

Research article

## Frequency of “PCOS” and “Being at Risk for PCOS” in Obese Adolescent Girls in Light of Current Definitions

Yüksel Ö et al. PCOS in Obese Adolescents

Özlem Yüksel<sup>1</sup>, Fatma Güliz Atmaca<sup>2</sup>, Fatma Dursun<sup>2</sup>, Gülcan Seymen<sup>2</sup>, Pınar Atla<sup>2</sup>, Esmâ Ebru Altun<sup>2</sup>, Ayşe Yaşar<sup>2</sup>, Heves Kırmızıbekmez<sup>2</sup>

<sup>1</sup>University of Health Sciences, Ümraniye Training and Research Hospital, Department of Pediatrics, Istanbul

<sup>2</sup>University of Health Sciences, Ümraniye Training and Research Hospital, Department of Pediatric Endocrinology, Istanbul

### What is already known?

Polycystic ovary syndrome (PCOS) has become an important comorbidity in obese adolescent girls. Obesity and insulin resistance are associated with an increased risk of PCOS.

The diagnosis of PCOS can be challenging in adolescent girls due to the physiological transition period following menarche until they reach full biological maturity.

The sensitivity and specificity of diagnostic tests are not very high and none of the tests used in diagnosis are perfect markers.

### What this study adds?

Previous studies examining the prevalence and characteristics of PCOS in obese adolescents have predominantly used the diagnostic criteria which were primarily validated for adult women.

This study indicates that the prevalence of PCOS according to the “current recommendations for adolescents” is 8.3% in obese Turkish girls. The prevalence of individuals classified as “at risk for PCOS” was 46%.

Our results indicated that among the diagnostic tests free androgen index was found to be the most useful marker. The cut-off value was 0.44 ng/ml for total testosterone and 11 for free androgen index, with an optimum sensitivity and specificity.

### Abstract

**Introduction:** Obesity is associated with an increased risk of PCOS. It can be difficult to differentiate between PCOS and physiological oligomenorrhoea/anovulation in adolescent girls. To date, studies of the prevalence of PCOS in adolescents have predominantly used diagnostic criteria validated primarily in adult women. The aim of this study was to investigate the prevalence of PCOS in obese girls using the current diagnostic criteria for adolescents.

**Methods:** A total of 421 patients were included in the study. The diagnosis of PCOS was based on the presence of menstrual irregularity, clinical hyperandrogenism and hyperandrogenemia and the exclusion of other causes. Patients with one or two of these conditions were classified as “at risk for PCOS”. The control group consisted of patients with obesity alone but no other comorbidity.

**Results:** The number of patients meeting the definition of PCOS was 35, representing a prevalence of 8.3%, while 200 patients (46%) were defined as “at risk for PCOS”. The diagnostic value of the free androgen index (FAI) was found to be adequate, while other tests were poor. The cut-off values were 11 for FAI and 0.44 ng/ml for total testosterone, with optimal sensitivity and specificity.

**Conclusion:** Despite the increasing number of studies, the diagnosis and management of PCOS in adolescents remains a puzzle. While efforts should be made to avoid overdiagnosis, it is also important to recognize that many more patients may be “at risk” of developing PCOS.

**Keywords:** Adolescent, Obesity, Polycystic ovary syndrome, total testosterone, free androgen index

Heves Kırmızıbekmez MD, Ümraniye Eğitim ve Araştırma Hastanesi, Adem Yavuz Cad. No:1, İstanbul - Turkey

Heveskirmizibekmez@yahoo.com

0000-0002-8663-3452

27.08.2024

25.01.2025

**Epub:** 31.01.2025

**Cite this article as:** Yüksel Ö, Atmaca FG, Dursun F, Seymen G, Atla P, Altun EE, Yaşar A, Kırmızıbekmez H. Frequency of “PCOS” and “Being at Risk for PCOS” in Obese Adolescent Girls in Light of Current Definitions. *J Clin Res Pediatr Endocrinol*. [Epub Ahead of Print]

**Conflict of interest:** None declared

### Introduction

Polycystic ovary syndrome (PCOS) is characterized by androgen excess, ovulatory dysfunction and dysfunction of the hypothalamic-pituitary-ovarian axis, resulting in a self-perpetuating vicious cycle of neuroendocrine and metabolic dysfunction. The disease is complex and multigenic, with environmental factors playing a role (1). Obesity and insulin resistance are associated with increased risk and more severe clinical manifestations of PCOS (2). During puberty, insulin resistance increases due to activation of the growth hormone axis. This leads to compensatory hyperinsulinemia, which increases ovarian and adrenal androgen production, decreases hepatic SHBG production and impairs ovarian follicular dynamics and function (3). Because of these physiological changes and environmental factors affecting metabolic health, PCOS has become an important comorbidity in obese adolescent girls.

