Relevant Factors of Estrogen Changes of Myopia in Adolescent Females

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Abstract

Background: Gender is one of the risk factors accounting for the high prevalence of adolescent myopia. Considerable research results have shown that myopia incidence of female is higher than that of male. This study aimed to analyze the correlation between ocular parameters and serum estrogen level and to investigate the vision changes along with estrogen change in menstrual cycle of adolescent females.
Methods: A total of 120 young females aged between 15 and 16 years, diagnosed with myopia were recruited. Spherical lens, cylindrical lens, axis, interpupillary distance (IPD), and vision in each tested eye of the same subject were measured by automatic optometry and comprehensive optometry, with repetition of all measurements in the menstrual cycle of the 2nd or 3rd days, 14th days, and 28th days, respectively. Serum estradiol (E_2) levels were assayed by chemiluminescence immunoassay at the same three times points of the menstrual cycle mentioned above.
Results: In young females with myopia, the spherical lens showed a statistically significant difference among all different time in menstrual cycle (all $P < 0.0001$). The cylindrical lens, axis, and IPD were changed significantly during the menstrual cycle ($P < 0.05$). The vision of the three different time points in menstrual cycle had a significant difference ($\chi^2 = 6.35$, $P = 0.042$). The vision during the 14th and 28th day was higher compared to that on the 2nd or 3rd days ($P = 0.021$). Serum E_2 levels were significantly different at different time points in menstrual cycle ($P < 0.05$). E_2 levels reached its maximum value on the 14th day and the minimum value on the 2nd or 3rd day.
Conclusions: In adolescent females, the spherical lens and other related ocular parameters vary sensitively with different levels of E_2 in menstrual cycle. Vision in late menstrual stage is significantly higher than that in premenstrual stage.

Key words: Adolescent Female; Estrogen; Menstrual Cycle; Myopia

Introduction

With the increasing dependence on smartphones, computers, and other electronic products, myopia has become the most common vision problem. In the latest nation-wide student physical health monitoring report,[1] the myopia percentage of 22% (nearly 400 million people) in China is 1.5 times of the world average level. In the high myopia group, the prevalence of adolescent myopia is as high as 70–80%. China is experiencing the highest incidence of myopia in the world, and the incidence also rises year by year. Poor vision can directly affect students' performance in school or at work and thus, will cause a negative influence on their future. Therefore, the prevention and control of adolescent myopia it is particularly important.[2] Genetic and environmental factors, including high heritability, sex, distance from home to workplace, time devoted for the rest and physical exercise, and habits related to eye utilization contribute to the onset and progression of myopia.[3-6]

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Through the recent surveys of the domestic and foreign population, results have indicated that the myopia prevalence of female was higher than that of male.[7,8] Researchers also found that the myopia prevalence fluctuated with age among adolescent females.[9] Based on those epidemiological data, it can be concluded that myopia is more prevalent in females. Relevant research result which indicates that myopia prevalence of males is different from that of females in the early development stages of growth,[7] and the difference becomes small in young adults, gives rise to the issue that gender is a risk factor for the high prevalence of juvenile myopia. After puberty, under the effect of growth hormone and estrogen, the growth and development of young females

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reach a peak. At this point, the organ dysfunction is prone to cause the change of the tissue structure, including those in eyes. Female myopia occurs earlier than male due to the fact that female puberty starts earlier than that of male and the degree also gradually increases with body growth and development.[10,11]

Wickham *et al*.[12] confirmed that estrogen receptor (ER) mRNA was expressed in the cornea, meibomian glands, retinal/choroidal and retinal pigment epithelial cells of rats, rabbits, and human beings.[13] Estrogen had a certain influence on cornea thickness, which was positively correlated to myopic diopter.[14,15] Therefore, this study is conducted aiming to evaluate the effect of estrogen on ocular parameters in adolescent females. The results may not only increase our understanding of the effects of reproductive hormones on myopia, but can also help elucidate that vision changes along with estrogen change in the menstrual cycle.

Methods

Study population

The study was approved by the Institutional Review Board of Wenzhou Medical University, and the research followed the tenets of the declaration of Helsinki. The nature of the study was explained to the participants and written informed consent was obtained.

