Effects of progesterone treatment in polycystic ovary syndrome on pulmonary functions

Polikistik over sendromunda progesteron tedavisinin pulmoner fonksiyonlara etkisi

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ABSTRACT

Objective: We aimed to evaluate patients with polycystic ovary syndrome in terms of respiratory function tests and to investigate the relationship between progesterone therapy and pulmonary functions.

Methods: Fifty patients, who were diagnosed polycystic ovary syndrome (PCOS) according to Rotterdam criteria, at gynecology and obstetrics clinic of a research and training hospital included in the study group. Fifty healthy person were included in the control group. Both groups were evaluated with pulmonary function tests (PFT) at pulmonary medicine clinic of a university hospital. Independent from PFT survey, the patient group was treated with two cycles of medroxyprogesterone acetate between 16 and 25 days of the cycle as the standart follow up and treatment at gynecology and obstetrics clinic. Afterwards they were evaluated with PFT again. Statistical analysis of independent measurements were analyzed by Student's t-test. Mann-Whitney U, Wilcoxon test was used to analyze the data without normal distribution. P value <0.05 was considered as significant.

Results: Post-treatment pulmonary function test values were compared with pre-treatment values. Post-treatment forced expiratory volume during the first

ÖZET

Amaç: Çalışmamızda, polikistik over sendromlu hastaların solunum fonksiyon testlerinin ve progesteron tedavisinin solunum fonksiyonlarına etkisinin değerlendirilmesi amaçlanmıştır.

Yöntem: Eğitim ve araştırma hastanesi kadın hastalıkları ve doğum kliniğinde Rotterdam Kriterleri'ne göre polikistik over sendromu (PKOS) tanısı almış hastalar ve PKOS olmadığı bilinen sağlıklı kadınlar üniversite hastanesi göğüs hastalıkları kliniğinde solunum fonksiyon testi (SFT) ile değerlendirildi. SFT'den bağımsız olarak, PKOS hastaları, kadın doğum kliniğinde iki siklus boyunca, siklusun 16. ve 25. günleri arasında medroksiprogesteron asetat ile tedavi edildi. Tedavi sonrasında hastalar tekrar SFT ile değerlendirildi. Bağımsız değişkenlerin karşılaştırılmasında Student's t-test, normal dağılım göstermeyen değişkenlerde Mann-Whitney U test ve Wilcoxon test kullanıldı. P<0.05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Tedavi sonrası FEV1 ve FVC değerleri tedavi öncesine göre anlamlı olarak artmış bulundu.

Sonuç: PKOS hastalarının tedavi öncesi SFT

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second (FEV1) and forced vital capacity (FVC) values were found increased after the treatment.

Conclusion: Although the pulmonary function of PCOS patients were not different from that of the healthy female population, progesterone treatment has been shown to increase FEV1 and FVC parameters.

Key Words: Polycystic ovary syndrome, medroxyprogesterone acetate, pulmonary function test

değerleri ile kontrol grubu arasında anlamlı farklılık saptanmazken, tedavi sonrası FEV1 ve FVC değerleri artmış bulundu.

Anahtar Kelimeler: Polikistik over sendromu, medroksiprogesteron asetat, solunum fonksiyon testi

