The effects of different hormone replacement therapy regimens on tear function, intraocular pressure and lens opacity

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Abstract

Objective. Estrogen may have adverse effects on the ocular surface, intraocular pressure (IOP), lens opacity and tear function. The aim of the present study was to elucidate the effects of different hormone replacement therapy (HRT) protocols on tear function, IOP and lens opacity.

Design and setting. This was a prospective, uncontrolled study carried out at the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Faculty of Medicine, Uludağ University, Turkey.

Patients and interventions. Thirty postmenopausal patients who had spontaneous or surgical menopause for at least 1 year and were not taking any medications were assigned to one of three groups. Group 1 comprised 19 patients (n = 38 observations) given conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg (Premelle 2.5®) daily; Group 2 contained six patients (n = 12 observations) given tibolone 2.5 mg (Livial®) daily; and Group 3 comprised five patients (n = 10 observations) treated with estradiol patch, 3.9 mg/12 cm² (Climara®). Tear function, evaluated with Schirmer’s test, IOP and lens opacity were determined before treatment and at 6 and 12 months of treatment.

Results. Mean Schirmer’s test score in each group and all eyes (n = 60) did not change significantly after 6 months of treatment but decreased significantly at 12 months. The percentage decrease in tear function was greatest in the estrogen-only group (Group 3). Mean IOP did not change significantly in Groups 1 and 2; however, in Group 3, IOP showed a statistically significant decrease from 14.63 ± 0.84 mmHg before treatment to 12.60 ± 0.68 mmHg (mean ± standard error) at the end of treatment. Lens opacity in women of all groups did not change during treatment.

Conclusions. HRT decreased tear production, the decrease being greater in the estrogen-only group. Woman who are taking or considering HRT should be informed of the potential increased risk of dry eye syndrome with this therapy. In addition, estrogen-only treatment decreased IOP while estrogen plus progesterone and tibolone had no effect. HRT did not affect lens opacity after 12 months of treatment.

Keywords: Hormone replacement therapy, Schirmer’s test, intraocular pressure, lens opacity, dry eye syndrome

Introduction

Hormone replacement therapy (HRT) is widely used; it has been shown to have a clear role in the treatment of a variety of menopausal symptoms and may confer other health benefits. Yet some deleterious effects of HRT are increasingly being recognized. The efficacy of HRT in recovery from dry eye symptoms and of tear function is currently under debate with regard to its therapeutic or promoting effect on this disease. HRT is also known to affect intraocular pressure (IOP) and lens opacity. Data suggest that changes in sex steroid levels may affect the physiology of eye and cause of the appearance of ocular symptoms [1–5]. However, there are insufficient data about the effects of HRT on the ocular system and results are contradictory. The presence of estrogen, progesterone and androgen receptors in this area could suggest a positive effect of HRT, but the role of these receptors is unclear at the present time – they could be doing nothing or even result in negative effects on tear function, IOP and lens opacity.
The aim of the present study was to elucidate the effects of different HRT protocols on tear function, IOP pressure and lens opacity.

**Materials and methods**

The study was planned as prospective and uncontrolled, and was conducted between February 1, 2000 and February 1, 2002 at the menopause outpatient clinic of the Department of Obstetrics and Gynecology and the Department of Ophthalmology, Uludağ University, Faculty of Medicine, Turkey. Thirty postmenopausal patients, who had spontaneous or surgical menopause for at least 1 year and were not taking any medications which could affect the ocular system, were included in the study. Menopause was confirmed by gonadotropin and estradiol levels. None of the patients took any form of HRT for at least 6 months prior to the study. In addition, all patients had normal renal, hepatic and thyroid functions, and none of them were diabetic or chronic hypertensive.

The patients were assigned to one of three different groups. Group 1 comprised 19 patients (n = 38 observations) given conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg (Premelle 2.5®; Wyeth, Philadelphia, USA) daily; Group 2 contained six patients (n = 12 observations) given tibolone 2.5 mg (Livial®, Organon, Amsterdam, The Netherlands) daily; and Group 3 comprised five patients (n = 10 observations) treated with estradiol patch, 3.9 mg/12 cm² (Climara®, Schering, Berlin, Germany).

