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Ultrasonographic Evaluation of Fibrocystic Breast Disease in Patients with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Hastalarda Memede Fibrokistik Hastalığın Ultrasonografi İle Değerlendirilmesi

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ABSTRACT

Objective: To evaluate whether polycystic ovary syndrome (PCOS) constitutes an increased risk for benign breast disease by assessing PCOS patients in terms of the presence of fibrocystic breast disease with breast ultrasound assessment. **Materials and Methods:** This prospective case-controlled study was conducted at a tertiary referral center. Study group consisted of 41 patients who were diagnosed with PCOS according to the Rotterdam criteria. Control group included 41 age-matched patients without any known diseases. All patients received a breast examination with ultrasound and findings were categorized according to BI-RADS. **Results:** A significantly higher percentage of patients in the study group were categorized as BI-RADS 2 and 3 in comparison to the patients in the control group; 26.8% vs. 9.8%, 9.8% vs. 2.4%, respectively ($p < 0.001$). Majority of patients in both groups were categorized as BI-RADS 1 and no malignancy or a suspicion of malignancy was reported in both groups. Additionally, a significant difference was observed between the groups in terms of parenchymal pattern ($p = 0.02$). No parenchymal change was observed in 36.6% of the control group whereas this number was 17.1% in the study group. A significantly higher number of patients with PCOS had fibrocystic breast disease (14.6%) when compared to the control group (2.4%). **Conclusion:** This study evaluated the association between PCOS and fibrocystic breast disease and the risk of fibrocystic breast disease was found to be higher in patients with PCOS. A routine breast evaluation of PCOS patients with ultrasonography is important for detection of fibrocystic breast disease and for long-term management of these patients.

Keywords: Polycystic ovary syndrome; fibrocystic breast disease; ultrasonography mammary

ÖZET

Amaç: Polikistik over sendromlu (PKOS) hastaların meme ultrasonu ile fibrokistik meme hastalığı varlığı açısından değerlendirerek PKOS'un iyi huylu meme hastalığı için artmış risk oluşturup oluşturmadığını değerlendirmek. **Gereç ve Yöntemler:** Bu prospektif vaka kontrollü çalışma üçüncü basamak bir merkezde gerçekleştirildi. Çalışma grubunu Rotterdam kriterlerine göre PKOS tanısı alan 41 hastadan oluşturdu. Kontrol grubuna bilinen herhangi bir hastalığı olmayan çalışma grubu ile benzer yaş grubunda 41 hasta dahil edildi. Tüm hastalara ultrason ile meme muayenesi yapıldı ve bulgular BI-RADS'a göre sınıflandırıldı. **Bulgular:** Çalışma grubundaki hastalar kontrol grubundaki hastalara kıyasla anlamlı derecede yüksek oranda BI-RADS 2 ve 3 olarak kategorize edildi; sırasıyla %26,8'e karşı %9,8, %9,8'e karşı %2,4 ($p < 0,001$). Her iki gruptaki hastaların çoğunluğu BI-RADS 1 olarak sınıflandırıldı ve her iki grupta da herhangi bir malignite veya malignite şüphesi bildirilmedi. Ayrıca gruplar arasında parenkim paterni açısından da anlamlı fark gözlendi ($p=0,02$). Kontrol grubunun %36,6'sında herhangi bir parenkim değişikliği gözlenmezken, bu sayı çalışma grubunda %17,1 idi. Kontrol grubuyla (%2,4) karşılaştırıldığında PKOS'lu hastaların önemli bir kısmında fibrokistik meme hastalığı (%14,6) izlendi. **Sonuç:** Bu çalışmada PKOS ile fibrokistik meme hastalığı arasındaki ilişki değerlendirilmiş ve PKOS'lu hastalarda fibrokistik meme hastalığı riskinin daha yüksek olduğu bulunmuştur. PKOS'lu hastaların ultrasonografi ile rutin meme değerlendirmesi, fibrokistik meme hastalığının saptanması ve bu hastaların uzun süreli yönetimi açısından önemlidir.