In 1990, the National Institutes of Health (NIH) criteria for PCOS were defined as “hyperandrogenism and/or hyperandrogenemia and oligo-anovulation, and exclusion of other diseases” (4). In 2003, the Rotterdam criteria were established, in which the diagnosis of PCOS requires the presence of two or more of the following criteria: oligo-ovulation/anovulation, clinical or laboratory androgen excess, the presence of multiple ovarian cysts, and the exclusion of other diseases (5). According to the criteria established by the Androgen Excess Society in 2006, PCOS was diagnosed when ovarian dysfunction and/or polycystic ovarian morphology and clinical and/or biochemical findings of hyperandrogenism were present and other causes were excluded (6).

Due to the physiological transition from menarche to full biological maturity in adolescent girls, it can be difficult to differentiate true cases of PCOS from those who are normal. To date, studies investigating the prevalence and characteristics of PCOS in obese adolescents have predominantly used the above diagnostic criteria, which have been validated primarily in adult women. In 2020, Pena et al published an international evidence-based guideline for adolescents (7). This latest guideline, which focuses on the specific recommendations for PCOS in adolescents, aims to avoid misdiagnosis or delayed, under- or over-diagnosis, to avoid unnecessary specific tests and to identify adolescents 'at risk' of PCOS. In this guideline, the definition of PCOS in adolescent girls is met by the criteria of "clinical and/or biochemical hyperandrogenism" in the presence of "irregular menstrual cycle" and exclusion of other possible causes. It was also noted that ultrasound findings should not be used for diagnostic purposes and that biochemical hyperandrogenism should be determined using appropriate high-quality assays. An international consortium update by Ibanez et al has previously recommended that confirmation of biochemical hyperandrogenism in adolescents is important before a definitive diagnosis of PCOS is made, due to ethnic and racial differences in the clinical signs of androgen excess (8).

The aim of this study was to investigate the prevalence of PCOS and the prevalence of being at risk of PCOS in obese adolescent girls in the context of the current diagnostic criteria, which are more appropriate for adolescents. In addition, the study aimed to investigate the clinical and biochemical characteristics of these girls, thereby contributing updated information to the existing literature on this topic.

#### **Methods**

The present study was conducted on female patients who presented to the Pediatric Endocrinology outpatient clinic because of excessive weight gain between January 1, 2019, and March 1, 2023. Of the 1,000 patients aged 15-18 years who presented with excessive weight gain, 421 girls with a body mass index above the 95th percentile, who had reached the final height and pubertal stage (Tanner-5) and had menarche at least one year prior were included in the study. The study population consisted of individuals who completed the study forms in full and consented to undergo examination of all body parts for hirsutism. Individuals with a medical history of congenital or acquired systemic diseases, or drug use that could lead to menstrual irregularities and abnormal body hair, were excluded from the study.

A questionnaire was administered to patients inquiring about their age at the onset of menstruation, the frequency of their menstrual cycles, the number of days and amount of bleeding, the presence of acne, and the presence of abnormal hair growth outside the genital and axillary regions. Obesity was defined as BMI >95th percentile according to age and gender or >30 kg/m<sup>2</sup> (whichever is lower) in adolescents who reached their final height (9). The World Health Organization (WHO) defines obesity as "mild" if the BMI is between 30 and 35 or greater than 100 and 120% of the 95th percentile, "moderate" if the BMI is between 35 and 40 or greater than 120 and 140% of the 95th percentile, and "severe" if the BMI is greater than 40 or greater than 140% of the 95th percentile. In this study, the BMI reference values for Turkish children were employed (10, 11). The diagnosis of PCOS was made based on the presence of menstrual irregularity, clinical hyperandrogenism (confirmed through biochemical hyperandrogenemia), and the exclusion of other potential causes. In instances where patients exhibited one or two of these conditions but did not fully meet the diagnostic criteria for PCOS, they were classified as "at risk for PCOS."

#### Menstrual irregularity:

The patients who had menstrual cycles for at least 1 year were included in the study. The definition of irregularity was made as follows according to the latest guideline recommendations (7):

- 1-3 years after menarche: Inter-cycle interval < 21 or > 45 days
- > 3 years after menarche: Inter-cycle interval < 21 or > 35 days or < 8 cycles per year
- >90 days for any cycle >1 year after menarche
- No menstruation at age 15 or 3 years after thelarche (primary amenorrhea)

#### Clinical hyperandrogenism:

On physical examination, male-type terminal hair in hormone-sensitive areas (Ferriman-Gallwey score >5-6) was considered "hirsutism" (12), and moderate and/or severe inflammatory-nodular acne on the face, back, and extensor faces with more than 10 lesions on the face was considered "severe acne" (13). Hirsutism and/or severe acne were accepted as clinical hyperandrogenism.

