Original Study

# Diagnostic Characteristics and Metabolic Risk Factors of Cases with Polycystic Ovary Syndrome during Adolescence

Zeynep Sıklar MD *, Merih Berberoğlu MD, Emine Çamtosun MD, Pınar Kocaay MD

*Department of Pediatric Endocrinology, Ankara University School of Medicine, Ankara, Turkey*

A B S T R A C T

*Study Objective:* Polycystic ovary syndrome (PCOS) is a disorder without definite consensus on its diagnosis and management during adolescence. According to Amsterdam-2012 consensus, as physiological characteristics of adolescence may overlap with PCOS signs, it has been indicated that all Rotterdam criteria should be met. In this present study, characteristics of adolescents with different phenotypes who were diagnosed with PCOS were evaluated; and presence of differences for metabolic risk factors between phenotypes were investigated.

*Design:* The study was performed on adolescent females. According to phenotypic application models, individuals with all Rotterdam diagnostic criteria [hyperandrogenism (HA), polycystic ovarian morphology (PCOM), and chronic anovulation (CA) on the ultrasonography] were in Group 1 (n = 26); with HA and CA were in Group 2 (n = 10); with HA and PCOM were in Group 3 (n = 7); and with CA and PCOM were in Group 4 (n = 10).

*Results:* The most common application complaint (87%) among 53 cases enrolled in the study was menstrual irregularities, and 57% of cases were not obese. When PCOS was evaluated according to phenotypes, it was realized that cases that meet all 3 diagnostic Rotterdam criteria according to the current recommendation in adolescents. (Group 1) was the most common phenotype. Hyperandrogenism was associated with more metabolic abnormalities.

*Conclusion:* The close monitoring of adolescents, who have 2 diagnostic criteria is advisable among PCOS phenotypes. Potentially Groups 2 and 3 which have hyperandrogenism, in particular should warrant closer follow-up although they do not meet current diagnostic criteria for adolescents.

*Key Words:* Polycystic ovary syndrome, Adolescents, Diagnosis

## Introduction

Polycystic ovary syndrome (PCOS) is the most commonly encountered endocrinological problem among women in the reproductive age, and it is one of the disorders with difficulty in diagnosis especially during adolescence, without definite consensus. PCOS causing infertility manifests itself by menstrual irregularities, and hyperandrogenism, which are encountered generally starting at the peripubertal period. It can be considered as a multifactorial disease, which appears as the result of synergistic effect of some system's dysfunctioning, such as hypothalamo-hypophyseal dysfunction, steroidogenesis defect, intraovarian factors, insulin resistance, obesity, genetic factors, enzymatic defects in granulosa cells, and its etiology has not been definitely described yet.[1–3]

Different criteria are being used for PCOS definition. For example, according to NIH criteria chronic anovulation and biochemical or clinical hyperandrogenemia are required for the diagnosis, but polycystic ovary morphology (PCOM) is not. According to Rotterdam diagnostic criteria, 2 out of 3 criteria (oligo-anovulatory cycle, clinical and/or biochemical hyperandrogenism, polycystic ovary appearance in ultrasonography (US)) are diagnostic for PCOS.[2–4] According to these criteria, cases with chronic anovulation and hyperandrogenemia, hyperandrogenemia and PCOM, oligo-ovulation and PCOM signs can also form phenotypes in addition to cases with chronic anovulation, hyperandrogenism and PCOM.

There are still debates about PCOS diagnosis in the adolescent age group. Because physiological characteristics of the adolescent period can overlap with PCOS signs, it was reported in the consensus meeting held in Amsterdam in year 2012 that 3 of the Rotterdam criteria should be met for the diagnosis of PCOS in adolescents.[5] There are cases among adolescents that do not satisfy all criteria, but complain of hyperandrogenism or menstrual irregularities. The future risk of those cases in developing PCOS should not be underestimated. Moreover, because PCOS is frequently encountered, and a cause of morbidity such as anovulatory infertility, menstrual dysfunction, and hirsutism, it is a disorder recommended to be diagnosed early.[2] Risk factors for PCOS development such as low birth weight, and premature pubarche have been suggested for the early diagnosis.[6] Early treatment is one of the most important interventions, which may prevent morbidity. Requirement of all 3 Rotterdam criteria even for patients, who have had menarche for 2 years in the adolescent period, can be a factor hindering early diagnosis of PCOS. Metabolically, these cases may be under the same risk.

In this study, the aim is to determine the characteristics of adolescents who have been diagnosed with PCOS according to Rotterdam criteria, with different phenotypic admission

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* *Address correspondence to:* Zeynep Sıklar, Çiğdem Mahallesi 1577. Sokak No: 2/1 06530 Çankaya, Ankara, Türkiye; Phone: +90 5053422169

*E-mail address:* zeynepsklr@gmail.com (Z. Sıklar).

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models; it was investigated whether there was any metabolic differenced between phenotypic PCOS models, especially in patients with all 3 diagnostic Rotterdam criteria and in patients with 2 different diagnostic criteria.

## Cases and Methods

### *Subjects*

The study was performed among adolescents (aged 12.7 to 18.3 years with PCOS related symptoms, who applied to the Adolescent Outpatient Clinic in the Pediatric Endocrinology Division of the Department of Pediatrics at Ankara University, and accepted participation in the study.

