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Corneal Endothelial Cell Density and Morphology in Patients with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Hastalarda Kornea Endotel Hücre Yoğunluğu ve Morfolojisi

Zeynep ÖZCAN DAĞ,[a]
Nurgül ÖRNEK,[b]
Kemal ÖRNEK[c]

Departments of
[a]Gynecology and Obstetrics,
[b]Ophthalmology,
Kırıkkale University Faculty of Medicine, Kırıkkale
[c]Private Practitioner, Ankara

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Correspondence:
Nurgül ÖRNEK
Kırıkkale University Faculty of Medicine, Department of Ophthalmology, Ankara, TURKEY/TÜRKİYE
nurgul_ornek@hotmail.com

ABSTRACT Objective: To evaluate corneal endothelial cell density and morphology in patients with polycystic ovary syndrome (PCOS). **Material and Methods:** This prospective study included 46 (46 eyes) PCOS patients. An age-matched group of 46 (46 eyes) volunteers served as controls. Corneal measurements were performed using a specular microscopy (Noncon Robo SP8000, Konan Medical, Hyogo, Japan). Cell density (CD), hexagonal cell ratio (HEX) and coefficient of value (CV) of the endothelial cell layer were calculated at central, superior, inferior, nasal and temporal cornea. **Results:** The mean ages of the PCOS patients and the control group were 25.54±5.29 years (range 20–38) and 28.55±4.78 years (range 22–37) respectively (p>0.05). There were no significant differences between the mean refractive errors and intraocular pressure (IOP) obtained in two groups (p=0.455, p=0.511 respectively). Central corneal thickness was lower in PCOS group compared to age-matched controls (561.63±39.22µ versus 576.96±44.55µ), but it did not show a statistically significant difference (p=0.083). There was no statistically significant difference in endothelial cell density at all measured areas in PCOS patients compared to controls (p central=0.541, p superior=0.881, p inferior= 0.855, p nasal=0.509, p temporal=0.758). Although in comparision to control group hexagonal cell ratio of PCOS patients were higher at all areas except for superior cornea, but statistically significant difference was not found at any measured areas (p central=0.593, p superior=0.889, pinferior=0.418, p nasal=0.626, p temporal=0.205). Comparison between the study groups also did not reveal any significant difference for the coefficient of value (p central=0.288, p superior=0.522, p inferior=0.772, p nasal=0.233, p temporal=0.497). **Conclusion:** We did not find any significant change in corneal thickness and endothelial cell layer parameters in PCOS patients.

Keywords: Endothelium; cornea; polycystic ovary syndrome

ÖZET Amaç: Polikistik over sendromlu (PKOS) hastalarda kornea endotel hücre yogunluğu ve morfolojisini değerlendirmek. **Gereç ve Yöntemler:** Bu prospektif çalışmaya 46 PKOS hastası (46 göz) dahil edildi. Yaş uyumlu 46 gönüllü (46 göz) kontrol grubu oldu. Korneal ölçümler speküler mikroskop (Noncon Robo SP8000, Konan Medical, Hyogo, Japan) kullanılarak gerçekleştirildi. Merkez, üst, alt, nazal ve temporal korneada endotel hücre tabakasının hücre yoğunluğu (HY), hekzagonal hücre oranı (HHO) ve değişim katsayısı (DK) hesaplandı. **Bulgular:** PKOS hastalarının ve kontrol grubunun ortalama yaşları sırasıyla 25,54±5,29 yıl (aralık 20-38) ve 28,55±4,78 yıl (aralık 22-37) idi (p>0,05). Her iki gruptan elde edilen ortalama refraktif hata ve göz içi basıncı (GIB) arasında anlamlı farklılık mevcut değildi (p=0,455, p=0,511 sırasıyla). Merkezi kornea kalınlığı yaş uyumlu kontrollerle karşılaştırıldığında PKOS grubunda daha inceydi (561,63±39,22µ karşı 576,96±44,55µ), fakat istatistiksel olarak anlamlı farklılık göstermemekteydi (p=0,083). PKOS hastaları kontrollerle karşılaştırıldığında ölçüm yapılan tüm alanlarda endotel hücre yogunluğu açısından istatistiksel olarak anlamlı farklılık mevcut değildi (p merkez=0,541, p üst=0,881, p alt=0,855, p nazal=0,509, p temporal=0,758). Hekzagonal hücre oranı PKOS hastalarında üst kornea dışındaki tüm alanlarda kontrol grubuna göre daha yüksek olmasına rağmen, ölçülen hiçbir alanda istatistiksel anlamlı farklılık bulunamadı (p merkez=0,593, p üst=0,889, p alt=0,418, p nazal=0,626, p temporal=0,205). Çalışma grupları arasındaki karşılaştırmada değişim katsayısı değeri açısından da anlamlı farklılık ortaya çıkmadı (p merkez=0,288, p üst=0,522, p alt=0,772, p nazal=0,233, p temporal=0,497). **Sonuç:** PKOS hastalarında kornea kalınlığı ve endotel hücre tabakası parametreleri açısından anlamlı farklılık saptamadık.