#### Hyperandrogenemia:

The total testosterone and free androgen index (total testosterone (nmol/L) / SHBG (nmol/L) x100) parameters were used. Blood samples were collected within the first week of the follicular phase. In our laboratory, total testosterone is quantified by means of an electrochemiluminescence immunoassay method, employing the Roche E801® brand device and Roche® brand test kits. The sex hormone binding globulin (SHBG) is determined by an electrochemiluminescence immunoassay method, utilizing Elecsys SHBG kits on a Cobas-e immunoassay analyzer. A value of >0.48 ng/ml for total testosterone, which is the upper limit of the adult female reference value provided by our test kit, and a value of >5 for free androgen index (FAI) according to the recent literature were accepted as biochemical hyperandrogenemia (14). In the presence of clinical hyperandrogenism, total testosterone >0.48 ng/ml and/or FAI>5 was considered hyperandrogenism.

#### Polycystic ovarian morphology:

In patients in whom ultrasound was required to support the diagnosis, the appearance characterized by multiple peripheral cysts with any ovarian volume above 12 ml was considered "polycystic ovarian morphology (PCOM)." Ultrasonography findings were not used for diagnostic purposes because they were not appropriate for the gynecologic age of our patient group.

Insulin resistance: A baseline HOMA-IR value of >3.8 in girls or elevated serum insulin levels (>300 µU/mL) in oral glucose tolerance test, with/without impaired glucose metabolism, is considered "insulin resistance" in the presence of clinical findings such as truncal obesity, keratosis pilaris and acanthosis nigricans (15).

#### Exclusion of other causes:

Among patients with 17OHP levels >2 ng/ml, those who demonstrated normalization on repeated measurements or normal results on the ACTH stimulation test were included in the study group. Patients with DHEAS levels >600 µg/dl underwent ultrasonography, and those with no adrenal mass were included in the study. Among patients with prolactin levels >25 ng/ml, a clinical evaluation was conducted, and those whose prolactin levels normalized on repeated measurements in the follow-up were included in the study group. Those whose prolactin levels continued to increase were excluded. Patients with abnormal thyroid hormones at the time of diagnosis and for three months prior were excluded. Patients receiving thyroid hormone replacement therapy and euthyroid within the last three months were included in the study group. Patients receiving corticosteroids, antipsychotics, or antidepressant drugs were excluded from the study.

**Statistical Method:** Data were analyzed using SPSS 25.0 package program.

The control group consisted of patients with obesity alone, without menstrual irregularities, clinical or biochemical primary hyperandrogenism, or any other comorbidity. Patients with insulin resistance and metformin users were also excluded from the control group. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Descriptive statistical methods were employed to evaluate the study data. Data that conformed to a normal distribution were expressed as the mean and standard deviation, while those that did not conform were expressed as the median and interquartile range (IQR). The independent samples t-test was employed for the comparison of normally distributed data between two

groups, while the one-way ANOVA test was utilized for the comparison of more than two groups. The Mann-Whitney U test was applied for the comparison of non-normally distributed data between two groups, and the Kruskal-Wallis test was utilized for the comparison of more than two groups. If the results were found to be significantly different in more than two group comparisons, the post-hoc Bonferroni test was applied. Pearson correlation analysis was employed for data that exhibited a normal distribution, whereas Spearman correlation analysis was utilized for data that did not. The objective was to ascertain the relationship between the study parameters. The chi-square test was utilized to evaluate categorical data. The significance level was set at  $p < 0.05$  for all tests. The receiver operating characteristic (ROC) curve analysis was employed to determine the sensitivity and specificity ratios, the area under the curve (AUC), the value of the diagnostic test, and the optimal cut-off values for diagnostic and supportive biochemical markers. Tests with an area under the curve (AUC) value greater than 0.6 were considered "usable but inadequate," while those with an AUC value greater than 0.7 were considered "satisfactory".

#### Results:

The mean age of the 421 adolescent female patients included in the study was  $16.29 \pm 0.94$  years. The gynecologic age (post-menarche period) was between 1 and 8 years, with a mean of  $4.01 \pm 1.41$  years. The age at which menstruation first occurred ranged from 8 to 17.5 years, with a mean of  $12.27 \pm 1.24$  years. Twenty-four patients (5.7%) had menstruated at the age of 10 years or younger, while 14 patients (3.3%) had started menstruating at the age of 15 years or older.

