

# Variations in corneal biomechanical parameters and central corneal thickness during the menstrual cycle

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**PURPOSE:** To assess variations in the biomechanical properties and central corneal thickness (CCT) throughout the female menstrual cycle.

**SETTING:** Department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin Israel.

**DESIGN:** Case series.

**METHODS:** Young healthy women were prospectively recruited. Every participant was assessed at the beginning of the menstrual cycle, at ovulation, and at the end of the cycle. At every time point, corneal hysteresis (CH) and the corneal resistance factor (CRF) were measured with the Ocular Response Analyzer and the CCT was measured with an ultrasonic pachymeter.

**RESULTS:** Twenty-two eyes of 22 women (mean age 19.5 years  $\pm$  1.5 [SD]) were included. The CH was statistically significantly decreased at ovulation (10.1 mm Hg) compared with the beginning (11.1 mm Hg,  $P < .001$ ) and the end (11.4 mm Hg,  $P < .001$ ) of the cycle. The CRF was also significantly decreased at ovulation (9.8 mm Hg) compared with the beginning (10.6 mm Hg,  $P < .001$ ) and the end (10.5 mm Hg,  $P < .001$ ) of the cycle. The central cornea was thinnest at the beginning (535  $\mu$ m) and statistically significantly thicker at ovulation (542  $\mu$ m,  $P < .001$ ) and at the end of the menstrual cycle (543  $\mu$ m,  $P < .001$ ).

**CONCLUSIONS:** The CCT and biomechanical parameters significantly varied during the menstrual cycle. The CH and CRF were temporarily decreased at ovulation. The cornea was thinnest at the beginning and thicker at ovulation and at the end of the cycle. Such corneal changes may be important to consider during screening of candidates for laser refractive surgery.

**Financial Disclosure:** No author has a financial or proprietary interest in any material or method mentioned.

*J Cataract Refract Surg 2011; 37:1507–1511 © 2011 ASCRS and ESCRS*

The cornea of women can be influenced by hormonal changes that occur during the monthly menstrual cycle. Indeed, cyclic variations in corneal topography and corneal thickness have been described.<sup>1–3</sup> These changes are probably driven by the direct interaction of sex hormones with sex hormone receptors located in the human cornea.<sup>4,5</sup>

The Ocular Response Analyzer (ORA) (Reichert, Inc.) can be used to assess in vivo corneal biomechanical properties, which are presented by 2 parameters—corneal hysteresis (CH) and the corneal resistance factor (CRF). Incorporation of this device into the screening process of laser refractive candidates was recently proposed.<sup>6</sup> Conceptually, aggregate analysis of these biomechanical parameters together with corneal thickness

and topographic characteristics can be used for improving screening for corneal ectasia before performing laser refractive surgery. It has been shown that examination of young healthy women at different time points during the menstrual cycle may yield varying results of corneal pachymetry and topography due to their cyclic fluctuations.<sup>1–3</sup> Behavior of ORA parameters during the menstrual cycle has not been described. The aim of our study was to evaluate whether there is a variation in corneal biomechanical properties measured by ORA during the menstrual cycle.

## SUBJECTS AND METHODS

Young healthy women were prospectively recruited from among the service staff of the Assaf Harofeh Medical Center.

The study was approved by the center's institutional review board, and written informed consent was obtained from each subject. The study protocol was consistent with the tenets of the Declaration of Helsinki. Inclusion criteria were age over 18 years, regular menstrual cycle lasting between 24 and 32 days, and no previous or concurrent pregnancy. The length of the menstrual cycle was defined as the number of days from the first day of menstrual bleeding to the day before the onset of the next bleeding. Excluded were subjects with known systemic disease, with known ophthalmic disorders, and with a refractive error exceeding  $\pm 3.00$  diopters or with any type of previous eye surgery. Subjects wearing contact lenses and those using contraceptive medications were also excluded.

Initially, every subject was invited for a screening interview during which inclusion and exclusion criteria were assessed. Slitlamp examination was performed to exclude anterior and posterior segment ocular pathology. Every participant was assessed at the beginning of the menstrual cycle, during ovulation, and at the end of the cycle. The beginning of the menstrual cycle was determined as the first days (days 1 to 3) of menstrual bleeding. The ovulation day was self-determined using a luteinizing hormone (LH) urine ovulation test (Senso-Test, Atlas Link, Inc.). This test detects the surge of LH in the urine, which occurs 24 to 36 hours before ovulation. The self-test kit is based on monoclonal enzyme immunoassay of LH in the urine. According to the manufacturer, this test has a reported LH sensitivity of as low as 15 mIU/mL and an accuracy of 98.7%.