INTRODUCTION

The polycystic ovary syndrome (PCOS) is an important cause of both menstrual irregularities and androgen excess, affecting between 5% and 15% of women of reproductive age (1). PCOS is characterized by impairment of ovulation, reduced fertility, miscarriage, and imbalance of reproductive hormones (2). Previous studies have demonstrated that women affected by PCOS show higher rates of respiratory disorders in comparison to the general population (3, 4). It is possible that hormonal changes in women affected by PCOS such as hyperandrogenism, hyperestrogenism and variable levels of gonadotropins in the blood may cause pulmonary function problems (2). PCOS and asthma share many common features regarding metabolic control, systemic inflammation, allergy, menstrual cycle and female sex hormones. Both conditions are aggravated by obesity and improved by weight loss (5). According to a study, 10.6% of patients with PCOS, were admitted to hospital because of asthma compared to only 4.5% among the control group without PCOS. Furthermore, a higher prevalence of respiratory diseases in general was seen among the patients with PCOS (6). Furthermore, there are growing evidences proving that progesterone is potent respiratory stimulant. Physiological effects of progesterone can affect various systems, including immune and cardiorespiratory systems. Progesterone is known to cause a decrease in upper airway resistance. However there is no clear understanding of how progesterone mediates its stimulant respiratory effects. Mechanistically, it was demonstrated that this hormone elicits some of its respiratory effect via the classical mechanism of the nuclear progesterone receptor. Moreover, experimental results indicate that the membrane progesterone receptors could have a key role in the regulation of the respiratory control system (7). Menstrual irregularity and/or oligomenorrhea, which is a hallmark of PCOS, has a detrimental effect on lung function. Women with menstrual irregularity and/or oligomenorrhea are known to have a significantly lower forced vital capacity (FVC) than women with regular menstruations. The lung function is also affected by body mass index (BMI). At BMI 25 (kg/m2) FVC and FEV1 (forced expiratory volume during the first second) were at their maximum. Higher or lower BMI is associated with a lower FVC and FEV1 among women with irregular menstruations (8). We also aimed to evaluate patients with polycystic ovary syndrome in terms of respiratory health and to investigate the relationship between progesterone therapy and pulmonary functions, which is one of the treatment options of policystic ovary syndrome.

MATERIAL and METHOD

One hundred premenopausal women were included into the study, whose diagnosis and treatment were done in the research and training hospital gynecology clinic. Study was approved by the university hospital Ethics Committee. Participants were informed about the study design and they signed the consent form to participate to the study. Fifty patients between the ages of 15 and 45, who had polystic ovary syndrome diagnosis according to Rotterdam criteria, having no systemic disease, no history of smoking, no asthma and chronic obstructive pulmonary disease (COPD) were included in the study group. Non-classic adrenal 21-hydroxylase deficiency, hyperprolactinemia and androgen secreting tumors were excluded by appropriate tests before the diagnosis of PCOS was made. Diagnosis is based on the Rotterdam criteria, comprising two of the following three conditions: (a) hyperandrogenism, (b) oligo- and/or anovulation, and (c) polycystic ovaries on ultrasound (9). Fifty patients who had regular menstrual cycles, no ultrasonographically diagnosed polycystic ovary syndrome, no signs of hyperandrogenism, 15-45 years of age, no systemic disease, no smoking, no asthma and no COPD were included in the control group. Patients were assessed by pulmonary function tests (PFT) when they were diagnosed with polycystic ovary syndrome and the control group was assessed by PFT when they applied for outpatient examinations. Pulmonary function tests were explained to the participants prior to measurement and a test was performed for adaptation with a spirometer (Quark b2, Cosmed S.r.l., Italy). The procedure required the patient to wear a nose clip and perform a forced expiratory maneuver. Before the mouthpiece was placed into the patient's mouth, patient was instructed to inhale completely then take a deep and rapid expiration as much as she could. Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), forced expiratory flow at 25–75% vital capacity (FEF25-75), peak expiratory flow (PEF) were measured, and FEV1/FVC ratio was calculated. Acceptability criteria were applied to all participants (10). The patient group was then treated with two cycles of 10 mg/day medroxyprogesterone acetate between 16 and 25 days of the cycle. Afterwards they were evaluated by PFT again. Demographic data such as age, gravida, parity, body weight, body mass index of the patients were recorded in the application. Patients were also tested for follicle-stimulating hormone (FSH), luteinising hormone (LH), 17b-estradiol (E2), values before and after progesterone treatment. FEV1, FVC, FEV1/FVC, FEF 25-75, PEF were also evaluated before and after treatment in PFT. The obtained data were analysed using SPSS 18.0 (SPSS, Chicago, IL) package programs. Continuous quantitative data are given as n, mean value and standard deviation, and qualitative data are expressed as n, median and 25th and 75th percentiles, respectively. Statistical analysis of independent measurements and continuous data showing normal distribution were analyzed by Paired Sample t-test. Mann-Whitney U, Wilcoxon test was used to analyze data with no normal distribution or the data of score variables. Chi-square test was performed for data sets in categorical structure. P value <0.05 was accepted as statistically significant.