In our cohort of obese adolescent girls, 126 patients exhibited menstrual irregularities, 139 patients demonstrated clinical hyperandrogenism, and 120 of 157 patients with laboratory tests exhibited biochemical hyperandrogenism. Of the 139 patients with clinical hyperandrogenism, 83 exhibited hirsutism alone, 21 exhibited severe acne, and 35 exhibited both hirsutism and severe acne. Of the 112 patients who underwent pelvic ultrasound examination, 57 were found to have PCOM. Acanthosis nigricans was identified in 144 patients, and 81 of them were diagnosed with insulin resistance supported by laboratory findings, and metformin treatment was initiated in addition to lifestyle change recommendations. The number of patients meeting the definition of PCOS was 35, representing an 8.3% prevalence. Meanwhile, 200 patients (46%) were defined as "at risk for PCOS" based on the presence of one or two of the following criteria: menstrual irregularities, clinical hyperandrogenism, or biochemical hyperandrogenism.

Among the 35 patients diagnosed with PCOS, 14 had been prescribed metformin due to insulin resistance, while 5 had a family history of type 2 diabetes mellitus. Among the 200 patients considered to be at risk of PCOS, 45 had been prescribed metformin due to insulin resistance, while 47 had a family history of type 2 diabetes mellitus.

There were no statistically significant differences in age, age at menarche, gynecological age, or anthropometric measurements between the PCOS, PCOS risk, and control groups. Fasting insulin, HOMA-IR, LDL parameters were higher in those at risk for PCOS compared to the control group ( $p=0.009$ ,  $p=0.010$ ,  $p=0.043$ , respectively). In addition, AST and ALT were higher in PCOS group than in control group ( $p=0.026$ ,  $p=0.006$ , respectively).

The levels and comparison of hormone tests of patients in the "PCOS" and "at risk" groups are shown in Table 1. The results indicated that, except for biochemical hyperandrogenism and insulin resistance, there were no significant differences in clinical presentations according to the severity of obesity (see Table-2).

In correlational analyses, a positive correlation was observed between total testosterone and LH/FSH ratio, as well as 1,4-androstenedione ( $r=0.274$ ;  $p=0.00$ ;  $r=0.493$ ;  $p=0.000$ , respectively). The free androgen index demonstrated a positive correlation with total testosterone, 1,4 androstenedione, and LH/FSH ratio ( $r=0.609$ ;  $p=0.000$ ,  $r=0.534$ ;  $p=0.000$ ,  $r=0.292$ ;  $p=0.000$ , respectively). Furthermore, the LH/FSH ratio demonstrated a positive correlation with the inter-cycle interval ( $r=0.364$ ;  $p=0.003$ ).

Data were analyzed from 167 patients (35 with PCOS and 132 at risk for PCOS) in whom the parameters total testosterone, FAI, 1,4 androstenedione and LH/FSH ratio were measured as diagnostic markers. The area under the curve (AUC) values in the ROC curve were statistically significant and usable for all tests, but their diagnostic values were low. Among the diagnostic tests, FAI was found to be adequate (AUC=0.703,  $p=0.000$ ), while the AUC values of the other tests were poor (Figure-1).

According to the ROC curve, the cut-off value for the free androgen index was 11, with an optimal sensitivity and specificity of 59% and 72%, respectively. The cut-off value for total testosterone was 0.44 ng/ml, with an optimal sensitivity and specificity of 76% and 60%, respectively. Although not used for diagnostic but as a supporting and follow-up parameter, the cut-off value for 1,4 Androstenedione was found to be 3.5 ng/ml with an optimal sensitivity of 82% and specificity of 56%. The cut-off for the early follicular phase LH/FSH ratio, a parameter known to increase in chronic anovulation but not used for diagnostic purposes, was found to be  $>2$  with an optimal sensitivity of 59% and specificity of 60%.

#### Discussion:

The prevalence of obesity and, in parallel, the frequency of polycystic ovary syndrome (PCOS), one of the most important comorbidities of obesity in adolescent girls, is increasing. Environmental and epigenetic changes may also increase the propensity for PCOS independently of obesity. Our study was conducted to provide updated information on the prevalence in accordance with current diagnostic criteria, clinical features, and influential factors of PCOS in Turkish adolescent girls with obesity. The results of this study indicate that the prevalence of PCOS, defined as clinical hyperandrogenism (hirsutism and/or severe acne) that has been biochemically confirmed (early follicular phase total testosterone  $>0.43$  ng/ml and/or FAI  $>5$ ) in the presence of irregular menstrual cycles, is 8.3% in obese Turkish girls aged 15-18 years. The prevalence of individuals classified as "at risk for PCOS," defined as having one or two of these conditions but not meeting the criteria for PCOS, was 46%.