Every woman was given an LH ovulation kit containing 7 tests. Subjects were instructed to begin using these tests daily according to a supplied table depending on the expected menstrual cycle length. Once the test was positive, the participants were asked to come for examination the next day. The end of the menstrual cycle was determined as 3 days before the anticipated next menstrual bleeding.

All participants had assessment with the ORA biomechanical waveform analyzer (version 1.10) that included noncontact measurement of corneal biomechanical parameters, CH and CRF, and assessment of intraocular pressure (IOP) (Goldmann-correlated IOP and corneal-compensated IOP). Reproducibility<sup>7</sup> and a detailed description<sup>8</sup> of this instrument have been published.

Three readings of good quality were obtained for each subject. Good quality was defined as readings having a waveform with 2 distinct peaks. The average for each parameter was recorded as previously described.<sup>7</sup>

The CCT was measured by the handheld ultrasonic pachymeter attached to the biomechanical waveform analyzer. One drop of topical oxybuprocaine hydrochloride 0.4% (Localin) was instilled, after which the examinee was asked to fixate on a target to minimize eye movements. The probe was gently placed in a perpendicular orientation on the central cornea. Three separate readings were made each time, and the mean value was recorded. To ensure that no subject had keratoconus, corneal topography was performed using a Pentacam Schempflug system (Oculus Optikgeräte GmbH). Only the right eye was examined. To avoid possible diurnal variations in measured parameters, all measurements were performed between 11 AM and 3 PM.<sup>9</sup>

### Statistical Analysis

Two kinds of linear mixed models were used to examine the influence of the time and subject effects on each dependent variable (CCT, CH, CRF, Goldmann-correlated IOP, and corneal-compensated IOP). Both models used time as fixed effect and subject as random effect. In the case of CH and CRF, the CCT, Goldmann-correlated IOP, and corneal-compensated IOP were used as effects in addition to the effect of time and subject.

In the first model, time functions as ordinal effect. Thus, the coefficients of its dummy variables express the marginal change in the dependent variable due to sequential change in time. In the second model, time functions as the nominal effect. Therefore, its dummy variables serve as indicators for each category of time in comparison to the base category; that is, the first one. Thus, the coefficients of its dummy variables express the marginal change in the dependent variable when changing to some category of time, with comparison to the base category. The distributions of values within each data set were evaluated graphically. A *P* value of 0.05 was selected for the threshold of statistical significance. Analyses were performed using JMP-8 statistical software (SAS Institute, Inc.).

### RESULTS

Twenty-two eyes of 22 women with a mean age of 19.5 years  $\pm 1.5$  (SD) were included. The mean menstrual cycle length was 28  $\pm 1.7$  days (range 26 to 31 days). The mean maximum keratometry (K) was 44.07  $\pm 1.7$  D (range 42.7 to 46.6 D). Table 1 shows the measurements of the biomechanical waveform analyzer parameters (CH, CRF, Goldmann-correlated IOP, and corneal-compensated IOP) and the CCT at the onset of the menstrual cycle, at ovulation, and at the end of the cycle. The central cornea was thinnest at the beginning and significantly thicker at ovulation and at the end of the cycle. Corneal hysteresis and the CRF were statistically significantly decreased at ovulation compared with the other 2 time points, with no statistically significant difference between the values at the beginning and the end of the cycle. Figures 1 to 3 show the distribution of these parameters during the menstrual cycle. The Goldmann-correlated IOP and corneal-compensated IOP were decreased at the

Submitted: October 22, 2010.

Final revision submitted: January 21, 2011.

Accepted: March 6, 2011.

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**Table 1.** Mean change in study parameters and intraindividual mean difference with range of differences during menstrual cycle.