Anahtar Kelimeler: Endotel; kornea; polikistik over sendromu

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age. Despite various clinical and experimental data published, the pathogenesis still remains obscure. It is characterized by the presence of polycystic ovary, oligoovulation, hyperandrogenism and/or hirsutism and the exclusion of the related disorders.[1]

It has been shown that gender exerts a significant influence on the anatomy and physiology of the cornea. Thus, previous studies have revealed significant, gender-related differences in the diameter, curvature, thickness and sensitivity of the cornea. In addition to these findings, investigators have found that gender-related differences in the cornea may also occur during the menstrual cycle, pregnancy and menopause. These include changes in the thickness, hydration, curvature and sensitivity of the cornea, incidence of central corneal endothelial pigmentation, foreign body sensation, contact lens tolerance and visual acuity.[2-11]

To our knowledge, as a common endocrine disorder in women, no studies have been conducted on corneal endothelial cell changes in patients with PCOS. In the present study, we hypothesized that there may be alterations in the corneal endothelial cell density and morphology in patients with PCOS.

MATERIAL AND METHODS

This prospective clinical study was performed in accordance with the Helsinki Declaration. The study protocol was approved before initiation. Permission from ethical committee was taken and informed consent was obtained from all subjects before examination. Forty-six PCOS patients and 46 healthy age-matched volunteers with regular menstrual cycle as control group were enrolled into this study. Both the PCOS patients and healthy volunters were in follicular phase of menstrual cycle. Polycystic ovary syndrome was diagnosed according to the 2003 Rotterdam Consensus Workshop by expert obstetricians when two of the following criteria were recognized: oligomenorrhea and/or anovulation, clinical or biochemical signs of hyperandrogenism and ultrasound findings of polycystic ovary.[7]

Exclusion criteria for the study were refractive error (in spherical equivalent) of >±1.00 diopter, any previous intraocular surgery, corneal surgery, scleral or corneal disease, uveitis, connective tissue disease, history of contact lens use, pregnancy, oral contraseptive usage, systemic diseases, other endocrinopathies, smoking and alcohol consumption.

Each participant underwent a complete ophthalmological examination including best-corrected visual acuity, intraocular pressure measurement, slit-lamp examination including fundus examination. They were all in follicular phase of menstrual cycle when ophthalmological examination performed. A single examiner performed all the corneal measurements between 09:30 and 11:00 am. on the same day using specular microscopy (Konan Noncon Robo SP8000, Konan Medical, Hyogo, Japan). Patients were asked always to look at the central fixation target and the auto-alignment function was used. All corneal endothelial cells which were clearly visible on the picture were marked manually. At least 110 cells per measurement were included in each analysis. We used the center method which is a common technique incorporated into the specular microscope (Figure 1). Cell density (CD), hexagonal cell ratio (HEX) and coefficient of value (CV) of the endothelial cell layer were calculated at central, superior, inferior, nasal and temporal cornea by the software.

The data are presented as mean ± standard deviation (SD). We used non-parametric version of one-way analysis of variance (ANOVA) followed by post hoc test. The Dunnett's corrections for comparisons between patient groups were used when the overall ANOVA showed significant difference across groups. Statistical significance is considered a value of $p<0.05$. All statistical analyses were performed using SPSS software.