The diagnosis of PCOS is challenging due to the complex nature of the physiological transition period in adolescence, the variability of individual, racial, and environmental factors among populations, and the frequent overlap between normal and pathological conditions. Treatment approaches also vary in this age group. This study has considered the current recommendations for the diagnosis of PCOS, including irregular menses and a rational evaluation of hyperandrogenism due to the features of the population.

For many years, until an international consortium published by Ibanez et al. (8) in 2017, the Rotterdam criteria (oligo-anovulation, hyperandrogenism and polycystic ovaries ( $\geq 12$  follicles measuring 2-9 mm in diameter and/or an ovarian volume  $> 10$  mL in at least one ovary)) were used to diagnose PCOS in adolescents. However, more recent data suggest that the presence of PCOM in an adolescent who does not have hyperandrogenism and oligo-anovulation does not indicate a diagnosis of PCOS. In 2020, Pena et al. (7) published a guideline that builds upon the evidence-based international guidelines on adolescent PCOS by Teede et al. in 2018 (16). The guideline offers further recommendations to enhance diagnostic accuracy and prevent overdiagnosis. The Pena et al. guideline defined irregular menstrual cycles according to the gynecologic age. Irregular menstrual cycles  $\leq 1$  year post-menarche represent a normal pubertal transition. The definition of hyperandrogenism required the presence of hirsutism and/or severe acne, while the definition of biochemical hyperandrogenism required measurements using validated, high-quality assays. Pelvic ultrasound was not recommended for the diagnosis of PCOS within 8 years post menarche, and anti-mullerian hormone levels were not recommended for PCOS diagnosis. Pena et al. also published a literature review on the diagnostic criteria in 2022 defining PCOS as irregular -menstrual cycles and hyperandrogenism (clinical and/or biochemical); after excluding other conditions that mimic PCOS (17). In this

study, irregular menstruation was defined as described in the guideline by Pena et al. clinical hyperandrogenism was defined as severe acne resistant to topical therapy and/or a Ferriman Gallwey score of >6 (7). In adult guidelines and current adolescent criteria, androgen excess is defined using clinical findings and/or biochemical tests. However, since there are no ultra-sensitive methods for androgen measurements and again considering the genetic characteristics of our population, we considered the recommendation that clinical hyperandrogenism findings should be confirmed with laboratory tests (8). As a consequence of the forementioned recommendations, the diagnosis of PCOS in this study was made in case of irregular menstruation and clinical hyperandrogenism, together with a total testosterone level of >0.48 ng/ml (the upper limit for adult woman given by our laboratory) and/or FAI of >5.

The results of our study once again showed that the sensitivity and specificity of diagnostic tests are not very high and that none of the tests used in diagnosis are perfect markers.

In a study conducted in our country, clinical hyperandrogenism was detected in 44 (84.6%) while biochemical hyperandrogenism was detected in 40 (76.9%) of 52 adolescents with PCOS (18). Another study by Yüce et al. showed clinical hyperandrogenism in 76 (67.9%) of 112 PCOS adolescent patients, while biochemical hyperandrogenism was detected in 30 (30.9%) (19). It is thought that the variability between clinical hyperandrogenism rates and biochemical hyperandrogenism rates in different studies in the literature is related to differences in measurement methods and accepted cut-off values. In addition, since hirsutism is determined clinically by observational scoring, it is a highly subjective assessment. There may also be differences in the evaluation of acne as androgen excess.

Despite the control group comprising obese adolescents, fasting insulin, HOMA-IR, and LDL parameters, which support the insulin resistance and metabolic syndrome profile, were higher in those at risk for PCOS than in the control group. Additionally, ALT and AST, which are the markers used to screen for fatty liver, were higher in PCOS patients than in controls. Our findings are consistent with the existing knowledge that insulin resistance and metabolic syndrome in obese adolescents are more strongly associated with chronic anovulation and hyperandrogenism, and that hyperinsulinism plays an important role in the pathogenesis of PCOS (20-23). Obesity-associated hyperandrogenemia also occurs due to expanded adipose tissue and potential effects of abnormal adipokine/cytokine levels (24). An increased risk of cardiovascular disease has been reported in women with PCOS, regardless of the severity of obesity. Due to differences in body composition and genetic factors, individuals with similar BMIs have different levels of systemic inflammation, insulin resistance and metabolic dysfunction. Studies have shown that PCOS is more common in obese women who have an unhealthy metabolic profile (25).

