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Polycystic Ovary Syndrome in Adolescent Period: Physical, Metabolic, and Hormonal Features

Adölesan Dönemde Polikistik Over Sendromu: Fiziksel, Metabolik ve Hormonal Özellikler

Mustafa HARI[1]
0000-0002-2314-2103
Ramazan GEN[2]
0000-0001-6558-6354
Mahmut Bakır KOYUNCU[3]
0000-0002-0507-9294
Hüseyin DURUKAN[4]
0000-0001-5894-3421
Mehmet Burak Yavuz ÇİMEN[5]
0000-0002-1274-3499

[1]Department of Internal Medicine, Mersin University Faculty of Medicine, Mersin, Türkiye

[2]Department of Endocrinology, Mersin University Faculty of Medicine, Mersin, Türkiye

[3]Department of Hematology, Mersin University Faculty of Medicine, Mersin, Türkiye

[4]Department of Gynecology and Obstetrics, Mersin University Faculty of Medicine, Mersin, Türkiye

[5]Department of Medical Biochemistry, Mersin University Faculty of Medicine, Mersin, Türkiye

Corresponding Author
Sorumlu Yazar
Mustafa HARI
mustafa_hari@hotmail.com

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ABSTRACT

Aim: The Rotterdam criteria are used in the diagnosis of polycystic ovary syndrome (PCOS). However, since menstrual irregularities and acne are seen more frequently in adolescents, it is theoretically difficult to use the Rotterdam criteria. The aim of this study was to investigate whether the Rotterdam criteria are sufficient for the diagnosis of PCOS in adolescence.
Material and Methods: Thirty patients and thirty healthy individuals between the ages of 16 and 18 years were included in the study. Anthropometric measurements, Ferriman Gallwey score (FGS), ultrasonographic ovarian volumes, androgens, and other hormone levels of the participants were recorded.
Results: There was a statistically significant positive correlation between the homeostatic model assessment of insulin resistance (HOMA-IR) and waist circumference/hip circumference ratio in the patient group ($r=0.656$, $p<0.001$). The mean luteinizing hormone (LH) levels of the patient group were found to be statistically significantly higher than the control group ($p=0.048$). The median FGS of the patient group was statistically significantly higher than the control group ($p<0.001$). Serum total testosterone levels of adolescent girls who have polycystic ovaries were statistically significantly higher than the ones who have not ($p=0.001$). The median FGS of those with polycystic ovarian appearance on ultrasonography was found to be statistically significantly higher than those without ($p=0.034$).
Conclusion: Among the Rotterdam diagnostic criteria, oligoanovulation, acne, and polycystic ovarian appearance on ultrasonography can be seen in healthy adolescents without PCOS. In this study, the most supportive finding for the diagnosis of PCOS was the appearance of polycystic ovaries accompanying moderate hirsutism.
Keywords: Polycystic ovary syndrome; adolescent; free androgen index; HOMA-IR.