Tear function was evaluated with Schirmer’s test, IOP was measured and lens opacity was examined in the Department of Ophthalmology by the same ophthalmologist (R.A.) before treatment and after 6 and 12 months of treatment.

The Schirmer test was done by placing the folded end of a Whitman filter paper strip (Alcon Laboratories, Fort Worth, Texas) gently over the lower palpebral conjunctiva at its lateral third. After 5 min, the strip was removed and the amount of wetting was measured from the folded end. Schirmer’s test is a valid indicator of lacrimal secretion at the clinical level. IOP was measured using a Goldman applanation tonometer (HAAG-STREIT, Bern, Switzerland). Lens opacity was determined as visual inspection.

**Statistical analysis**

Data were analyzed using the Wilcoxon signed ranks test and the Mann–Whitney test. Values are expressed as mean ± standard error of the mean (SEM). SPSS software (SPSS Inc., Chicago, IL, USA) was used for calculations. Significance was accepted at p < 0.05.

**Results**

Mean age of the patients was 48.3 ± 0.59 years in Group 1, 51.83 ± 1.62 years in Group 2 and 51.40 ± 2.58 years in Group 3; the groups were homogeneous.

At the beginning of the study, there were no statistically significant differences between the groups regarding mean Schirmer’s test score. After 6 months of treatment, mean Schirmer’s test score remained unchanged for each group and in all eyes (n = 60), indicating that HRT did not affect tear function during this period. However, after 12 months of treatment, mean Schirmer’s test score decreased significantly in each group and for all eyes (n = 60). The percentage decrease in tear function was greatest in the estrogen-only group (Group 3) (Table I).

Mean IOP increased slightly in Group 1, but not statistically significantly so, from 13.84 ± 0.43 mmHg at the beginning of treatment to 14.18 ± 0.39 mmHg after 12 months of treatment. In Group 2, IOP did not change during treatment. In Group 3, IOP decreased from 14.63 ± 0.84 mmHg before treatment to 12.60 ± 0.68 mmHg at the end of treatment, which was statistically significant (Table II).

Lens opacity in women of all groups did not change during treatment.

**Discussion**

HRT is most commonly prescribed for the relief of vasomotor symptoms among postmenopausal women in the treatment of short-term problems and the prevention of long-term complications of menopause. Since sex steroid receptors are present in lacrimal gland, acinar epithelial cells of the lacrimal gland, meibomian gland, lid, palpebral and bulbar conjunctiva, cornea, iris/ciliary body, lens, retina/uvuea, retina/choroids and retinal pigment epithelial cells of rats, rabbits and humans, the eye may be susceptible to hormone action following either local synthesis and/or topical or systemic application [1,6–11]. Epidemiological studies have shown that some eye complaints are most common in women, a finding that would be consistent with either a detrimental effect of estrogen or a beneficial role of androgens, or both [2]. There are insufficient data in the literature about the effects of HRT on the eye.