Anahtar Kelimeler: Polikistik over sendromu; fibrokistik meme hastalığı; ultrasonografi, meme ile ilgili

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Polycystic ovary syndrome (PCOS) is both an endocrinological and a gynecologic condition without a clear etiology or pathogenesis, which affects 12-18% of women within the reproductive ages.[1-5] PCOS is seen in 50-70% of cases with insulin resistance and hyperinsulinemia both of which play central roles in the pathophysiology of this condition.[6-8] In addition to hyperinsulinemia, increased luteinizing hormone (LH) secretion, decreased levels of insulin-like growth factor-binding protein 1 (IBP-1), increased androgen synthesis in theca cells due to the activation of insulin-like growth factor 1 (IGF-1) receptors, and increased levels of serum androgens due to decreased synthesis of sex hormone binding globulin (SHBG) are observed in PCOS.[9-11] The risk of developing type 2 diabetes mellitus (DM) is also increased in these patients because of increased insulin resistance and hyperinsulinemia.[12] Furthermore, an increased risk for hypertension, metabolic syndrome, dyslipidemia, and atherosclerosis has also been reported in PCOS patients.[10,12-15] The hyperandrogenemia leads to menstrual dysregulations, acne, alopecia and hirsutism.[16] Elevated LH secretion and hyperandrogenemia cause long-term anovulatory periods and hyperestrogenic environment in PCOS patients, which underlie the dysfunctional uterine bleeding, endometrial hyperplasia, infertility and increased risk for endometrium cancer in these patients.[17,18]

Growth of mammary glands are dependent on the balance between estrogen and progesterone hormones. It has already been shown that anovulation plays and important role in the etiology of benign breast diseases. Several studies have shown an association between breast density and infertility related hormonal factors caused by anovulation and/or luteal insufficiency.[19,20] In addition, hyperestrogenism is considered as one of the risk factors for the development of breast disease.

An association between PCOS and benign breast pathologies have been shown in the literature. However, there are contradictory results on this subject. Some studies reported a significant association between PCOS and fibrocystic breast disease whereas others found no association.[21-23] The aim of this study is to evaluate whether PCOS constitutes an increased risk for benign breast disease by assessing PCOS patients in terms of the presence of fibrocystic breast disease with breast ultrasound assessment.

MATERIALS AND METHODS

This prospective case-controlled study was conducted at University of Health Sciences Turkey Istanbul Kanuni Sultan Suleyman Training and Research Hospital between May 2019 and November 2019. An ethical approval was obtained from the institution's ethics committee (KAEK/2019.05.122). A written informed consent was obtained from all subjects recruited to the study and the study was conducted in accordance with the principles set forth in the Helsinki Declaration 2008.

A total of 82 patients who visited the outpatient gynecology clinic of the above-mentioned hospital were included in the study. Study group consisted of 41 patients who were diagnosed with PCOS according to the Rotterdam criteria; the presence of oligo/amenorrhea, clinic or biochemical hyperandrogenism and polycystic ovary appearance with transvaginal ultrasonography (TVUS).[24] Those presenting with at least two of these criteria were considered as having PCOS. Patients with additional endocrinological conditions (Cushing syndrome, adrenal hyperplasia, hyperprolactinemia, etc.), patients receiving medical/hormonal treatment, pregnant and lactating women, those with a history of breast operation and patients with other chronic diseases were excluded from the study. Control group included 41 age-matched patients without any known diseases who visited the gynecology clinic for routine control.