ÖZ

Amaç: Polikistik over sendromu (PKOS) tanısı için Rotterdam kriterleri kullanılmaktadır. Bununla birlikte, adolesanlarda adet düzensizlikleri ve sivilceler daha sık görüldüğünden teorik olarak Rotterdam kriterlerini kullanmak zordur. Bu çalışmanın amacı ergenlik çağındaki PKOS tanısı için Rotterdam kriterlerinin yeterli olup olmadığını incelemektir.
Gereç ve Yöntemler: Çalışmaya 16 ve 18 yaş arası 30 hasta ve 30 sağlıklı birey dahil edildi. Çalışmaya dahil edilenlerin antropometrik ölçümleri, Ferriman Gallwey skoru (FGS), ultrasonografik over hacimleri, androjenler ve diğer hormon seviyeleri kaydedildi.
Bulgular: Hasta grubunda insülin direncinin homeostatik model değerlendirmesi (HOMA-IR) ile bel çevresi/kalça çevresi oranı arasında istatistiksel olarak anlamlı pozitif bir korelasyon vardı ($r=0,656$; $p<0,001$). Hasta grubunun ortalama luteinizing hormone (LH) düzeyleri kontrol grubuna göre istatistiksel olarak anlamlı derecede daha yüksek olarak bulundu ($p=0,048$). Hasta grubunda medyan FGS kontrol grubundan istatistiksel olarak anlamlı derecede daha yüksekti ($p<0,001$). Polikistik overi olan adolesan kızların serum total testosteron düzeyleri polikistik overi olmayanlara göre istatistiksel olarak anlamlı derecede daha yüksekti ($p=0,001$). Ultrasonografide polikistik over görünümü olanların ortanca FGS'si polikistik over görünümü olmayanlara göre istatistiksel olarak anlamlı derecede daha yüksek olarak bulundu ($p=0,034$).
Sonuç: Rotterdam tanı kriterlerinden oligoanovulasyon, akne ve ultrasonografide polikistik over görünümü, PKOS olmayan sağlıklı adolesanlarda da görülebilir. Bu çalışmada PKOS tanısını en çok destekleyen bulgu, orta derecede hirsutizme eşlik eden polikistik over görünümü idi.
Anahtar kelimeler: Polikistik over sendromu; ergen; serbest androjen indeksi; HOMA-IR.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrinological disorder characterized by menstrual irregularity and hyperandrogenism (1). At least two of the following Rotterdam 2003 criteria are necessary for diagnosis (2). These criteria include oligo-anovulation over six months, clinical or laboratory findings of hyperandrogenism, and polycystic appearance of ovaries on ultrasonography.

The most common earliest findings of PCOS start with the maturation of the Hypothalamic-hypophyseal-ovarian axis. Due to this axis's developmental delay in some adolescents, it is sometimes difficult to differentiate the menstrual pattern from the anovulation associated with puberty. Although most adolescents start to have regular periods in the second year after the first menstruation, the irregularity may continue without reason (3). Studies showed that the responsible cause is PCOS in 20% of the patients with amenorrhea and 75% of infertile women. Even though 25% of the women of childbearing age have a polycystic appearance on ultrasonography, only 10% of these women have a PCOS diagnosis (4,5).

Excess androgen has an essential role in PCOS pathophysiology. More than 80% of the patients with PCOS have hyperandrogenism (6). Clinical findings of high serum androgen levels, such as acne and hirsutism, may not be optimal for adolescent girls' PCOS evaluation because 90% of the average teenage population has acne. The frequency of acne drops to 23% in adulthood age (7). Hirsutism is a more reliable clinical criterion to predict hyperandrogenism (8). As there is no other scale to evaluate hirsutism, the Ferriman Gallwey score (FGS) is also used in adolescents (9).

PCOS is a disorder characterized by menstrual irregularity and hyperandrogenism, in which Rotterdam criteria are used to diagnose. Since menstrual irregularities and acne are seen more frequently in adolescents, it is theoretically difficult to use the Rotterdam criteria. We examine to show whether the Rotterdam diagnostic criteria are sufficient for the diagnosis of PCOS in adolescence.

MATERIAL AND METHOD

In this study carried out to investigate the parameters used in the diagnosis of PCOS in adolescents, two groups, the PCOS group (16-18 years old, 2 years past the first menstrual period) and the control group (16-18 years old, 2 years past the first menstrual period), were used. The smallest significant difference between the luteinizing hormone (LH) values, which is one of the parameters to be calculated between groups, is 6.2 units of source (IU/L), and it is necessary to study with a minimum of 27 in each group and a minimum of 54 adolescents in total, with 80% power and 5% type I error (10).

We included 30 newly diagnosed patients with PCOS and 30 healthy volunteers without any complaints or diseases aged between 16 and 18 years who were admitted to the Endocrinology outpatient clinic at Mersin University between 01.10.2016 and 01.10.2017.

This age group was included because people over the age of 16 can apply to the adult endocrinology polyclinic. Cases with any chronic disease or using oral contraceptives were excluded. All of the patients had a dermatological examination in terms of acne or acanthosis nigricans. We determined the hirsutism level according to the FGS. Patients who had FGS ≥8 and/or acne were accepted as clinically hyperandrogenic.