RESULTS

When the demographic characteristics of the patient and the control group were compared, it was observed that there was statistically significant difference between the two groups in terms of age, gravidity and parity. Median age was 20 in the patient group and 24.5 in the control group ($p <0.001$). However, body weight and body mass index (BMI) was not significantly different between the groups. Median weight was 61.5 kilograms in the patient group and 60.5 kg in the control group ($p> 0.05$), median BMI was 24 kg/m2 in the patient group and 23.4 kg/m2 in the control group ($p> 0.05$). Demographic characteristics of the patient group and control group are shown in table 1. Also, hormone values were

compared before and after the treatment in the patient group and the difference in hormone levels is considered as statistically significant (p <0.001) (Table 2). Pulmonary function tests were performed in the follicular phase before treatment and after 2 cycles of cyclic progesterone treatment in the patient group. PFT were performed in the control group when they applied for polyclinic examination at the follicular phase. The PFT results of the control group were compared with the results of the patient group before the progesterone treatment. There was no statistically significant difference between the values obtained from the PFT in the two groups (p> 0.05) (Table 3). Also, pre-treatment pulmonary function test values were compared with post-treatment values in the patient group. Post treatment FEV1 and FVC values increased after the treatment (p<0.001) (Table 4).

Table 1. Demographic and clinical characteristics of the study population

		Patient (PCOS) Group N=50 (%)	Control group N=50 (%)	P value
Age (years)		20(17.5-23.5)	24.5(21-29)	p<0.001
Gravidity	**0**	30(60%)	10(20%)	p<0.001
	1	6(12%)	15(30%)	
	2	9(18%)	19(38%)	
	3	4(8%)	6(12%)	
	4	1(2%)	0	
Parity	**0**	30(60%)	10(20%)	p<0.001
	1	11(22%)	24(48%)	
	2	8(16%)	12(24%)	
	3	1(2%)	4(8%)	
Weight (kg)		61.5(52-71.5)	60.5(54-64.2)	p>0.05
BMI (kg/m2)		24(21.4-29.3)	23.4(21.8-27.6)	p>0.05

PCOS, Polycyctic ovary syndrome; BMI, Body mass index

Table 2. Patients' (PCOS) hormonal characteristics before and after treatment

	Before Treatment	After Treatment	P value
FSH (mIU/mL)	7.3(5.8-8.3)	5.4(4.3-6.2)	p<0.001
LH (mIU/mL)	11.8(8.6-14.7)	5.3(4.7-6.2)	p<0.001
Estradiol (pg/mL)	77(48-95)	25(21-29)	p<0.001

PCOS, polycystic ovary syndrome; FSH, follicle-stimulating hormone; LH, luteinising hormone

Table 3. Pulmonary function test results in the PCOS group before treatment and in the control group

	Patient (PCOS) Group (Before treatment) N=50	Control Group N=50	P value
FEV1	2.92±0.54	2.90±0.52	p>0.05
FVC	3.35±0.54	3.31±0.57	p>0.05
FEV1/FVC %	88.65 (85-92.6)	89.55 (85.5-92.15)	p>0.05

FEV1. forced expiratory volume in 1 second; FVC. forced vital capacity

Table 4. Pulmonary function test results in the PCOS group before and after progesterone treatment

	Patients (PCOS) Group Before Treatment N=50	Patients Group After Treatment N=50	P value
FEV1	2.84 (2.55-3.2)	3.23 (3-3.8)	p<0.001
FVC	3.33 (2.99-3.64)	3.62 (3.44-4.24)	p<0.001
FEV1/FVC %	88.65 (85-92.3)	92 (87-95)	p>0.05

FEV1. Forced expiratory volume in 1 second; FVC. forced vital capacity

DISCUSSION

The present study provides evidence that progesterone supplementation results in better pulmonary function test results in patients with PCOS. Changes in the pulmonary function tests were evaluated in patients with PCOS after progesterone treatment and compared with the results of the control group. While the body weight and BMI were similar between the two groups, age, gravida and parity were found to be higher in the control group. This can be explained by the fact that oligo-ovulation is a common occurrence in women with PCOS and the duration of the conception is generally prolonged in these patients. As it is known, most women with PCOS and oligo-ovulation, require ovulation induction treatments in order to have pregnancy and women with PCOS have an increased risk of pregnancy loss (11). No significant differences were reported between the study and control groups' pulmonary function tests before the progesterone treatment (p>0.05) (Table 3). Ucok et. al. (12), also could not find any difference at FEV1, FVC, FEF25-75 and PEF values between PCOS patients and normal controls .