The participants of this study were recruited from Wenzhou Ouhai Middle School. A total of 120 girls (15–16 years old) with myopia was included in the study. Eligibility criteria were: (1) Without family hereditary myopia, hyperopia, or dyschromatopsia and visual acuity of 5.0 or higher (bare or corrected); (2) normal external eye and fundus examination; (3) non had use hormones or any drugs with a potential vision effect within the last 6 months; (4) good health and normal body mass ± 10% were maintained during the investigation; (5) regular menstrual cycle (average length of cycle = 28.52 days, standard deviation = 1.65) without severe premenstrual or menstrual syndrome; (6) intraocular pressure <21 mmHg; (7) normal anterior segment examination by slit lamp and no retinopathy or glaucoma. Subjects with a history of eye diseases, glaucoma excimer laser eye operation, diabetes, hypertension, and other systemic diseases were not included in the study.

Study design

Eye examination was performed by experienced optometrists and ophthalmologists. Cycloplegia was induced with two drops of 1% cyclopentolate (S.A. Alcon-Couvreur N.V., Belgium). One hour later, each participant was administered with automatic optometry (Nidek ARK-710A, Japan). The automatic three-measurement mode was adopted to obtain an average value.

The routine for comprehensive eye examination was the same for each subject. Unaided or aided visual acuities were taken within the far and short distances before commencing refraction. Retinoscopy was then performed on the same eye, whose result was used as a starting point for subjective refraction, which was also performed on the same eye firstly. The best sphere lens degree was determined through the red-green test. The crossed-cylinder technique was used to determine the cylinder direction and power. One diopter was added, and the power was reduced to give the best visual acuity. Monocular subjective refraction was performed based on subjective refinement of the autorefractor readings until the best-corrected visual acuity was achieved. Binocular subjective refraction test was also performed in a similar way.

Main outcomes of the eye examination included spherical lens, cylindrical power, axis, interpupillary distance (IPD), and vision.

All participants provided the information of their menstrual cycle (the average cycle length, the length of menstrual period, and the prediction of the next menstruation date). We gave each subject an oral thermometer to measure basal body temperature every day before getting up in a month before the test. The rise of temperature to a high level (about 0.3°C) indicated ovulation. After being exposed to the items (learning phase), the participants enter the test phase.

Data collection

After an overnight, fast blood samples were drawn from an antecubital vein for clinical routine laboratory diagnosed in the second Affiliated Hospital of Wenzhou Medical University on the 2nd or 3rd day, 14th and 28th day after menstruation, respectively according to participants' menstrual cycles. In the same way, cylindrical lens, spherical lens, IPD, and visual acuity were detected by the outpatient department of ophthalmology based on automatic optometry method and comprehensive optometry detection.

Blood specimens were drawn and immediately centrifuged at 2000 r/min for 10 min at 4°C to obtain serum or ethylenediaminetetraacetic acid plasma, which were stored at −75°C for further analysis. Serum was absorbed by capillary burette and then divided into two parts, which were marked as A and B, respectively. Serum estradiol (E_2) levels were detected using the ACCESS automatic microparticle chemiluminescence immunoassay analyzer (Beckman Coulter, USA). If the detection data of specimen A were significantly abnormal, specimen B would be re-detected for revising the data.

Statistical analysis

The visual parameter data did not follow a normal distribution and were paired, so the Wilcoxon matched-pairs ranks test of SAS proc univariate was used to determine the magnitude of the differences of related ocular parameters between two different time points in menstrual cycle. The matrix difference was established through the comparison of two paired data. Friedman M test was used to compare visual acuity differences at different time points. For univariate significance levels, $P < 0.05$ indicates the significance of statistical difference.

Results

A total of 120 participants with myopia had a mean age of 15.6 ± 0.4 years and body mass index of 20.7 ± 1.2 kg/m^2; the differences were nonsignificant ($P > 0.05$).

The spherical lens varies within the menstrual cycle. There was the statistically significant difference of the spherical lens among all different times in menstrual cycle ($P < 0.0001$), as shown in Table 1.

In young females with myopia, the cylindrical lens, axis, and IPD were changed significantly during the menstrual cycle ($P < 0.05$), as shown in Table 2. The correlation was verified through Wilcoxon matched-pairs ranks test.

Friedman M test results of the vision changes during the menstrual cycle suggested a statistically significant difference of vision in three time points of the menstrual cycle ($\chi^2 = 6.35$, $P = 0.042$) [Table 3]. Interestingly, the vision of the 2nd or 3rd day showed statistically significant difference of vision on the 14th day and the 28th day ($P = 0.021$).