We collected 10-15 ml of blood samples from each patient between 3-5 days of the menstrual cycle for biochemical and hormonal tests. Patients not having had menstruation for more than three months were started on 10 mg/day of medroxyprogesterone for seven days. Blood samples of these patients were collected on the third day of menstrual bleeding under medroxyprogesterone treatment. As the test results may vary according to hunger and satiety, the sample collection time was between 8:00-10:00 am. The height, weight, waist circumference (WC), and hip circumference (HC) of all cases were measured and recorded. We used a homeostatic model assessment of insulin resistance (HOMA-IR) to calculate insulin resistance. It is the value obtained by dividing the product of plasma insulin level and plasma glucose level (mg/dl) by 405.

The same gynecologist evaluated all cases' ovaries by ultrasonography between 3-5 days of the menstrual cycle. Length, thickness, width, number of follicles, and parameters of the largest and smallest follicles of patients' ovaries were recorded. Ovarian volume was calculated as the following formula (11-14):

length x thickness x width x pi number / 6 (Figure 1).

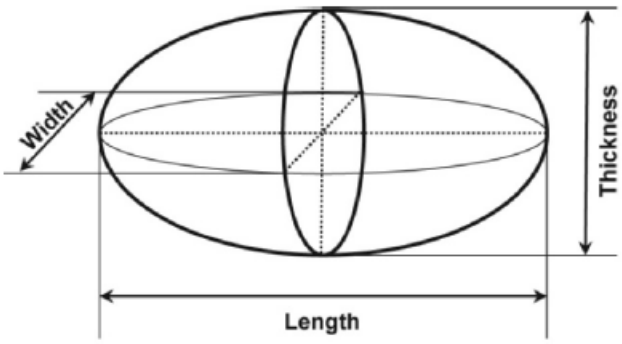

Figure 1. Dimensions of the ellipsoid ovary

The presence of 12 or more antral follicles of 2-9 mm in one or both ovaries; or ovarian volume over 10 cm^3 was evaluated in favor of PCOS (15,16). This study was conducted in accordance with the Declaration of Helsinki. It was approved by the Mersin University Ethics Committee (06.10.2016, 305). Written informed consent of all patients and controls were obtained.

Statistical Analysis

The Shapiro-Wilk test was used for normal distribution control. Numerical variables that provide normality assumption were summarized in terms of mean±standard deviation, and variables that do not provide are outlined in terms of the median (minimum-maximum). In comparing the two groups, the independent sample t-test was used when the normality assumption was provided, and the Mann-Whitney U test was used when it was not provided. Pearson and Spearman correlation coefficient was calculated for the relationship between two continuous variables. $p<0.05$ was taken as the significance level, and statistical analyses were done with SPSS v.20 package.

RESULTS

A total of 60 adolescent girls aged between 16 and 18 years, 30 of whom were in the patient group newly diagnosed with PCOS and 30 in the control group, were included in the study. The menstrual cycle length of the patient group was significantly longer than the control group (p<0.001). While the menstrual period in the patient group was 40-90 days, it was 24-35 days in the control group. One (3.3%) of the cases in the patient group did not have oligomenorrhea. 60% (n=18) of the patients had six or fewer, 23.3% (n=7) had four or fewer, and 13.3% (n=4) had three or fewer menstrual cycles per year. The annual number of menstrual cycles in the control group was ten or more. General anthropometric and ultrasonographic characteristics of the groups were shown in Table 1.

The mean WC (78.93±16.56 cm) of the patient group was found to be statistically significantly higher than the mean WC (68.37±10.33 cm) of the control group (p=0.006). Also, the mean HC (100.75±12.38 cm) of the patient group was found to be statistically significantly higher than the HC (91.23±8.22 cm) of the control group (p=0.001). While the mean WC/HC ratio of the patient group was 0.77±0.08, the mean WC/HC ratio of the control group was 0.75±0.12. The WC/HC ratio of the patient group was not statistically different from the control group (p=0.345). While the mean body mass index (BMI) index of the patient group was 24.00±6.81, the mean BMI of the control group was 20.72±3.92. The BMI of the patient group was found to be statistically significantly higher than the control group (p=0.031).