RESULTS

The mean ages of the PCOS patients and the control group were 25.54±5.29 years (range 20-38) and 28.55±4.78 years (range 22-37) respectively ($p>0.05$). There were no significant differences be-

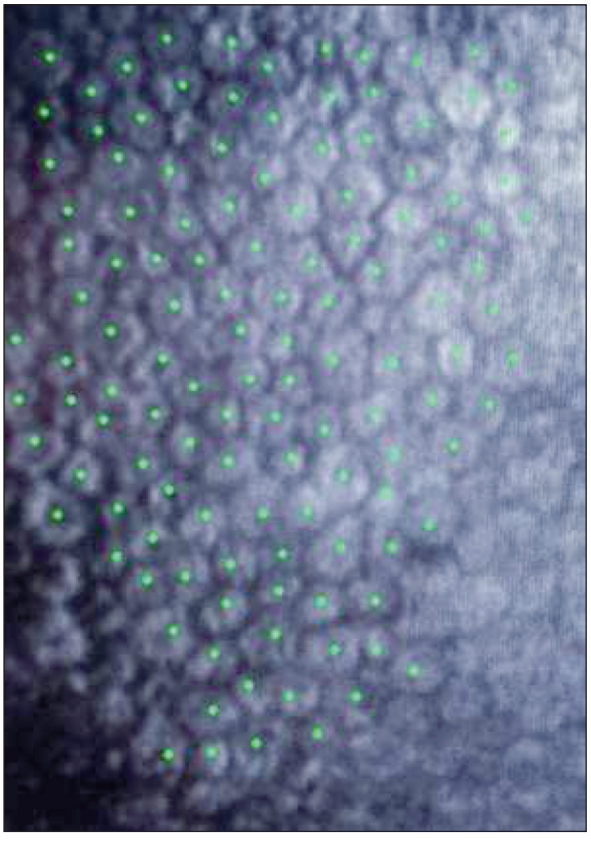

FIGURE 1: An image from specular microscope after center method processing for corneal endothelium.

tween the mean refractive errors and IOP obtained in two groups (p=0.455, p=0.511 respectively). Slit-lamp examination of the cornea did not reveal any abnormalities.

Central corneal thickness was lower in PCOS group compared to age-matched controls (561.63±39.22μ versus 576.96±44.55μ), but it did not show a statistically significant difference (p=0.083). Although being not statistically significant, endothelial cell density of PCOS patients were higher in central and nasal areas and lower in superior, inferior and temporal areas in comparison to control group (p central=0.541, p nasal= 0.509, p superior=0.881, p inferior=0.855, p temporal=0.758). It was the highest at central cornea in PCOS patients. In comparision to control group hexagonal cell ratio of PCOS patients were higher at all areas except for superior cornea, but the difference was not statistically significant at any measured areas (p central=0.593, p superior=0.889, p inferior=0.418, p nasal=0.626, p temporal= 0.205). Hexagonal cell ratio was the highest at central cornea in both PCOS and control groups. Comparison between the PCOS and control groups also did not reveal any significant difference for the coefficient of value (p central=0.288, p superior=0.522, p inferior=0.772, p nasal=0.233, p

TABLE 1: Corneal endothelial cell density, hexagonal cell ratio and coefficient of value in PCOS group and controls. (PCOS: Polycystic ovary syndrome).

Measured parameters	Measured areas	PCOS group (n=46)	Control group (n=46)	P value
Cell density (mean±SD)	Central	2982±192	2949±174	P=0.541
	Superior	2960±146	2966±179	P=0.881
	Inferior	2968±180	2975±162	P=0.855
	Nasal	2971±135	2969±165	P=0.509
	Temporal	2956±134	2966±144	P=0.758
Hexagonal cell ratio (mean±SD)	Central	51.23±7.4	49.30±8.9	P=0.593
	Superior	47.1±10.1	47.3±5.6	P=0.889
	Inferior	49.2±8.3	47.8±7.5	P=0.418
	Nasal	44.8±7.4	44.0±7.9	P=0.626
	Temporal	43.2±6.8	41.41±7.3	P=0.205
Coefficient of value (mean±SD)	Central	28.1±2.8	29.0±4.2	P=0.288
	Superior	29.8±3.9	29.2±4.1	P=0.522
	Inferior	28.5±3.6	28.8±4.3	P=0.772
	Nasal	31.5±4.7	30.3±4.8	P=0.233
	Temporal	30.5±5.4	31.3±4.9	P=0.497

Values were given as mean±SD.

temporal=0.497) (Table 1). CD, HEX and CV of corneal endothelium in controls and PCOS patients are shown in figures (Figures 2-4).