Parameter	Mean $\pm$ SD			P value			Intraindividual Change	
	Onset	Ovulation	End	Onset Vs Ovulation	Ovulation Vs End	Onset Vs End	Mean Difference	Range of Differences
CCT ( $\mu$ m)	535 $\pm$ 40	542 $\pm$ 41	543 $\pm$ 42	.0001	.71	.0001	11.1	3, 29
CH (mm Hg)	11.1 $\pm$ 1.4	10.1 $\pm$ 1.1	11.4 $\pm$ 1.8	.001	.001	.17	1.6	0.2, 4.8
CRF (mm Hg)	10.6 $\pm$ 1.7	9.8 $\pm$ 1.6	10.5 $\pm$ 2.0	.001	.001	.92	1.3	0.5, 3.3
IOPcc (mm Hg)	14.3 $\pm$ 2.7	15.3 $\pm$ 3.9	13.6 $\pm$ 2.8	.15	.01	.31	3.7	0.1, 10.9
IOPg (mm Hg)	14.6 $\pm$ 3.2	14.9 $\pm$ 4.2	13.9 $\pm$ 3.1	.53	.05	.19	2.8	0.5, 7.7

CCT = central corneal thickness, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure

end of the cycle compared with the ovulation time point.

## DISCUSSION

We found significant changes in CCT and biomechanical parameters during the menstrual cycle. The CCT increased significantly between the beginning of the menstrual cycle and ovulation, with the increase maintained at the end of the cycle. Corneal hysteresis and the CRF were significantly decreased at ovulation compared with at the beginning and the end of cycle.

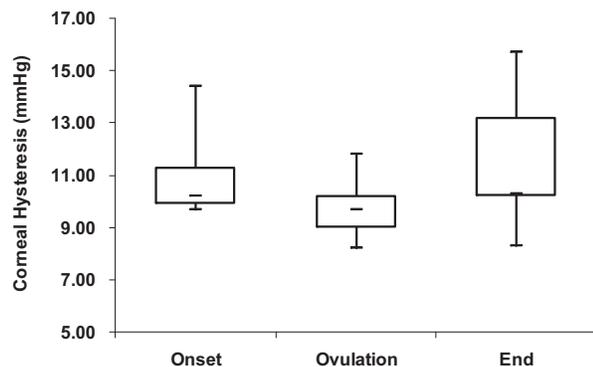
Similar to our findings, previous studies<sup>1-3</sup> report increased corneal thickness measured during ovulation and the end of the menstrual cycle. In a small study that included 6 women, Leach et al.<sup>1</sup> showed that the corneal thickness curve during the cycle closely paralleled the bimodal nature of the plasma estrogen levels and that the maximum thickening occurred close to ovulation. Kiely et al.<sup>2</sup> studied 6 women who were 19 years old and reported increased corneal thickness around ovulation and on day 21. In both studies, the time of ovulation was estimated based on previous cycles and was not precisely

determined using a hormonal assay. Results closely resembling ours were recently reported by Giuffrè et al.,<sup>3</sup> with the thinnest cornea observed at the beginning of the menstrual cycle, significantly greater thickness at ovulation and at the end of the cycle, and no significant difference between the last 2 time points.

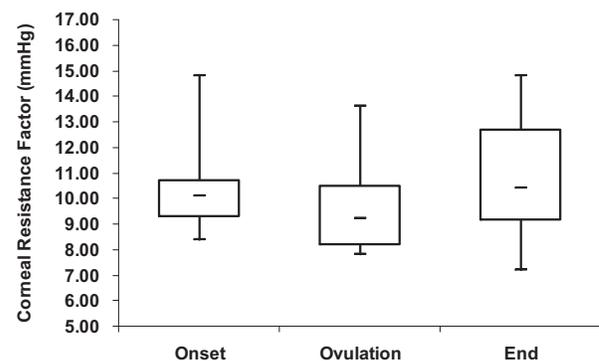
A weakness of our study is the relatively small study cohort. This problem is typical of other studies of ophthalmic changes during the menstrual cycle.<sup>1-3</sup> It is genuinely difficult to recruit young women who are not or have not been pregnant, have no hormonal abnormalities, are not using contraceptive medications, are free of ocular disease and are not using contact lenses, and are willing to commit to several self-assessments and study examinations during an entire menstrual cycle.

We used the urine ovulation test to recognize the LH peak as an accurate indicator of ovulation time. This determination of ovulation allows accurate comparison between subjects with different durations of menstrual cycle.

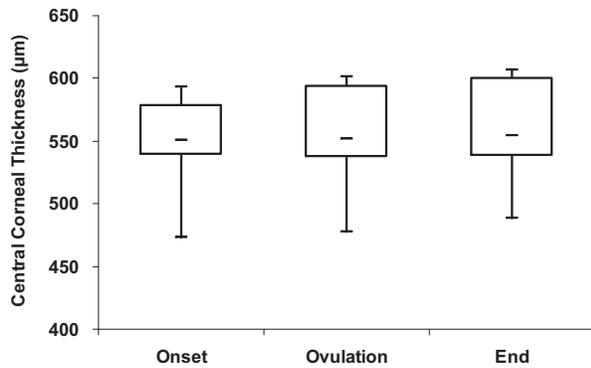
The menstrual cycle is characterized by variations in hormonal levels, specifically of estrogen and progesterone. The level of estrogen is minimal at the time of



**Figure 1.** Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing CCT ( $\mu$ m) at the onset, at ovulation, and at the end of the menstrual cycle.