Acne was detected in 26 (86.7%) adolescents in the patient group, while 14 (46.7%) adolescents in the control group had acne (p=0.001).

When the patient group was compared with the control group in terms of HOMA-IR, there was no statistically significant difference (p=0.871). The median HOMA-IR level was found to be 2.5 (range, 0.6-17) in the patient group, and 2.45 (range, 1-8.7) in the control group. HOMA-IR ≥2.5, as an indicator of insulin resistance, was considered high. The HOMA-IR was found to be high in 13 (43.3%) patients in the patient group and 15 (50.0%) adolescents in the control group (p=0.605).

There was a statistically significant positive correlation between HOMA-IR and WC/HC ratio (r=0.656, p<0.001) in the patient group, also a statistically significant positive correlation was found between HOMA-IR and BMI in the patient group (r=0.645, p<0.001).

The mean LH level (9.43±6.55 IU/L) of the patient group was found statistically significantly higher than the mean LH level (6.61±3.88 IU/L) of the control group (p=0.048). There was no significant difference between the groups in terms of serum sex hormone binding globulin (SHBG) levels and dehydroepiandrosterone sulfate (DHEAS) levels (p=0.987, and p=0.857, respectively). A significant difference was found between the groups of serum total testosterone (p=0.032) and 17-OH progesterone (p=0.039) levels, and both parameters were higher in the patient group. The mean total testosterone level was found to be 0.34±0.18 ng/ml in the patient group and 0.25±0.13 ng/ml in the control group. The median 17-OH progesterone level was 0.56 (range, 0.20-1.62) ng/ml in the patient group, while it was 0.46 (range, 0.20-1.34) ng/ml in the control group (Table 2).

There was no significant difference in the free androgen index (FAI) level between the two groups (p=0.264). FAI reference sample was 1-3%. The number of adolescents with FAI >3% was determined as 8 (26.7%) in the patient group and as 4 (13.3%) in the control group (p=0.197). Although it was not statistically significant the number of adolescents with high FAI was higher in the patient group than in the control group.

The total number of follicles (22.87±7.71) in the patient group was found to be statistically significantly higher than the total number of follicles (13.39±5.59) in the control group (p<0.001). There was no statistically significant correlation between FAI and the total number of follicles in the patient group (r=0.161, p=0.432).

The median FGS (13.5; range, 3-29) of the patient group was found statistically significantly higher than the median FGS (3, range, 1-11) of the control group (p<0.001).

In the patient group, the number of patients with a polycystic ovarian appearance on ultrasonography was 23 (76.7%), while 8 (26.7%) of the control group had a polycystic ovarian appearance in the ovaries on ultrasonography (p<0.001).

An inverse difference was found between polycystic ovarian appearance and HOMA-IR (p=0.020). HOMA-IR was found to be higher in adolescents without polycystic ovarian appearance with a median of 3.2 (range, 1-17) than in adolescents with polycystic ovarian appearance with a median of 2.2 (range, 0.6-8.7). There was no significant difference between adolescents with and without a polycystic ovarian appearance in terms of serum SHBG levels (p=0.743) and DHEAS (p=0.315). Serum total testosterone level (0.36±0.16 ng/ml) of adolescent girls who have a characteristic sonographic appearance of polycystic ovaries were statistically significantly higher than the serum total testosterone level (0.23±0.14 ng/ml) of the ones who had not a characteristic sonographic appearance of polycystic ovaries (p=0.001). Serum 17-OH progesterone levels of adolescent girls who have a characteristic sonographic appearance of polycystic ovaries were statistically significantly higher than the ones who had not (p=0.001). The median FGS of those with a polycystic ovarian appearance on ultrasonography was found to be statistically significantly higher than those without polycystic ovarian appearance (p=0.034, Table 3).

