Hormone-Induced Changes on Women's Corneas

A decreased estrogen level may cause a steepening of corneal horizontal curvature.

BY ERDINC AYDIN, MD, AND HELIN DENIZ DEMIR, MD

Gender-related differences may play a role in the etiology of some diseases (eg, coronary disease, osteoporosis), drug sensitivities, and changes in tissue structures. In the eye, gender differences related to ocular anatomy and physiology have been investigated. A woman's ocular lens has a lower mass and shorter axial length compared with a man's. Traditional formulas for IOL power calculations, however, do not take gender into account.[1,2] With the development of corneal topography, the features of pathologic and normal corneas can be evaluated in detail. The criteria for separating normal from abnormal corneas are still uncertain, and gender-related factors have usually been ignored. In sum, gender should be considered when ophthalmologists inspect corneal topographies, calculate IOL power, and select refractive procedures.

CHANGES OBSERVED ON THE CORNEA OF HEALTHY WOMEN

Changes in corneal curvature, thickness, and sensitivity during the woman's menstrual cycle have been detected and attributed to endocrine influences.[3-5] The precise mechanisms underlying these changes remain controversial. Gonadal (ie, sex steroid) hormones may affect ocular tissue by classical genomic and rapid nongenomic pathways.[6] These hormones also take part in homeostasis and function of the cornea,[7] which are mediated by the alpha- and beta-estrogen, progesterone, and androgen receptors in the nuclei of human corneal epithelial, stromal, and endothelial cells.[8-10]

Plasma estrogen levels increase on two occasions during the menstrual cycle: ovulation and the luteal phase. Progesterone levels rise shortly before ovulation and rapidly during the luteal phase, until estrogen levels are paralleled. The main action of estrogen is on sodium and chloride balance and on the hydration of tissues; it enhances sodium reabsorption by the tissues leading to water retention and edema.[11] Estrogen and progesterone can readily gain access to the cornea via the aqueous humor or tear film due to their high lipid solubility[12] and exert their direct effect on the corneal tissue. An indirect effect on the cornea can also take place via their action on tear film osmolarity.

Estrogen and progesterone can gain access to the cornea via the aqueous humor or tear film and exert their direct effect on the corneal tissue.

Kiely et al[5] studied the changes in a woman's corneal curvature and demonstrated that a steepening occurs in both horizontal and vertical corneal meridians at the beginning of the menstrual cycle, and a flattening occurs after ovulation. Oliver et al,[13] however, reported no detectable temporal effect on corneal curvature due to the menstrual cycle. These conflicting findings are explained by the fact that irregular changes in thickness across the cornea may lead to alterations in curvature and aberrations.

Changes in corneal thickness have previously been shown to fluctuate with gonadal hormone levels.[3,14,15] Soni et al[14] reported that female corneas attained minimal thickness just before ovulation and maximal thickness at the beginning or end of the menstrual cycle. Giuffré et al[3] recently showed that corneal thick-

(Courtesy of Reichert, Inc.)

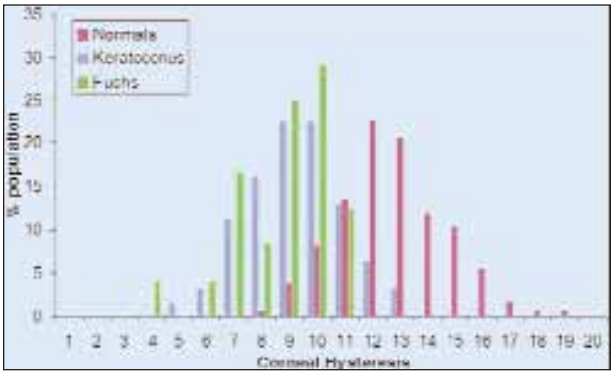
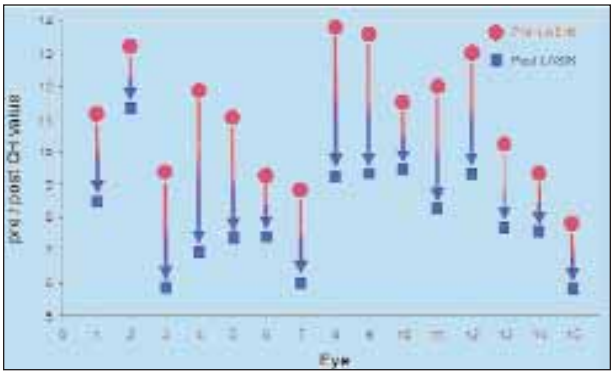


Figure 1. Comparison of corneal hysteresis distribution of normal, keratoconic, and Fuchs' patients.



(Courtesy of Reichert, Inc.)