Females who had menarche for at least 2 years were included in the study. Individuals with other systemic diseases (such as thyroid dysfunction, congenital adrenal hyperplasia, androgen secreting adrenal tumor, hyperprolactinemia), who were receiving any drugs (such as oral contraceptives (OC), steroid, metformin or other insulin sensitizer), and who refused participation in the study (n = 2), were excluded from the study. A total of 57 patients were screened and only 4 patients were excluded from the study. Other conditions that might cause hyperandrogenism were excluded. Polycystic ovary syndrome diagnosis was defined according to the Rotterdam criteria.[4] According to phenotypic application models, individuals with all Rotterdam diagnostic criteria [hyperandrogenism (HA), PCOM and chronic anovulation (CA) in the ultrasonography] were in Group 1; with HA and CA were in Group 2; with HA and PCOM were in Group 3; and with CA and PCOM were in Group 4.

After informed consent was provided, presence of PCOS in the family, hyperandrogenism, obesity, hypertension, dyslipidemia and type 2 diabetes mellitus (DM) were inquired in the history. Presence of small for gestational age (SGA) in the birth history, premature pubarche, and age of menarche were determined in the cases. Regularity of menstruation cycles were inquired to determine whether there were irregular menstrual bleeding such as infrequent menstrual bleeding (oligomenorrhea, 1 or 2 episodes in a 90-day period), absent menstrual bleeding (amenorrhea, no menstrual bleeding in a 90-day period), 2 years after the menarche.[7] Physical examinations of cases were performed, and body weight, height and other anthropometric measurements were determined. Body weight was measured when there were light clothes on by using a SECA height measuring and weight scale. Height was measured without shoes, while heels, hips, and heads were leaned against the wall by using a fixed meter with 1 mm intervals. Measurements were evaluated according to normal values of Turkish children, which were modified by age and gender. BMI was calculated by using the body weight (kg)/height ($m^2$) formula. Children within $85^{th}$-$95^{th}$ percentiles were accepted as overweight, whereas at and above $95^{th}$ percentile were accepted as obese.[8] Weight percentage with respect to height was calculated by using the formula of measured BMI ($kg/m^2$)/required BMI of the patient × 100.

Waist circumference was measured at the middle of distance between the 10th rib and upper border of iliac crest while children were sitting upright, and the abdomen was relaxed, whereas hip circumference was measured at the widest portion of gluteal region. Measurements were evaluated according to waist circumferences determined for Turkish children.[9]

Blood pressure measurements were performed while subjects were relaxed and in the sitting position in the morning by using the appropriate cuff-size (fit for 2/3 of the right arm) and sphygmomanometer, and they were evaluated according to Tumer standards, age and gender normals.[10] Cases which were defined to have acanthosis nigricans by physical examination were recorded and puberty staging of all children was performed according to Tanner-Marshall classification.[11]

Hyperandrogenism was defined when total testosterone was above 55 ng/ml biochemically, and the score was at or above 8 according to Ferriman-Gallwey (FG) classification clinically.[12,13]

Blood samples for laboratory evaluations were drawn during early follicular phase (on day 3-5 of menstrual cycle) in patients with menses or on the day of clinical examination after a 12-hour fasting during the night at 8:00 am. Fasting blood glucose, fasting insulin, lipid profile, prolactin, LH, FSH, E2, testosterone, 17-OH progesterone, and dehydroepiandrosterone sulfate (DHEAS) were studied in blood samples. Biochemical evaluations were performed in the Central Biochemistry and Endocrinology laboratories in the Medical School of Ankara University. Glucose was studied by using glucose hexokinase method; total cholesterol was studied enzymatically by oxidase method; high-density lipoprotein (HDL) cholesterol was studied by using direct non-immunological method; if triglyceride (TG) was <400 mg/dl, then it was studied by Friedewald formula or if TG analyzer biochemistry was >400 mg/dl, then it was studied enzymatically by using automated Roche Modular (Germany); fasting insulin was studied by using radioimmunoassay (RIA) method. Levels of LH, FSH, free testosterone, total testosterone were studied by chemiluminescent immunoassay. DHEAS and 17-OHP were determined by RIA.

Ovarian morphology was determined by abdominal ultrasonographic imaging of ovary and uterus. According to the Rotterdam criteria, >12 follicles with the diameters of 2-9 mm in ovaries or ovary volume of ≥10 ml in pelvic US was accepted as consistent with the polycystic ovary morphology.[14]

Fasting insulin and Insulin resistance homeostasis model of assessment (IRHOMA) values were used in evaluation of insulin resistance.[15] IRHOMA was calculated by using the formula of IRHOMA = fasting insulin (mIU/mL) × fasting blood glucose (mmol/L)/22.5, and cases with IRHOMA value of >3.82 was accepted as insulin resistant.[16] Oral glucose tolerance test (OGTT) was performed by giving 1.75 g/kg (maximum 75 g) glucose. Evaluation of OGTT response was performed according to American Diabetes Association criteria.[17]

Presence of metabolic syndrome was evaluated according to International Diabetes Federation (IDF) criteria, which indicated metabolic syndrome in cases with the age range of 10 to <16 years, if waist circumference was ≥$90^{th}$ percentile, TG ≥ 150 mg/dl, HDL-C <40 mg/dl, systolic