All gynecological examinations were performed by a single gynecologist. TVUS was performed by the same gynecologist with an 8.5 MHz transvaginal transducer (ATL 5000 HDI, Philips, Netherlands). Ovarian volume was calculated using the simplified formula: lengthxwidthxthicknessx0.5. Breast ultrasonography was performed by a trained radiologist using a linear 12-5 MHz transducer (ATL 5000 HDI, Philips, Netherlands). Breast Imaging-Reporting and Data System (BI-RADS) classification was used for assessment.[25] BI-RADS consists of 7 categories: BI-RADS 0: incomplete, BI-RADS 1: negative, BI-RADS 2: benign, BI-RADS 3: probably benign,

BI-RADS 4: suspicious for malignancy, BI-RADS 5: highly suggestive of malignancy, BI-RADS 6: known biopsy- proven malignancy.[26] Additionally, subdermal areolar tissue evaluation, parenchymal pattern, presence of solid/cystic lesion, axillary lymph node evaluation and presence of ductal ectasia were reported.

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean and standard deviation (SD), median (min-max) values, number (n), and frequency (%). The Kolmogorov-Smirnov test was used to evaluate the normality of data. Mann Whitney U Test was used to compare nonparametric variables. Chi square test and Fisher's exact test was used to compare categorical variables. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 82 patients, 41 in the study group and 41 in the control group, were included in the study (Table 1). Ovarian volume in the study group was calculated to be 13690.91±3051.81 and in the control group the volume was 8651.41±1578.06. As expected mean ovarian volume of PCOS patients was significantly higher ($p < 0.001$).

A significant difference was observed between the study and the control group in terms of BI-RADS categories ($p < 0.001$) (Table 2). A higher percentage of patients in the study group were categorized as BI-RADS 2 and 3 in comparison to the patients in the control group; 26.8% vs. 9.8%, 9.8% vs. 2.4%, respectively. Majority of patients in both groups were categorized as BI-RADS 1 and in none of the patients malignancy or a suspicion of malignancy was observed. Additionally, a significant difference was observed between the groups in terms of parenchymal pattern ($p = 0.02$) (Table 2). No parenchymal change was observed in 36.6% of the control group whereas this number was 17.1% in the study group. A significantly higher number of patients with PCOS had fibrocystic breast disease (14.6%) when compared to

TABLE 1: Biometrical evaluation of the control and the study group.

		Control Group (n=41)	Study Group (n=41)	p value
Age (years±SD)		34.24±3.7	34.24±3.7	>0.05
Medicine	no	41(100%)	9(22%)	**<0.001**
	yes	0(0)	32(78%)	
Systemic disease	no	28(68.3%)	17(41.5%)	**0.04**
	yes	13(31.7%)	24(58.5%)	
Ovarian volume (cm^3)		8651.41±1578.06	13690.91±3051.81	**<0.001**

TABLE 2: Ultrasonographic evaluation of the breast.

		Control Group (n = 41)	Study Group (n = 41)	p value
BI-RADS	0	11(26.8%)	0(0)	<0.001
	1	25(61%)	26(64.4%)	
	2	4(9.8%)	11(26.8%)	
	3	1(2.4%)	4(9.8%)	
Parenchymal pattern	None	15(36.6%)	7(17.1%)	0.02
	Fibroglandular	25(61%)	28(68.3%)	
	Fibrocystic	1(2.4%)	6(14.6%)	
Lesion type	None	34(82.9%)	33(80.5%)	0.61
	Cystic	7(17%)	7(17.1%)	
	Solid	0(0)	1(2.4%)	
Reactive axillary lymph nodes	Negative	36(87.8%)	35(85.4%)	0.74
	Positive	5(12.2%)	6(14.6%)	
Ductal ectasia	Negative	40(97.6%)	39(95.1%)	0.55
	Positive	1(2.4%)	2(4.9%)	

the control group (2.4%). In terms of lesion type, presence of reactive axillary lymph nodes and ductal ectasia, there were no differences between the groups and majority of patients in both groups were negative for these changes.