Figure 2. Corneal hysteresis of 15 eyes pre- and post-LASIK.

ness immediately increased after two peaks of plasma estradiol occurred during the cycle.

A preovulatory peak in estrogen may cause decreased corneal sensitivity, which occurs just before or during ovulation. However, a change in corneal sensitivity prior to menstruation was not observed.[16]

In recent years, estrogen has been emphasized as a modulating factor in the biomechanic properties of the cornea. In experimental studies, porcine corneas that were incubated in culture medium with estradiol displayed almost twice the increase in corneal thickness as a group incubated in culture medium without estradiol (control group). When the biomechanic stress values at 10% strain were evaluated by Young's modulus, a 36% reduction in stiffness was detected in the estradiol-incubated group, which could not be explained by an increased swelling alone.[17]

> The ORA can be used to evaluate candidates for postsurgical complications.

Corneal biomechanics reflect more than central pachymetry. When there is little change in central pachymetry, profound changes in corneal rigidity can be seen. Biomechanic properties (eg, pachymetry, hydration, viscoelasticity) can change following LASIK flap creation and/or laser ablation and cause mismeasurement of postoperative intraocular pressure (IOP). A more accurate IOP measurement requires instruments that perform dynamic (rather than static) applanation measurements and therefore assess and

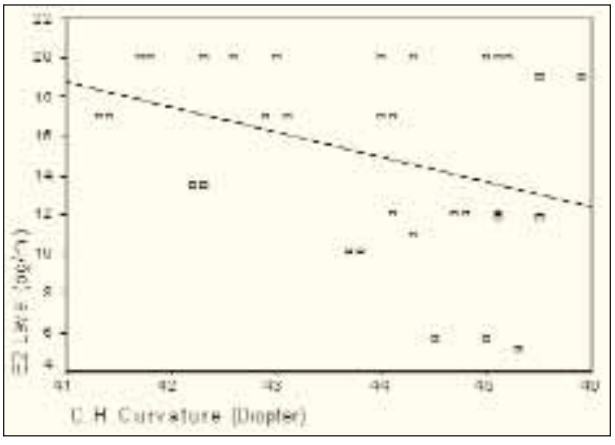


Figure 3. The reverse correlation between estradiol and corneal horizontal curvature in postmenopausal women.

compensate for the corneal biomechanics in this metric. These considerations become particularly important in patients who undergo corneal surgery (eg, LASIK, penetrating keratoplasty) or who have corneal pathology (eg, keratoconus, pellucid marginal degeneration) where both corneal thickness and rigidity vary. Two newer devices, the Ocular Response Analyzer (ORA; Reichert, Inc., Buffalo, New York) and the Pascal Dynamic Contour Tonometer (SMT Swiss Microtechnology AG, Port, Switzerland), may be helpful tools that provide more dynamic measurements. The ORA may provide refractive surgeons with corneal hysteresis to estimate the risk of developing future corneal disorders.

IMPORTANCE OF CORNEAL CHANGES

These corneal changes may result in miscorrections and further ectasia. Corneal ectasia is the most dreaded potential side effect in corneal refractive surgery and results from predisposed factors such as irregular

> We investigated a negative, but significant, correlation between estrogen levels and horizontal corneal curvatures in postmenopausal women.

corneal thickness, different ablation rates, and ultrasound pachymetry errors. The analysis of a pachymetry map and its relationship to corneal curvature patterns is critical to identify and provide additional data to alert the surgeon of a risk for ectasia.[18]

The ability of the ORA to characterize biomechanic properties of the cornea means that potential refractive surgery candidates can be more effectively evaluated for postsurgical complications such as corneal ectasia. It is a more effective predictor than central corneal thickness and topography alone (Figures 1 and 2).

CHANGES THAT EVOLVE ON A WOMAN'S CORNEA

Previous studies have reported that as a person ages, astigmatism changes from with-the-rule to against-the-rule.[19,20] Hayashi et al[21] evaluated age changes in corneal shape and detected that the average maps of patients aged from less than 20 years to 40 years showed a vertical bow-tie-rule astigmatism. In patients aged between 50 and 60 years, the central steep area gradually extended horizontally until it became a round configuration.

Until recently, no reports about corneal curvature changes in postmenopausal women were published. In our study, we did not find a significant astigmatic shift within pre- and postmenopausal groups; however, we did detect with-the-rule astigmatism in young patients and against-the-rule astigmatism in older patients. Mean astigmatism values were also similar between groups. No significant correlations were found among estrogen, progesterone, and corneal curvatures in premenopausal women.