Table 1. Comparison of demographic, anthropometric, and ultrasonographic measurements

	PCOS (n=30)	Control (n=30)	p
Age (year)	17.27±0.83	16.80±0.71	**0.023**
First menstrual age	12.57±0.97	12.80±0.66	0.283
Height (cm)	163.89±5.83	165.03±5.79	0.458
Weight (kg)	66.21±20.96	57.17±10.93	**0.048**
WC (cm)	78.93±16.56	68.37±10.33	**0.006**
HC (cm)	100.75±12.38	91.23±8.22	**0.001**
WC/HC ratio	0.77±0.08	0.75±0.12	0.345
BMI (kg/m^2)	24.00±6.81	20.72±3.92	**0.031**
Right OV (cm^3)	6.48±3.32	5.67±2.99	0.335
Left OV (cm^3)	6.15±3.12	5.07±2.29	0.144

PCOS: polycystic ovary syndrome, WC: waist circumference, HC: hip circumference, BMI: body mass index, OV: ovarian volume

Table 2. Comparison of laboratory and hormonal parameters

	PCOS (n=30)	Control (n=30)	p
Fasting blood glucose (mg/dl)	89.90±6.65	88.37±8.19	0.429
Insulin (IU/ml)	11 (15.8) [3-84]	11 (6) [5-37]	0.982
Homeostatic model assessment for insulin resistance	2.5 (3.9) [0.6-17]	2.45 (1.4) [1-8.7]	0.871
Triglyceride (mg/dl)	86.07±26.83	90.40±30.15	0.563
Total cholesterol (mg/dl)	159.76±26.41	164.00±26.94	0.544
Low density lipoprotein cholesterol (mg/dl)	84.68±22.27	85.00±21.57	0.956
High density lipoprotein cholesterol (mg/dl)	56.62±13.93	60.53±13.60	0.280
Thyroxine (pmol/L)	15.95±3.371	16.02±2.42	0.926
Thyroid stimulating hormone (IU/ml)	1.99±1.21	1.85±0.91	0.608
Follicle stimulating hormone (IU/L)	5.37±1.81	5.30±2.33	0.888
Luteinizing hormone (IU/L)	9.43±6.55	6.61±3.88	**0.048**
Prolactin (ng/ml)	22.44±10.02	19.52±9.41	0.249
Sex hormone binding globulin (mg/L)	4.84 (4.52) [0.76-17.85]	4.78 (2.50) [1.81-8.92]	0.987
Total testosterone (ng/ml)	0.34±0.18	0.25±0.13	**0.032**
17-OH progesterone (ng/ml)	0.56 (0.35) [0.20-1.62]	0.46 (0.18) [0.20-1.34]	**0.039**
Dehydroepiandrosterone sulfate (ug/dl)	313.40±164.95	306.87±108.17	0.857
Free androgen index	2.05 (2.77) [0.12-18.01]	1.22 (1.59) [0.33-6.05]	0.264
Ferriman Gallwey score	13.5 (6) [3-29]	3 (4) [1-11]	**<0.001**

Table 3. Comparison of adolescents with and without a polycystic appearance

	With PA (n=31)	Without PA (n=29)	p
Homeostatic model assessment for insulin resistance	2.2 (2.0) [0.6-8.7]	3.2 (3.4) [1-17]	**0.020**
Sex hormone binding globulin (mg/L)	4.84 (3.08) [0.76-14.72]	4.82 (4.45) [1.29-17.85]	0.743
Total testosterone (ng/ml)	0.36±0.16	0.23±0.14	**0.001**
17-OH progesterone (ng/ml)	0.56 (0.42) [0.26-1.62]	0.44 (0.19) [0.20-1.34]	**0.001**
Dehydroepiandrosterone sulfate (ug/dl)	327.65±154.56	290.75±120.54	0.315
Free androgen index	2.10 (2.44) [0.33-18.01]	1.19 (0.81) [0.12-10.40]	0.266
Ferriman Gallwey score	10 (10) [1-29]	4.5 (10) [1-18]	**0.034**

DISCUSSION

The primary aim of this study was to examine whether the Rotterdam diagnostic criteria are sufficient for PCOS diagnosis in adolescence. The secondary purpose was to establish the relationships of HOMA-IR and FAI with clinical and laboratory findings of PCOS.