DISCUSSION

Polycystic ovary syndrome affects millions of women on earth. It is estimated that between 5-10% of women suffer from PCOS and it makes the condition as the most common hormonal disorder in women of childbearing age. The clinical consequences of PCOS seem to arise from the fact that levels of sex hormones in PCOS patients are altered.[1,5-11] In this study, we studied for the first time, corneal endothelial cell density and morphology changes in women with PCOS using specular microscope.

Changes in the anterior segment parameters due to gender-related factors have usually been ignored and different studies have reported conflicting results. During pregnancy, changes in corneal curvature and steeping have occured particularly in the second and third trimesters. As a consequence of corneal edema resulting from increased water retention during pregnancy, corneal thickness has been shown to be increased.[12-17]

Changes in corneal thickness during menstrual cycle have been reported in previous studies. Soni[11] reported that minimal corneal thickness occured before ovulation and thickest cornea was at the beginning and end of the menstrual cycle. The study of Feldman et al. reported that the cornea was thinnest before ovulation but he did not find correlation between the blood level of hormones and corneal thickness.[18] On the other hand, Hashemi et al. investigated cornea during menstrual cycle using Scheimpflug imaging technique and did not find any significant differences during this period.[19]

There are very limited data on the effect of PCOS on anterior segment of the eye, in particular on cornea. Persistent ocular surface discomfort characterized by itching, excessive mucus production, dryness, and contact lens intolerance was described in a group of PCOS patients.[20] In an other study by Kebapcilar et al. corneal thickness measurements were reported higher in PCOS patients

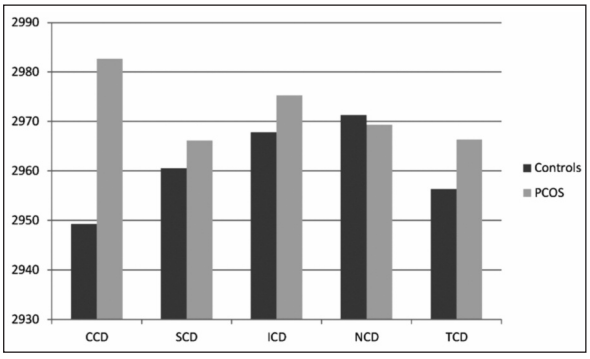

FIGURE 2: Corneal endothelial cell density in controls and PCOS patients. (**PCOS:** Polycystic ovary syndrome, **CCD:** Central corneal endothelial cell density, **SCD:** Superior corneal endothelial cell density, **ICD:** Inferior corneal endothelial cell density, **NCD:** Nasal corneal endothelial cell density, **TCD:** Temporal corneal endothelial cell density).

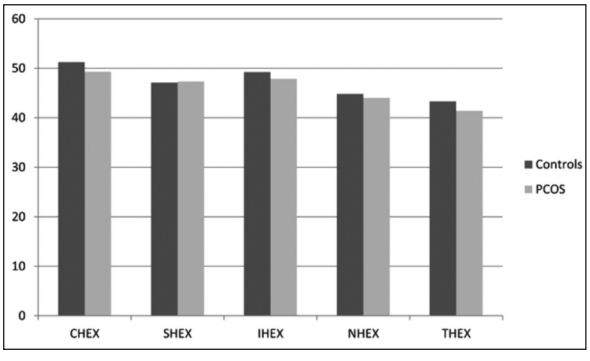

FIGURE 3: Corneal endothelial cell hexagonality in controls and PCOS patients. (**PCOS:** Polycystic ovary syndrome, **CHEX:** Central hexagonal cell ratio, **SHEX:** Superior hexagonal cell ratio, **IHEX:** Inferior hexagonal cell ratio, **NHEX:** Nasal hexagonal cell ratio, **THEX:** Temporal hexagonal cell ratio).

