and Bron<sup>36</sup> have documented increased meibomian gland disease and evaporative tear deficiency in postmenopause and with aging. In addition, androgens and estrogens can have profound effects on both the cellular and humoral immune systems. For example, androgens can enhance T-cell suppressor activity and decrease autoreactive antibody formation.<sup>37</sup> This may be one of the reasons that autoimmune diseases are more common in women than in men.<sup>38</sup> The exact pathologic mechanisms of POF remain unclear; however, there is evidence that autoim-

**Table 4. OSDI and NEI-VFQ Scores**

	Controls (n = 36), Mean (Range)	POF Patients (n = 65), Mean (Range)	Control vs POF Patients, OR* (95% CI)	P Value†
<b>OSDI</b>				
Ocular discomfort	2.1 (0-33.3)	15.4 (0-62)	0.87 (0.81-0.94)	<.001
Visual function	1.4 (0-20.8)	10.0 (0-83)	0.85 (0.76-0.95)	.006
Environmental triggers	3.5 (0-41.7)	15.3 (0-88)	0.94 (0.89-0.99)	.013
Overall	2.1 (0-14.6)	12.5 (0-67)	0.82 (0.73-0.92)	<.001
<b>NEI-VFQ</b>				
General vision	95 (80-100)	89 (40-100)	1.07 (1.02-1.13)	.01
Ocular pain	96 (62-100)	85 (50-100)	1.10 (1.04-1.17)	.001
Near vision	99 (92-100)	96 (67-100)	1.21 (1.03-1.42)	.02
Distance vision	98 (83-100)	92 (50-100)	1.12 (1.03-1.22)	.01
Social function	100 (all 100)	99 (62-100)	1.38 (<.001-∞)	.99
Mental function	98 (88-100)	91 (19-100)	1.15 (1.04-1.28)	.009
Role function	98 (75-100)	94 (50-100)	1.06 (0.98-1.14)	.13
Dependency	100 (all 100)	98 (50-100)	3.78 (<.001-∞)	.95
Driving	97 (88-100)	92 (62-100)	1.15 (1.05-1.25)	.002
Peripheral vision	98 (50-100)	97 (50-100)	1.02 (0.96-1.08)	.6
Overall	98 (93-100)	94 (60-100)	1.47 (1.17-1.84)	.001

Abbreviations: CI, confidence interval; NEI-VFQ, National Eye Institute Visual Function Questionnaire; OR, odds ratio; OSDI, Ocular Surface Disease Index.  
\*Logistic regression model adjusted for age and race.

munity may play a role in some cases. For example, POF can be seen in autoimmune polyglandular syndrome type I, a disorder characterized by the destruction of endocrine glands, impaired cellular immunity, and ectodermal dystrophy.<sup>39</sup> In contrast, a mutation in *FOXL2*, a forkhead transcription factor gene that causes blepharophimosis-ptosis-epicanthus-inversus syndrome may be associated with POF.<sup>40</sup> None of the patients in our study demonstrated any eyelid abnormalities. Local ocular disruption of sex hormone homeostasis or androgen deficiency alone may be responsible for the ocular surface disease that we found in women with POF. A common genetic factor could be responsible for both the ovarian and ocular disease; perhaps a shared structural protein or other factor is required to maintain both developing ovarian follicles and a stable tear film and healthy ocular surface. It is possible that the dry eye phenotype may signal a particular cause of POF since not all patients had dry eye.

Our study had several limitations. There were more white women in the POF group than in the control group; however, to date, there is no evidence for a racial difference in the prevalence of dry eye. Furthermore, adjustment for race did not modify any of the differences we found between the groups. The average tear breakup time in 129 normal women aged 20 to 24 years has been reported as 18.9 seconds.<sup>41</sup> While the mean tear breakup time of 6.3 seconds in our POF group is less than these previously published values, this difference may have been due to our method of coding values greater than or equal to 10 seconds as 10. There are few publications that document sex- and age-specific data for normal tear production, and most studies have shown that Schirmer test results are highly variable. Normal scores on the Schirmer test with anesthesia have been reported to range from 23.71 mm (range, 14-30 mm) in normal men and women<sup>42</sup> to 33.3 mm in a sample of 48 normal Indian women.<sup>43</sup> Feldman and Wood<sup>44</sup> found wide variability in scores

on the Schirmer test with anesthesia in 10 healthy women (age range, 19-38 years) tested daily for 30 days; mean values ranged from 8.5 to 21 mm, and SDs ranged from 2.7 to 7.6. The mean tear production in our controls (Schirmer 1 = 13.2 mm, Schirmer 2 = 9.6 mm) was lower than we expected for healthy young women with no history of ocular disease. These findings may indicate that the published normal values for these measures are not applicable to women in the 18- to 40-year-old age group, or that our controls or procedures were different from those in published studies. However, this difference would tend to make the controls appear more like dry eye cases, thus tending to diminish any associations observed (ie, any bias would be in a conservative direction).

The women with POF and dry eye in this study had somewhat better scores on the overall NEI-VFQ and OSDI than those published for dry eye cases. In a previous study of 75 patients with dry eye evaluated with the NEI-VFQ,<sup>45</sup> the mean ± SD overall score was 87.9 ± 8.4, and the mean ocular pain score was 69.5 ± 18.7. In our study, the women with POF who met the more stringent diagnostic criteria for Sjögren syndrome–related dry eye (Schirmer I ≤ 5 mm and/or van Bijsterveld ≥ 4) had a somewhat higher (better) mean NEI-VFQ overall score of 93 ± 7. However, their mean ± SD ocular pain subscale score was 82 ± 15, lower (worse) than reported scores for patients with cataract (86 ± 19)<sup>46</sup> and low vision (97.3 ± 8.3).<sup>47</sup> For women with POF meeting the same criteria, the overall mean ± SD OSDI score was 12.2 ± 13.3, lower (better) than the published overall OSDI scores for 83 patients with mild to moderate dry eye (18.1 ± 17.1).<sup>21</sup>

We found an increased prevalence and severity of both signs and symptoms of ocular surface disease in patients with karyotypically normal spontaneous POF compared with age-matched normal women. The dysregulation of sex hormones or immunologic dysfunction seen in POF may play a role in the pathogenesis of the ocular surface disease. Epithelial dysfunction or lacrimal gland

disease may play a role. An abnormality in tear composition likewise could result in the corneal and conjunctival damage seen. The key role of sex hormones in ocular surface homeostasis is further supported by these findings; however, the specific pathophysiologic mechanisms involved in dry eye in POF remain to be determined. Additional studies are needed to further characterize the pathologic mechanisms of dry eye in POF.

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