One of the clinical signs of hyperandrogenism is acne vulgaris. While 26 (86.7%) of the patients included in this study had acne, 14 (46.7%) of those included in the control group had acne vulgaris. According to the study by Kaewnin et al. (17), the presence of moderate acne in adolescence was determined as the most decisive risk factor for PCOS.

One of the diagnostic criteria for PCOS, according to Rotterdam 2003 consensus, is oligoanovulation. In this study, 26 (86.7%) of the 30 patients had oligoanovulation for at least six months. In a study by van Hooff et al. (18) involving school-age children in adolescence, it was found that oligoanovulation continued at the age of 18 due to unknown reasons in 52% of those aged 15-18 years.

Although a significant positive correlation was found between BMI and HOMA-IR in our study, the detection of insulin resistance in thin individuals shows that this relationship is not clear. Zeng et al. (19), showed that the relationship between obesity and insulin resistance was disproportionate. The BMI was more than 25 kg/m^2 in only 6 (20%) of the patients in the patient group participating in this study. The reason why insulin resistance is not related to polycystic appearance may be due to the lower BMI of the patients included in this study. Again, the presence of insulin resistance in the adolescent group without PCOS may also explain this situation. In this study, no significant relationship was found between HOMA-IR and the total number of follicles. Similarly, in the study of Reid et al. (20), no significant relationship was found between HOMA-IR and the number of follicles.

There was no significant difference between the groups in terms of serum SHBG levels. Many studies are showing that low levels of SHBG are associated with PCOS. Qu et al. (21), reported that the SHBG levels were associated with an increased risk of PCOS.

In this study, no significant difference was found between the groups regarding DHEAS levels. Kumar et al. (22) found the total T, free T, A4, DHEAS, and BMI were higher in women with PCOS than in control women.

Besides, there was no significant difference in FAI and HOMA-IR between both groups, there was a significant difference in FGS. In a comparative study by Hernandez et al. (23), including 25 patients with clinical findings of hyperandrogenism and 21 healthy adolescents, FAI, FGS, free testosterone, and total testosterone levels were significantly higher in the patient group.

Higher levels of total testosterone and 17-OH progesterone were found in patients with a polycystic ovarian appearance on ultrasonography compared to those without a polycystic ovarian appearance on ultrasonography. There was a statistically significant difference between the patient and control group for those with and without a polycystic ovarian appearance on ultrasonography.

There were 23 (76.7%) patients with a polycystic ovarian appearance on ultrasonography, while the number of patients with a polycystic ovarian appearance on ultrasonography was 8 (26.7%) in the control group. The most common PCOS subtype in the literature is the classic type with polycystic ovarian morphology. This group constitutes approximately 2/3 of the cases. In a study by Rosenfield et al. (24), the polycystic ovary rate on ultrasonography was 95%.

Mean FGS was significantly higher in the patient group than in the control group. Likewise, mean FGS was higher in patients with a polycystic appearance on ultrasonography than those without. In a cross-sectional study involving adolescent girls, Ybarra et al. (25), found the high FGS patients rate to be 16.8%.

CONCLUSIONS

In conclusion, among the Rotterdam diagnostic criteria, oligoanovulation, acne, and the polycystic appearance of ovaries on ultrasonography can be seen in healthy adolescents without PCOS. In our study, in terms of PCOS diagnosis in adolescents, polycyclic ovaries accompanying moderate hirsutism are the findings that support the diagnosis most. At the end of the study, some of the Rotterdam diagnostic criteria we used for adolescents can also be seen in healthy adolescents. This makes the diagnosis of PCOS difficult in adolescents. Studies involving more patients and control groups in the adolescent age group are required to obtain more precise results.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Mersin University (06.10.2016, 305).

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