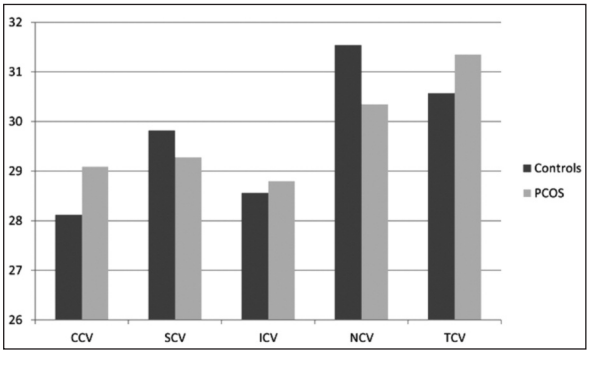

FIGURE 4: Corneal endothelial cell coefficient of value in controls and PCOS patients. (**PCOS:** Polycystic ovary syndrome, **CCV:** Central coefficient of value, **SCV:** Superior coefficient of value, **ICV:** Inferior coefficient of value, **NCV:** Nasal coefficient of value, **TCV:** Temporal coefficient of value).

compared to controls.[21] Also in a recent study Adıyeke and et al. found that central corneal thickness were higher and dry eye symptoms were more severe in PCOS patients when compared to healthy reproductive-age volunteers.[22] Contrary to these studies, we found decreased corneal thickness in PCOS group compared to controls, but the difference was not statistically significant. Also comparision between the PCOS patients and control group did not show any statistically significant difference for corneal endothelial cell density, hexagonal cell ratio and the coefficient of value.

Sex hormones may affect ocular tissues and take part in homeostasis and function of the cornea, which are mediated by the alpha- and beta-estrogen, progesterone, and androgen receptors in the nuclei of human corneal epithelial, stromal, and endothelial cells.[5,9] There is a significant change in corneal hydration during the menstrual cycle. The access of these hormones to cornea may be via aqueous humor or tear film because of their high lipid solubility. An indirect effect on the cornea can also take place via their action on tear film functions. During pregnancy, sex hormones have been suggested to have effects like systemic water retention due to estrogen-induced upregulation of the renin-aldosterone system on the cornea. It is also possible that other factors such as insulin resistance are also involved in the pathogenesis of the ocular surface alterations reported in PCOS patients. Kebapcilar et al. found a positive correlation between corneal thickness and insulin like growth factor levels.[21] Ocular changes in these patients seem to be modulated by abnormal sex hormone profiles, insulin resistance and possible local regulatory factors. Adıyeke and et al. also reported that physiological and structural changes of cornea caused by PCOS were correlated with serum testosterone and estradiol levels.[22]

It seems that there is still much to be done to define the precise role of sex hormones on corneal functions in normal or diseased stages, current data suggest these hormones as potaential modifiers. A detailed understanding of the effects of sex hormones on corneal tissue may allow us to identify the pathogenetic mechanisms and newer treatment modalities.

Investigating corneal endothelial cell layer parameters in PCOS patients is the strenght of this study. On the other hand, we did not find significant changes in endothelial cell layer measurements of the patients. Small number of study participants may be another limitation of the study. Also it would be better to analyse hormonal status of these patients and correlation of hormonal levels with corneal thickness and endothelial cell layer parameters.

In this study, we aimed to evaluate the possible role of PCOS which is the most common endocrine abnormality of women, on corneal endothelial cell density and morphology. Our data did not provide enough evidence for a statistically significant relation between corneal endothelial cell density and morphology changes and PCOS.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kemal Örnek;* ***Design:*** *Kemal Örnek, Nurgül Örnek;* ***Control/Supervision:*** *Kemal Örnek, Nurgül Örnek;* ***Data Collection and/or Processing:*** *Zeynep Özcan Dağ, Nurgül Örnek;* ***Analysis and/or Interpretation:*** *Nurgül Örnek, Kemal Örnek* ***Literature Review:*** *Kemal Örnek, Nurgül Örnek;* ***Writing the Article:*** *Kemal Örnek, Nurgül Örnek;* ***Critical Review:*** *Kemal Örnek;* ***References and Funding:*** *Kemal Örnek, Nurgül Örnek;* ***Materials:*** *Zeynep Özcan Dağ, Kemal Örnek, Nurgül Örnek.*