In the present study we aimed to elucidate the effect of different HRT regimens on the eye, mainly tear function, IOP pressure and lens opacity. Dry eye syndrome damages the ocular surface and can cause debilitating symptoms or dryness and irritation. The literature contains a few prospective and epidemiological studies that directly assess the potential relationship of exogenous estrogen use with dry eye syndrome. A reduction of important ocular...
surface parameters such as tear production and stability has been found in postmenopausal women, and HRT has been shown by some authors to recover Schirmer test values in the normal range [12–14], although others did not report any role of HRT in tear production [15]. Two studies found no statistically significant relationship of HRT with the presence of self-reported dry eye symptoms [2,16]. Contrary to these reports, an epidemiological study carried out on more than 25,000 patients has considerably revised the true efficacy of HRT in improving dry eye symptoms and recovering tear function [3]. It was shown that women who never used HRT had the lowest prevalence of dry eye syndrome. Women who used estrogen alone had the highest prevalence and women who used a combination of estrogen plus progesterone had a prevalence that was intermediate between never users and users of estrogen alone. After adjusting for age and randomized treatment assignments, HRT was still significantly associated with clinically diagnosed dry eye syndrome for estrogen alone (odds ratio (OR) = 1.70) and for estrogen plus progesterone (OR = 1.30). Compared with no HRT use, the multivariable-adjusted OR for the combined endpoint of clinically diagnosed dry eye syndrome or severe symptoms was 1.69 for estrogen use alone and 1.29 for estrogen plus progesterone use. All these studies have analyzed a significant but limited number of patients, and moreover generally do not discuss whether differences in the response to treatment can be attributed to the type hormones, dose of therapy, way or time of administration. All of these parameters should be considered in the perspective to find a method (not yet currently available) to set HRT use on the basis of objective patient characteristics. In our study, the mean Schirmer's test score was 22.53 ± 1.13 in all patients at the beginning of the study. At 6 months of treatment, there was no statistically significant change in the mean score. However, after 12 months of treatment the score decreased significantly. According to these results, it can be said that HRT decreases tear production. These findings support the results of other studies in the literature showing the longer the duration of HRT, the higher the risk of dry eye syndrome.

When we analyzed the subgroups, we found that tear production did not change significantly in each group at 6 months but that it decreased significantly in each group at 12 months. The percentage decrease was greater in the estrogen-only group than in the groups receiving tibolone and estrogen plus progesterone.

Since laboratory and preliminary clinical studies suggest that androgens have a beneficial influence on lacrimal and meibomian gland function, and estrogen is known to have inhibitory effects on other sebaceous glands, the results of our study are not surprising [17–19]. The most interesting point of our study was the finding that tibolone has a negative effect on tear production. We were expecting tibolone to have a beneficial effect on tear production because of its androgenicity. According to our results, woman who are taking or considering HRT should be informed of potential increased risk of dry eye syndrome with this therapy.

Another important point is the relationship between IOP and HRT. The incidence of glaucoma is much higher in men than woman under 50 years of age. This difference between the sexes becomes less pronounced after this age, which leads to a relationship between IOP and estrogen [20–22]. It has been reported that the endothelium in ophthalmologic vessels influences local vascular tone by releasing nitric oxide. Since estradiol increases nitric oxide

### Table I. Mean Schirmer’s test scores of the study groups before and after 6 and 12 months of hormone replacement therapy.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n = 12)</th>
<th>Group 3 (n = 10)</th>
<th>Total population (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>23.81 ± 1.38</td>
<td>21.91 ± 2.36</td>
<td>18.41 ± 3.20</td>
<td>22.53 ± 1.13</td>
</tr>
<tr>
<td>After 6 months</td>
<td>23.73 ± 1.27</td>
<td>21.58 ± 1.73</td>
<td>17.90 ± 2.40</td>
<td>22.33 ± 0.99</td>
</tr>
<tr>
<td>After 12 months</td>
<td>20.28 ± 1.84</td>
<td>19.25 ± 1.55</td>
<td>14.60 ± 1.10</td>
<td>19.13 ± 0.74</td>
</tr>
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</table>

$n$, number of observations; Group 1, women received conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg (Premelle 2.5®); Group 2, women received tibolone 2.5 mg (Livial®); Group 3, women were treated with estradiol patch, 3.9 mg/12 cm² (Climara®); data are expressed as mean ± standard error of the mean.