SIGNIFICANT CORRELATION

On the other hand, we investigated a negative, but significant, correlation between estrogen levels and horizontal corneal curvatures in postmenopausal women[22] (Figure 3). With these findings, we speculated that a decrease in the estrogen level of women in the postmenopausal term may cause a steepening of corneal horizontal curvature. Refractive surgeons should keep these points in mind and consider precautionary measures in patients during their menstrual cycle or entering menopause. ■

Erdinc Aydin, MD, is an Associate Professor of Ophthalmology at the Gaziosmanpasa University School of Medicine, in Tokat, Turkey. Professor Aydin states that he has no financial interest in the products or companies mentioned. He may be reached at tel: +90 356 2129500; fax: +90 356 213 3179; or erdincaydin@yahoo.com.

Helin Deniz Demir, MD, is Assistant Professor at the Gaziosmanpasa University School of Medicine, in Tokat, Turkey. Dr. Demir states that she has no financial interest in the products or companies mentioned. She may be reached at tel: +90 356 2129500; fax: +90 356 213 3179; or helindeniz@hotmail.com.

1. Harding JJ, Rixon KC, Marriot FHC. Men have heavier lenses than women of the same age. *Exp Eye Res.* 1977;25:651.
2. Richards SC, Brodstein DE, Olson RJ, et al. differences between men and women as related to intraocular lens implantation. *Ophthalmic Surg.* 1986;17:82-87.
3. Giuffré G, Di Rosa L, Fiorino F, et al. Variations in central corneal thickness during the menstrual cycle in women. *Cornea.* 2007;26(2):144-146.
4. Leach NE, Wallis NE, Lothringer LL, Olson JA. *J Reproduct Med.* 1971;6(5):201-204.
5. Kiely PM, Carney LG, Smith G. Menstrual cycle variations of corneal topography and thickness. *Am J Optom & Physiol Optics.* 1983;60(10):822-829.
6. Gupta PD, Johar K Sr, Nagpal K, Vasavada AR. Sex hormone receptors in the human eye. *Surv Ophthalmol.* 2005;50:274-284.
7. Kovalevsky G. Female sexual dysfunction and use of hormone therapy in postmenopausal women. *Semin Reprod Med.* 2005;23:180-187.
8. Suzuki T, Kinoshita Y, Tachibana M, et al. *Curr Eye Res.* 2001;22:28-33.
9. Vecsei PV, Kircher K, Kaminski S, et al. Immunohistochemical detection of estrogen and progesterone receptor in human cornea. *Maturitas.* 2000;36:169-172.
10. Wickham LA, Gao J, Toda I, et al. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. *Acta Ophthalmol Scand.* 2000;78(2):146-153.
11. Bowman WC, Rand MJ, eds. Textbook of Pharmacology, 2nd ed. Oxford: Blackwell Scientific Publications, UK; 1980.
12 Schreiner WE. The ovary. In: Labhart A, ed. Clinical Endocrinology. Springer, NY, USA; 1997:511-665.
13. Oliver KM, Walsh G, Tomlinson A, et al. Effect of the menstrual cycle on corneal curvature. *Ophthal Physiol Opt.* 1996;16(6):467-473.
14. Soni PS. *Am J Optom & Physiol Optics.* 1980;57(11): 825-834.
15. Leach NE, Wallis NE, Lothringer LL, Olson JA. Corneal hydration changes during the normal menstrual cycle-A preliminary study. *J Reproductive Medicine.* 1971;6(5):201-204.
16. Riss B, Binder S, Riss P, Kemeter P. Corneal sensitivity during the menstrual cycle. *Br J Ophthalmol.* 1982;66(2):123-126.
17. Zubaty V, Spoerl E, Reiskup-Wolf F, et al. Estrogen-induced changes of biomechanics of the cornea as a possible reason for keratectasia. Paper presented at the ARVO 2007 Meeting; Fort Lauderdale, Florida; May 6-10, 2007.
18. Albe E, Epstein D, Vinciguerra P. Prevention of Corneal Ectasia in Refractive Surgery. *Cataract & Refractive Surgery Today Europe.* 2007;2:43-45.
19. Kamiya S. Age-dependence of human corneal astigmatism and corneal radius Folia. *Ophthalmol Jpn.* 1984;35:2011-2018.
20. Sanders H. Age-dependence of human refractive errors. *Ophthalmic Physiol Opt.* 1981;1(3):159-174.
21. Hayashi K, Hayashi H, Hayashi F. Topographic analysis of the changes in corneal shape due to aging. *Cornea.* 1995;l4:527-532.
22. Aydin E, Deniz Demir H, Demirturk F, et al. Corneal topographic changes in premenopausal and postmenopausal women. *BMC Ophthalmology.* 2007;14:7-9.

CONTACT US

Send us your thoughts via e-mail to letters@bmctoday.com.