DISCUSSION

PCOS is a common endocrine disease that can progress with anovulatory infertility, cardiovascular disease, type 2 DM, insulin resistance and obesity in women of reproductive age. There are various studies that show changes in breast pattern in patients with PCOS due to hyperinsulinemia, hyperandrogenemia and hyperestrogenemia.[27,28] In this study, BI-RADS 2-3 breast patterns were found to be significantly higher in PCOS patients ($p < 0.001$). In addition, a significant difference was observed between the PCOS patients and healthy subjects in terms of breast parenchyma ($p = 0.02$). While patients with no beast changes were more common in the control group (36.6% vs. 17.1%), fibrocystic changes (14.6% vs. 2.4%) were more common in the PCOS group.

Normal breast development in women of reproductive ages is dependent on the balance between estrogen and progesterone. Considering that the transformation from ductal proliferation to ectasia is due to the effect of estrogen, it is argued that the development of benign breast disease is caused by hyperestrogenemia.[29] Inappropriate estrogen secretion causes an irreversible proliferative response in the ductal system and interalveolar stroma.[30] In addition, in some studies the role of IGF-1 in breast carcinogenesis was already shown.[31,32]

The prevalence of fibrocystic breast disease in the general population ranges from 30% to 60%, and the rate of breast cancer development in those with fibrocystic breast disease is 2-4 times higher.[33] On the other hand, there are not enough studies reporting on the relationship between PCOS and breast cancer.[34,35] D'Amelio et al. evaluated the relationship between PCOS and fibrocystic breast disease with ultrasonographic evaluation in a prospective case-controlled study and found a statistically significant correlation between PCOS and benign pathologies of the breast.[36] Similar findings were reported in another study conducted by Gumus et al.[22] Conversely, several prospective cohort studies reported no significant difference between PCOS patients and healthy subjects in terms of the development of the benign breast disease.[21,23]

Hormonal imbalance observed in PCOS patients is believed to be the underlying cause of fibrocystic breast disease. Furthermore, Panaritis et al., observed longer breast terminal duct size in patients with PCOS and attributed this change to the hormonal changes.[37] Ozkaya et al., investigated the effects of these hormonal changes on the development of fibrocystic breast by evaluating different PCOS phenotypes. They reported that the risk of fibrocystic breast disease was low in patients with high free testosterone levels and high Ferriman-Gallwey scores, and concluded that hyperandrogenemia could be a protective factor.[38] Furthermore, Talaei et al. observed an improvement in fibrocystic breast disease in patients receiving metformin treatment.[39] Metformin is one of the main drugs used especially in overweight patients with PCOS. A reduction in cyst size has been reported with an early start in treatment, as well as an improvement in the fibrocystic breast disease.

One of the main limitations of this study is the relatively small sample size, which is due to the single center design. In spite of this limitation, the results were significant, which can be related to the existing literature. In order to address the contradictory results in the literature regarding the association between PCOS and fibrocystic breast disease, multicenter studies with larger cohorts and an updated meta-analysis of the literature is needed.

CONCLUSION

This study evaluated the association between PCOS and fibrocystic breast disease and the risk of fibrocystic breast disease was found to be higher in patients with PCOS. A direct relationship between PCOS and breast cancer has not yet been reported in the literature. However, an increased risk of breast cancer is known in fibrocystic breast disease. Therefore, a routine breast evaluation of PCOS patients with ultrasonography is important for detection of fibrocystic breast disease and for long-term management of these patients.

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: *Pınar Yalçın Bahat, Nura Fitnat Topbaş Selçuki;* ***Design:*** *Meriç Kabakcı, Kübra Bağcı;* ***Control/Supervision:*** *Pınar Yalçın Bahat, Nail Uzunlulu;* ***Data Collection and/or Processing:*** *Kübra Bağcı, Nail Uzunlulu;* ***Analysis and/or Interpretation:*** *Eda Üreyen Özdemir, Nura Fitnat Topbaş Selçuki;* ***Literature Review:*** *Meriç Kabakcı, Kübra Bağcı;* ***Writing the Article:*** *Nura Fitnat Topbaş Selçuki;* ***Critical Review:*** *Nura Fitnat Topbaş Selçuki, Pınar Yalçın Bahat.*

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