Correlation analyses indicate a positive correlation between total testosterone, 1,4-androstenedione, and the LH/FSH ratio, which supports the hypothesis of chronic anovulation. The elevated androstenedione and 17OHP levels observed in the PCOS group, in the absence of a difference in DHEAS levels, suggest that the increased androgens are of gonadal origin. None of the diagnostic tests were found to be highly predictive. The FAI marker was relatively the most reliable among them.

**Limitations:** As our study did not include a healthy control group in which diagnostic tests were performed, the cut-off values we determined were those that differentiate between individuals "at risk of PCOS" and individuals diagnosed with "PCOS." Since hyperandrogenism alone or menstrual irregularity alone is not diagnostic, in our clinical practice, biochemical tests are usually ordered if both are present, or the signs of clinical androgenism is significant. The majority of patients with only irregular menses did not undergo hormone tests, so only 132 of 200 patients who were defined as "at risk" were involved in the analyses for cut-off values. In addition, the subjective evaluation of the clinical findings required for the diagnosis, which constitutes a limitation in almost all PCOS studies in adolescents, was another limitation of our study.

**Conclusion:** The diagnostic value of laboratory tests depends on the presence of clinical criteria. It is therefore suggested that clinical findings not supported by laboratory tests should not be considered diagnostic of PCOS. Despite the increasing number of scientific studies and the constant updating of guidelines, the diagnosis and management of PCOS in adolescents remains a puzzle. While efforts should be made to avoid overdiagnosis, it is also important to recognize that many more patients may be 'at risk' of developing PCOS. It is recommended that obese girls at risk should be closely monitored clinically for progressive findings. The most recent publication on diagnostic criteria by Ibanez and Zegher in 2023 (12) proposed a diagnostic approach by combining criteria from a consortium rooted in pediatric endocrinology and criteria from a consortium rooted in adult endocrinology and gynecology. These recent combined criteria and the cut-offs for diagnostic tests identified in our study can be incorporated into the methodology of future studies.

#### References

1. Burt Solorzano CM, McCartney CR. Polycystic Ovary Syndrome: Ontogeny in Adolescence. *Endocrinol Metab Clin North Am.* 2021; 50(1):25-42.
2. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update.* 2012; 8(6):618-37.
3. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev.* 2012;33(6):981-1030.
4. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome; towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, Merriam G, eds. *Polycystic Ovary Syndrome.* Boston, MA: Blackwell Scientific. 1992:377-384.
5. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19(1):41-47.
6. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF; Androgen Excess Society. Positions statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab.* 2006;91(11):4237-45.
7. Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, Garad R, Dabadghao P, Teede H. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC Med.* 2020 Mar 24;18(1):72.
8. Ibañez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, Dabadghao P, Darendeliler F, Elbarbary NS, Gambineri A, Garcia Rudaz C, Hoeger KM, López-Bermejo A, Ong K, Peña AS, Reinehr T, Santoro N, Tena-Sempere M, Tao R, Yildiz BO, Alkhatayt H, Deeb A, Joel D, Horikawa R, de Zegher F, Lee PA. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. *Horm Res Paediatr.* 2017;88(6):371-395.
9. Joseph A Skelton, William J Klish. Definition, epidemiology, and etiology of obesity in children and adolescents. *UpToDate* (ed. Mitchell E Geffner). Last updated Dec 8,2023
10. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. *J Clin Res Pediatr Endocrinol.* 2015;7(4):280-93.
11. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. *J Clin Res Pediatr Endocrinol.* 2017;9(2):182-184.
12. Ibañez L, de Zegher F. Adolescent PCOS: A postpubertal central obesity syndrome. *Trends Mol Med.* 2023;29(5):354-363.