REFERENCES

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89(6):2745-9.
2. Gluffré G, Di Rosa L, Fiorino F, Bubella DM, Lodato G. Variations in central corneal thickness during the menstrual cycle in women. Cornea 2007;26(2):144-6.
3. Leach NE, Wallis NE, Lothringer LL, Olson JA. Corneal hydration changes during the normal menstrual cycle--a preliminary study. J Reprod Med 1971;6(5):201-4.
4. Kiely PM, Carney LG, Smith G. Menstrual cycle variations of corneal topography and thickness. Am J Optom Physiol Opt 1983;60(10):822-9.
5. Gupta PD, Johar K Sr, Nagpal K, Vasavada AR. Sex hormone receptors in the human eye. Surv Ophthalmol 2005;50(3):274-84.
6. Kovalevsky G. Female sexual dysfunction and use of hormone therapy in postmenopausal women. Semin Reprod Med 2005;23(2):180-7.
7. Suzuki T, Kinoshita Y, Tachibana M, Matsushima Y, Kobayashi Y, Adachi W, et al. Expression of sex steroid hormone receptors in human cornea. Curr Eye Res 2001;22(1):28-33.
8. Vécsei PV, Kircher K, Kaminski S, Nagel G, Breitenecker G, Kohlberger PD. Immunohistochemical detection of estrogen and progesterone receptor in human cornea. Maturitas 2000;36(3):169-72.
9. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand 2000;78(2):146-53.
10. Oliver KM, Walsh G, Tomlinson A, McFadyen A, Hemenger RP. Effect of the menstrual cycle on corneal curvature. Ophthalmic Physiol Opt 1996;16(6):467-73.
11. Soni PS. Effects of oral contraceptive steroids on the thickness of human cornea. Am J Optom Physiol Opt 1980;57(11):825-34.
12. Riss B, Riss P. Corneal sensitivity in pregnancy. Ophthalmologica 1981;183(2):57-62.
13. Park SB, Lindahl KJ, Temnycky GO, Aquavella JV. The effect of pregnancy on corneal curvature. CLAO J 1992;18(4):256-9.
14. Weinreb RN, Lu A, Beeson C. Maternal corneal thickness during pregnancy. Am J Ophthalmol 1988;105(3):258-60.
15. Millodot M. The influence of pregnancy on the sensitivity of the cornea. Br J Ophthalmol 1977;61(10):646-9.
16. Dinn RB, Harris A, Marcus PS. Ocular changes in pregnancy. Obstet Gynecol Surv 2003;58(2):137-44.
17. Omoti AE, Waziri-Erameh JM, Okeigbemen VW. A review of the changes in the ophthalmic and visual system in pregnancy. Afr J Reprod Health 2008;12(3):185-96.
18. Feldman F, Bain J, Matuk AR. Daily assessment of ocular and hormonal variables throughout the menstrual cycle. Arch Ophthalmol 1978;96(10):1835-8.
19. Hashemi H, Mehravaran S, Rezvan F. Changes in corneal thickness, curvature, and anterior chamber depth during the menstrual cycle. Can J Ophthalmol 2010;45(1):67-70.
20. Bonini S, Mantelli F, Moretti C, Lambiase A, Bonini S, Micera A. Itchy-dry eye associated with polycystic ovary syndrome. Am J Ophthalmol 2007;143(5):763-71.
21. Kebapcilar AG, Tatar MG, Ipekci SH, Gonulalan G, Korkmaz H, Baldane S, et al. Cornea in PCOS patients as a possible target of IGF-1 action and insulin resistance. Arch Gynecol Obstet 2014;290(6):1255-63.
22. Karaca-Adıyeke S, Karaca I, Yıldırım S, Adıyeke M, Uyar İ, Türe G. Anterior segment findings in women with polycystic ovary syndrome. Turk J Ophthalmol 2017;47(1):24-7.