Table 4 presents the serum E_2 levels during the menstrual cycle. The mean E_2 levels were significantly different at different time points in the menstrual cycle ($P < 0.05$). E_2 levels in all subjects reached the maximum value on the 14th day while the minimum value appeared on the 2nd or 3rd day. We found a significant positive correlation between serum E_2 levels and vision in the total group of participants, and the vision gradually became better with the increase of E_2 level after menstruation [Tables 3 and 4].

Discussion

Estrogen is a type of the female hormone mainly generated in the ovaries and placenta. After entering puberty stage, female teenagers' ovary begins to secrete estrogen, promoting the uterus development and menses formation. Several epidemiologic observations suggest a potential participation of estrogen in the homeostasis of the eye, but the mechanisms involved remain unclear. Some scholars believed that the modulatory properties of estrogen may be mediated by the expression of the ER in the ocular tissues through gene regulation or nongene regulation.[16] Estrogen also has an effect on the expression of more than 600 genes in corneal epithelial cells.[17] Estrogen treatments can change the transcriptional activities of many genes, thus affecting cell growth, cell communication, signal transmission and modification on corresponding eye tissues or organs.[18]

Juvenile myopia has been one of the hotspots in recent 150 years. At the current stage, the exact pathogenesis is not very clear while different pathogenesis opinions are available. The relationship between estrogen and juvenile myopia is rarely reported.[19,20] Estrogen has been shown to upregulate matrix metalloproteinase-2 (MMP-2) and/or MMP-9 in human ocular cells,[21] and MMP-2 upregulation was suggested as part of the scleral remodeling process in myopia development.[22]

In recent years, a large number of researchers have found that the myopia prevalence of female was higher than that of male and results indicated that myopia incidence between males and females showed the significant difference ($P < 0.005$).[7,8] Many factors are responsible for the higher myopia rate of girls than that of boys, including earlier growth conditions, more limited outdoor activity time than boys. However, certain internal factors, like hormone endocrine, are yet to be investigated.

The present cross-sectional study investigated the relation of ocular parameters and serum E_2 level as well as vision changes along with E_2 change in menstrual cycle of a total group of healthy female adolescent without severe menstrual diseases and with regular menstrual cycle. As a first important finding, the spherical lens varies with E_2 level in menstrual cycle of adolescent females. The significant difference of spherical lens was observed between the 2nd or 3rd day and the 14th day after menstruation when E_2 level reached the maximum value on the 14th day and the minimum value on the 2nd or 3rd day. Our study showed that during the menstrual cycle, not only the spherical lens but also cylindrical lens, axis, and IPD were changed significantly. Nevertheless, our results were inconsistent with what Zhao[23] had previously reported. Moreover, the data obtained and investigated in this study showed a positive relationship between vision and

Table 1: Sphere correlation between two different time points in menstrual cycle of the same subject

Menstrual cycle	The 2nd or 3rd day		The 14th day		The 28th day	
	Monocular	Binocular	Monocular	Binocular	Monocular	Binocular
The 2nd or 3rd day	1	1	0.0010	<0.0001	0.0051	<0.0001
The 14th day	0.0010	<0.0001	1	1	0.2901	<0.0001
The 28th day	0.0051	<0.0001	0.2901	<0.0001	1	1

Table 2: Related ocular parameters of the same subject at different time points in the menstrual cycle (mean ± SD)

Items	The 2nd or 3rd day	The 14th day	The 28th day	Minimum	Maximum
Cylinder (DC)	−1 ± 0.06	−0.75 ± 0.04	−1.25 ± 0.07	−1.25	−0.25
Axis (d)	162 ± 3.82	169 ± 2.67	173 ± 3.75	129.5	180.0
Distance (mm)	58.2 ± 1.06	60.0 ± 1.87	58.5 ± 1.24	53.0	67.0

SD: Standard deviation.

Table 3: Vision change of the same subject at different time in menstrual cycle (median, Q)

Items	Menstrual cycle				
	The 2nd or 3rd day	The 14th day	The 28th day	χ^2	*P*
Vision	1.0 (0.5-1.2)	1.0 (1.0-1.2)	1.2 (1.0-1.2)	6.35	0.042

Table 4: E_2 level of the same subject at different time in menstrual cycle

Menstrual cycle	E_2 (mean ± SD, pg/ml)	Minimum	Maximum
The 2nd or 3rd day	38.96 ± 26.25	7	138
The 14th day	221.54 ± 413.3	7	1982
The 28th day	87.71 ± 69.27	14	248

The mean E_2 level is significantly different among all different time points in menstrual cycle (all $P<0.05$). SD: Standard deviation; E_2: Estradiol.