13. Eichenfield LF, Krakowski AC, Piggott C, Del Rosso J, Baldwin H, Friedlander SF, Levy M, Lucky A, Mancini AJ, Orlow SJ, Yan AC, Vaux KK, Webster G, Zaenglein AL, Thiboutot DM; American Acne and Rosacea Society. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131 Suppl 3:S163-86.
14. Blume-Peytavi U, Blumeyer A, Tosti A, Finner A, Marmol V, Trakatelli M, Reygagne P, Messenger A, European Consensus Group. S1 guideline for diagnostic evaluation in androgenetic alopecia in men, women and adolescents. *Br J Dermatol*. 2011;164(1):5-15.
15. Kurtoglu S, Hatipoğlu N, Mazicioğlu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. *J Clin Res Pediatr Endocrinol*. 2010;2(3):100-6.
16. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril*. 2018 Aug;110(3):364-379.
17. Peña AS, Codner E, Witchel S. Criteria for Diagnosis of Polycystic Ovary Syndrome during Adolescence: Literature Review. *Diagnostics (Basel)*. 2022;12(8):1931.
18. Ağaçıran DK, Kızılkın MP, Akgül S, Kanbur N, Derman O. *Journal of Pediatric Health and Diseases*. 2020, 63 (1-4): 9. (Turkish)
19. Yüce E, Pabuccu R, Keskin M, Arslanca T, Papuccu EG. Evaluation of the Clinical, Endocrinological, and Biochemical Differences Between Adolescent and Adult Patients with Polycystic Ovary Syndrome. *Turkish Journal of Reproductive Medicine and Surgery*. 2020; 4(1):15-23.
20. Özalkak Ş, Bayramoğlu E, Erdevi ŞS, Çetinkaya S, Aycan Z. Evaluation of the Relationship of Polycystic Ovary Syndrome with Obesity and Insulin Resistance in Adolescents. *Firat Med J* 2023; 28(4): 273-279.
21. Li L, Feng Q, Ye M, He Y, Yao A, Shi K. Metabolic effect of obesity on polycystic ovary syndrome in adolescents: a meta-analysis. *J Obstet Gynaecol*. 2017;37(8):1036-1047.
22. Marzouk TM, Sayed Ahmed WA. Effect of Dietary Weight Loss on Menstrual Regularity in Obese Young Adult Women with Polycystic Ovary Syndrome. *J Pediatr Adolesc Gynecol*. 2015;28(6):457-61.
23. Kale-Gurbuz T, Akhan SE, Bastu E, Telci A, Iyibozkurt AC, Topuz S. Adiponectin, leptin and ghrelin levels in obese adolescent girls with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol*. 2013;26(1):27-30.
24. Anderson AD, Solorzano CM, McCartney CR. Childhood obesity and its impact on the development of adolescent PCOS. *Semin Reprod Med*. 2014 May;32(3):202-13.
25. Barrea L, Muscogiuri G, Pugliese G, de Alteriis G, Colao A, Savastano S. Metabolically Healthy Obesity (MHO) vs. Metabolically Unhealthy Obesity (MUO) Phenotypes in PCOS: Association with Endocrine-Metabolic Profile, Adherence to the Mediterranean Diet, and Body Composition. *Nutrients*. 2021;13(11):3925.

**Table-1:** A comparative analysis of diagnostic tests between patients with polycystic ovary syndrome (PCOS) and patients at risk for PCOS

|                            | PCOS<br>(n=35) | AT RISK<br>(n=200) | P             |
|----------------------------|----------------|--------------------|---------------|
| LH (IU/L)                  | 9.58± 4.20     | 9.34± 6.6          | 0.839         |
| FSH (IU/L)                 | 4.31 ±1.15     | 4.94± 1.44         | <b>0.033*</b> |
| Estradiol (pg/ml)          | 45.9 (27)      | 39.1 (22.6)        | 0.358         |
| Total testosterone (ng/ml) | 0.56 ±0.20     | 0.46 ±0.25         | <b>0.043*</b> |
| SHBG (nmol/L)              | 15.5 (8.18)    | 20.0 (12.5)        | <b>0.002*</b> |
| Free androgen index        | 11.6 (6.8)     | 8.0 (7.0)          | <b>0.000*</b> |
| 17-OH-Progesteron (ng/ml)  | 1.36 (1.04)    | 1.07 (0.97)        | <b>0.020*</b> |
| 14 Androstenedion (ng/ml)  | 4.36 (1.28)    | 3.33 (1.61)        | <b>0.003*</b> |
| DHEAS (mcg/dl)             | 289 (202)      | 313 (164)          | 0.598         |
| LH/FSH rate                | 2.24 ±0.89     | 1.92± 1.29         | 0.182         |