Then, two cycles of 10 mg/day medroxyprogesterone acetate treatment was given between the 16 and 25 days of the menstruel cycle in the patient (PCOS) group. The post-treatment FEV1 and FVC values were found to be significantly increased when compared both with the pre-treatment values of PCOS patients and with the control group. It can be the result of patient selection, which the PCOS

group and the control group were chosen from non-asthmatic patients. However, the mean FEV1/FVC values were not significantly different before and after the treatment (p> 0.05). This can be due to increase at both FEV1 and FVC values at the same time. According to these findings, as the PCOS group and control group did not have bronchial obstruction at the beginning, there might be no real correction of bronchial obstruction with progesteron therapy, Nonetheless, the difference between pre-treatment and post-treatment FEV1 and FVC values of PCOS patients should be based on the overall increase of lung volumes and capacity after progesterone treatment. Many studies in the literature report that women with PCOS are prone to respiratory problems. However, the mechanisms underlying such disorders remain unclear. Premenopausal women have been reported to experience drops in peak flow and worsening of asthma symptoms before and during menses, often experiencing relief after the onset of progesterone therapy (13). Moreover, in a study conducted with hormone replacement therapy (HRT), mean values of FEV1 and FVC were significantly higher among current HRT users than noncurrent users in the entire population of women and among women without asthma, former smokers, and never smokers (14). Our findings are also compatible with that, we found PFT values increased with progesterone therapy.

However, Ucok et. al. (15) suggest that there were no significant differences in the pulmonary function tests between women with PCOS and healthy controls. Negative correlations between the pulmonary function tests and anthropometric measurements observed in healthy controls are absent in PCOS women and this may indicate a disruption of relationship between the upper body anthropometry and respiratory function. Their results suggest that the upper body anthropometry and respiratory function relations might have impaired in patients with PCOS and this situation might support the increased tendency for poor health status in patients with PCOS . It has been shown that sex hormones play a role in the development of many physiological processes. There are many studies in the literature, showing that estrogen, progesterone and testosterone affect respiratory functions and effects of progesterone on respiration. As an example, progesterone reduces pulmonary inflammation, improves lung function, repairs the damaged lung epithelium, and promotes faster recovery following influenza A virus infection. Progesterone causes protection against severe outcome from influenza by inducing production of the epidermal growth factor, amphiregulin, by respiratory epithelial cells (16). Hyperventilation status during pregnancy is associated with increased progesterone levels. The findings of the Slatkovska et. al. (17) study support the hypothesis that phasic menstrual cycle changes in resting minute ventilation and PaCO2 may be due to the stimulatory effects of progsterone, estradiol and the strong ion difference on ventilatory drive. In the luteal phase where the progesterone level is elevated, hyperventilation and decreased ETCO2 have been shown. Some studies investigated the effect of progesterone on ventilation. Bayliss and Millhorn (18) showed that a progesterone receptor agonist, R5020, causes an increase in respiratory frequency. They revealed that respiratory response to progesterone is mediated at hypothalamic sites through an estrogen dependent progesterone receptor mediated mechanism requiring RNA and protein synthesis. The estrogen dependence of the respiratory response to progesterone is likely a consequence of the demonstrated induction of progesterone receptor mRNA and progesterone receptor in hypothalamic neurons by estrogen. In short, neural mechanisms underlying the stimulation of respiration by progesterone were similar to those mediating its reproductive effects. It has not been fully explained by which mechanisms the progesterone stimulates the respiration. There is upregulation of progesterone receptors in the brain and spinal cord after estrogen exposure in both men and females (19, 20). Based on the lesion studies, Feldman et. al.

(21) suggested that the respiratory stimulant effect of progesterone is due to stimulation of progesterone receptors in the hypothalamus after estrogen action. As our result; although the pulmonary function of PCOS patients is not different from that of the healthy female population, progesterone has been shown to increase these values. However, studies should continue to show which mechanisms these hormones have affected. A better understanding of the effects of sex hormones on respiration may lead to the application of hormone therapies in respiratory problems.

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