E_2, which corroborated the findings of previous research that showed diopter decreased with the increase of estrogen level during the menstrual cycle and was negatively correlated with estrogen level.[24]

Xie *et al*.[24] detected levels of various serum sex hormones (luteinizing hormone (LH), follicle-stimulating hormone (FSH), E_2, and testosterone) of young students (12–14 years old) in a large sample of different myopia degrees as well as nonmyopia controls. Our results were similar to that by Xie *et al*., in which myopic degree increased along with the decrease of estrogen level. However, Xie *et al*.[24] found a relationship between myopia and estrogen by detecting serum LH and FSH in adolescent females. In contrast, we further studied the vision changes of adolescent females along with the E_2 level in menstrual cycle by directly detecting serum E_2 levels. In that prior study, serum estrogen level in myopia adolescents was lower than that in nonmyopia group. Related ocular parameters, such as a spherical lens, cylindrical lens, axial, and IPD were further detected in our study. We found that the vision fluctuated with E_2 levels during the menstrual cycle. Based on the above data, it can be further confirmed that the serum level of E_2 is closely related to the occurrence and development of juvenile myopia.

The change of estrogen levels during the menstrual cycle can affect a person's vision for three reasons. First, metabolic disorders of estrogen in menses cause the hypothalamus and plant nerve function disorder. Therefore, the visual function of females may experience some temporary changes. Decreased vision, like refractive error, often fluctuates in menstruation and will be significantly reduced after. Second, the changes of sex hormone levels can cause retinal function change for some females.[25] Third, estrogen had a certain influence on the corneal thickness.[26] The corneal thickness of females shows the periodical change. The cornea varies during the menstruation process, being thinnest at the end of the menstrual cycle while thickest in the period of ovulation. Moreover, myopic diopter is positively correlated with corneal thickness. The corneal thickness in the low-degree myopia patients is much thicker than in the high-degree myopia patients.[17] By the reasons above, conclusions achieved in this study are supported and proved objectively, with the discovery that vision in late menstrual cycle is significantly ameliorated compared to the premenstrual cycle.

In our study, monocular vision is different from binocular vision in the results of computer automatic optometry and comprehensive optometry. The difference may be caused by the mismatch between ametropia adjustment and collection. In addition, anisometropia (especially mild anisometropia) interference with binocular vision is the second reason.[27] A substantial number of individuals exhibit binocular gain for low contrast targets indicates that the monocular assessment would result in an underestimate of the individual's function as they go about daily life. For our study, participants were performed both binocularly and monocularly, making us better understand the vision function of the individual participant. Spherical lens detected by binocular in this study all showed statistically significant differences.

The rather inhomogeneous and small group of female adolescents is an obvious limitation of our study. The difficult recruitment may at least in part be due to the fact that these participants, having to cope with an invasive procedure, may not easily agree to a three times repeated blood test and a time-consuming study. Second, in this study, the confounding factors produced by the rapid growth and development in the young stage were deliberately avoided. However, due to the special physiological features and condition limitations of the subjects involved in the study, we only studied one menstrual cycle. Finally, the estrogen level varies with each menstrual cycle, and may also be interfered by other hormones or presents periodic variation. All of these preliminary results should be confirmed in future studies, with greater sample size and longitudinal designs.

In conclusion, we found that estrogen level fluctuations in the menstrual cycle simultaneously occurred to the related eye parameters and vision sensitivity of healthy female teenagers. It can be used to explain the changes in visual acuity at different time points during the menstrual cycle. Through this study, we also obtained that myopia development of adolescent females is variable peculiarly with periodic fluctuation. According to our current study and other related research results, the sensitivity of ERs in human eyes varies with the estrogen levels during the menstrual cycle, thus inducing the change of vision.

The wide distribution of ERs in the ocular tissue helps us better comprehended the pathogenesis of several eye diseases and has opened up a new direction for the clinical prevention and treatment of myopia to us. Understanding the mechanism of the effect of estrogen on myopia may provide evidence of targeted drug therapy for individual treatment in the future. In addition, with hormone replacement therapy has become a research hotspot, the effects of HRP on eyes cannot be ignored. At present, the corresponding research literature indicating the relation between estrogen and myopia at home and abroad is rare. Therefore, we sincerely hope that some exploratory effort in theory and practice can be conducted by us at the following stage. We also believe that with the progress of basic studies, the development of new targeted drugs and new therapeutic approaches, a new platform for the clinical application of estrogen in adolescent myopia will be built and constructed.

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