### Table II. Mean intraocular pressures (mmHg) of the study groups before and after 6 and 12 months of hormone replacement therapy.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n = 12)</th>
<th>Group 3 (n = 10)</th>
<th>Total population (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>13.84 ± 0.43</td>
<td>15.08 ± 0.59</td>
<td>14.63 ± 0.84</td>
<td>14.21 ± 0.33</td>
</tr>
<tr>
<td>After 6 months</td>
<td>14.07 ± 0.34</td>
<td>15.16 ± 0.54</td>
<td>14.34 ± 0.44</td>
<td>14.33 ± 0.25</td>
</tr>
<tr>
<td>After 12 months</td>
<td>14.18 ± 0.39</td>
<td>15.58 ± 0.77</td>
<td>12.60 ± 0.68</td>
<td>14.20 ± 0.33</td>
</tr>
</tbody>
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$n$, number of observations; Group 1, women received conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg (Premelle 2.5®); Group 2, women received tibolone 2.5 mg (Livial®); Group 3, women were treated with estradiol patch, 3.9 mg/12 cm² (Climara®); data are expressed as mean ± standard error of the mean.
synthase in the endothelium, it seems that estrogen has an inevitable role in the regulation of IOP. The compromised ocular perfusion may contribute to the pathogenesis of this disease [23]. In animal and human studies, it has been observed that the vascular bed endothelium has specific estrogen-binding sites and that estrogen-dependent vasodilatation occurs owing to the blockage of calcium channels in vascular smooth muscle cells [24]. Progesterone antagonizes the estrogen-dependent vasodilatation and causes an increase in vascular resistance [25]. Reports in the literature have indicated that HRT reduces vascular resistance in either the central retinal artery or the ophthalmic artery, or both [26–30]. One study showed that IOP increased during the premenstrual period and decreased during ovulation [31]. Contrary to this study, another report showed that physiological changes associated with the menstrual cycle have no influence on IOP [32].

There is only one report in the literature showing that HRT, given as an oral dose of estradiol valerate 2 mg plus ten daily doses of medroxyprogesterone acetate 10 mg during the last ten days of each month of treatment, decreased IOP from 16.2 ± 2.0 to 14.0 ± 2.1 mmHg in the left eye and from 15.3 ± 2.3 to 14.0 ± 1.9 mmHg in the right eye after 12 weeks of therapy [33]. The authors concluded that HRT has a positive effect on IOP in menopausal women. Our results showed that estrogen alone decreased IOP in the postmenopausal period, while estrogen plus progesterone and tibolone had no effect.

Cataract is the most common eye disease of the elderly and a number of epidemiological studies using cross-sectional data have shown an increased prevalence of cataract in women compared with men. The cause of the gender differences in cataract occurrence is not clear but could be related to the hormone differences between women and men. The relationship between estrogen and cataract is unclear. A study conducted in 1992–93 found that later age at menarche was associated with increased prevalence of all types of cataract. According to these epidemiological data, estrogen may play a protective role in reducing the incidence of age-related cataract [34]. The patients in this study were re-examined after 5 years, with the finding that women who had ever used HRT had a decreased incidence of cortical cataract affecting any eye compared with never users (OR = 0.7) [35]. The protective mechanism of estrogen cataractogenesis is not clearly understood. One study reported a protective effect of estrogen in the rat model on age-related cataracts and concluded that it may be a direct receptor-mediated phenomenon [36]. In the Framingham studies, it was found that longer duration of estrogen use was associated with fewer posterior subcapsular opacities at a borderline level of significance [37]. A different study found a protective association between nuclear opacity and current recent HRT use [38], while another reported that current use of HRT was associated with lower odds of large drusen, which may be predictive of advanced of age-related macular degeneration [39]. In a population-based case–control study, estrogen-only and estrogen–progestrone HRT regimens were associated with a small reduced risk of cataract [40]. In our study, we did not find any difference in lens opacity after 6 and 12 months in all groups.

In conclusion, according to our results HRT decreased tear production. The percentage decrease was greater in the estrogen-only group. Woman who are taking or considering HRT should be informed of the potentially increased risk of dry eye syndrome with this therapy. Estrogen decreased IOP while estrogen plus progesterone had no effect on IOP. HRT did not affect lens opacity at the end of 12 months of treatment.

References