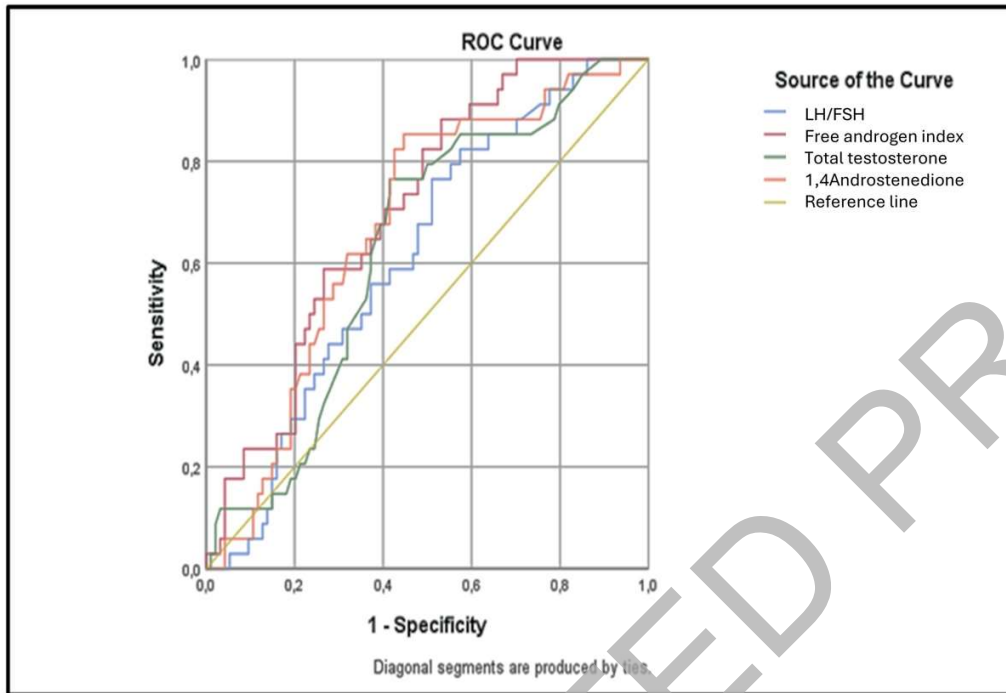
\*p<0.05. Normally distributed data were compared by Independent-samples T test and results were expressed as mean±standard deviation; non-normally distributed data were compared by Mann-Whitney U test and results were expressed as interquartile range (IQR). SHBG: Sex hormone binding globuline. DHEAS: dehydroepiandrosterone sulfate.

**Table-2:** A comparison of the distribution of patients' clinical features and diagnostic definitions according to the severity of obesity

|                                      | <b>MILD<br/>(n=124)</b> | <b>MODERATE<br/>(n=192)</b> | <b>SEVERE<br/>(n=105)</b> | <b>p</b>      |
|--------------------------------------|-------------------------|-----------------------------|---------------------------|---------------|
| <b>PCOS</b>                          | 9 (7.2%)                | 19 (9.9%)                   | 7 (6.6%)                  | 0.553         |
| <b>At risk for PCOS</b>              | 59 (47.5%)              | 93 (48.4%)                  | 48 (45.7%)                | 0.904         |
| <b>Menstrual irregularity</b>        | 39 (31.4%)              | 60 (31.2%)                  | 27 (25.7%)                | 0.553         |
| <b>Clinical hyperandrogenism</b>     | 47 (37.9%)              | 60 (31.2%)                  | 27 (25.7%)                | 0.384         |
| <b>Biochemical hyperandrogenemia</b> | 27 (21.7%) <sup>a</sup> | 59 (30.7%) <sup>b</sup>     | 34 (32.3%) <sup>b</sup>   | <b>0.014*</b> |
| <b>Polycystic ovary morphology</b>   | 16 (12.9%)              | 28 (14.5%)                  | 13 (12.3%)                | 0.926         |
| <b>Insulin resistance</b>            | 10 (8.0%) <sup>a</sup>  | 37 (19.2%) <sup>b</sup>     | 34 (32.3%) <sup>c</sup>   | <b>0.000*</b> |

\*p<0.05. Chi-square test was used for categorical data comparison. Bonferroni test was applied in post hoc analyses (differences and similarities are shown as superscript). PCOS: Polycystic ovary syndrome

Figure 1.



| Diagnostic test            | Area under curve (AUC) | Standart error | P      | Lower limit | Upper limit |
|----------------------------|------------------------|----------------|--------|-------------|-------------|
| <b>LH/FSH ratio</b>        | 0,615                  | 0,052          | 0,047* | 0,514       | 0,717       |
| <b>Free androgen index</b> | 0,703                  | 0,047          | 0,000* | 0,611       | 0,796       |
| <b>Total Testosterone</b>  | 0,630                  | 0,052          | 0,025* | 0,528       | 0,732       |
| <b>1,4 Androstenedione</b> | 0,673                  | 0,050          | 0,003* | 0,574       | 0,772       |