**Figure 2.** Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing CH (mm Hg) at the onset, at ovulation, and at the end of the menstrual cycle.



**Figure 3.** Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing CRF (mm Hg) at the onset, at ovulation, and at the end of the menstrual cycle.

menstrual bleeding, gradually increases until reaching peak before ovulation, and then decreases again. Toward the end of the cycle, there is a second peak, lower than the one at ovulation. Through the tear film and aqueous humor, estrogen can reach estrogen receptors in the corneal epithelial, stromal, and endothelial cells,<sup>4,5</sup> potentially affecting corneal thickness and biomechanics. The known pattern of estrogen cycling parallel the observations in our study. Although corneal thickness increased concurrently with both estrogen peaks, biomechanical parameters significantly decreased concurrently with the major peak. Others have reported alterations in corneal parameters influenced by changes in estrogen level. In a cross-sectional study, Weinreb et al.<sup>10</sup> compared corneal thickness in 89 pregnant women with that in control eyes of 18 nonpregnant and 17 postpartum women. They showed that in the pregnant group, the cornea was significantly thicker than in both control groups. As mentioned above, the variations in corneal thickness, as observed by Giuffrè et al.<sup>3</sup> during the menstrual cycle, closely corresponded to the changes in the levels of estrogen. In an *in vitro* study, Spoerl et al.<sup>11</sup> showed that estrogen is a modulating factor of the biomechanical properties of the cornea that is not explainable by increased corneal swelling only. They used microcomputer-controlled biomaterial tester and an ultrasonic pachymeter to compare stress-strain measures and the thickness of 12 porcine corneas incubated in culture medium with estrogen with 12 porcine corneas incubated in culture medium without estrogen. After 7 days of incubation, corneas exposed to estrogen had a significant increase in thickness and reduced corneal stiffness.

These changes are presumably caused by increased corneal hydration together with estrogen-mediated changes in corneal cells and corneal extracellular matrix.<sup>1,4,11</sup> Similar biomechanical changes associated with estrogen have been reported in nonocular tissue.

In a study using rabbits, artificially induced high serum estrogen levels caused reduced biomechanical stiffness of the anterior cruciate ligament.<sup>12</sup> Fluctuations in carotid arterial elasticity during the menstrual cycle was reported in young women.<sup>13</sup> A study that evaluated the knee stability of young women during the menstrual cycle found increased knee joint laxity and decreased stiffness at ovulation.<sup>14</sup>

Decreased Goldmann-correlated IOP and corneal-compensated IOP values at the end of the cycle probably reflect increased corneal hydration rather than a true IOP decrease. Additional study using intracameral manometry may be needed to provide true IOP measurements and to assess real IOP changes.

Corneal hysteresis and the CRF are new parameters that assess corneal biomechanical properties.<sup>8</sup> These parameters are reported to be decreased in biomechanically weak corneas, as in keratoconus or after laser *in situ* keratomileusis.<sup>8,15-17</sup> Recently, it was proposed that these biomechanical parameters be used in addition to corneal thickness and topography for screening for corneal ectasia before laser refractive procedures.<sup>6,A</sup> Although measuring preoperative corneal thickness to evaluate residual stromal bed thickness or measuring CH to evaluate potential corneal effects of treatment is sensible, it must be known whether these parameters are constant or not in a given subject. Our study suggests that corneal thickness and biomechanical parameters vary during the menstrual cycle. With confirmation by further studies, this may have clinically significant implications for the timing of preoperative evaluation and perhaps even the timing of corneal surgical procedures as a function of the menstrual cycle. It is intriguing to speculate that the observed corneal changes may have implications for the results of corneal refractive procedures if they are found to be related to refractive regression or development of postoperative ectasia. As we showed, overestimation of the CCT and underestimation of hysteresis can occur if the data collection takes place only at the ovulation time point.

In conclusion, we observed significant variation in corneal thickness and biomechanical parameters during the normal menstrual cycle. We presume this variation is dependant on cyclical hormonal changes. Cyclical corneal alterations may have to be considered when planning corneal refractive surgery.

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