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Polycystic Ovarian Syndrome In Some Sample Of Iraqi Adolescents: Implementation Of Consensus Guidelines

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Abstract

Background: The diagnosis of polycystic ovarian syndrome (PCOS) in adolescent girls can be difficult because symptoms are shared with normal pubertal development. The updated consensus guideline for PCOS diagnosis in adolescents sought to encourage accurate and timely diagnosis, optimize therapy, and improve health outcomes**.**

Aim: the present study aims to implement an updated consensus criteria in the diagnosis of PCOS in adolescents complaining of clinical features of hyperandrogenism or menstrual abnormalities **.**

Methods: A total of 60 patients with clinical features of hyperandrogenism and/or menstrual abnormalities were studied. A detailed history followed by clinical examination was taken. Serum Thyroid Stimulating Hormone, Cortisol, Total Testosterone, Dehydroepiandrosterone, Luteinizing Hormone (LH), and Prolactin were performed for all patients. Consensus criteria were used for PCOS diagnosis**.**

Results: Menstrual irregularity was reported by 20 (33.3%) and hyperandrogenism features in 21(35%) of the participants. PCOS was confirmed in 14 (23%) participants. Patients diagnosed with PCOS were shown to have substantially higher rates of menstrual irregularity, hirsutism, elevated serum testosterone, and LH (P0.001, P0.001, P=0.002, and P0.002 respectively). Seven patients (50%) had both clinical and biochemical hyperandrogenism. Association between testosterone rise was more significant with hirsutism (P<0.001) than with acne (P=0.001). Morbid obesity was observed in 21% of patients, 7% had their diastolic blood pressure 90mm Hg, and 39% had and fasting blood sugar ≥100 mg/dL**.**

Conclusion: PCOS was diagnosed in 23% of adolescent girls who had features of hyperandrogenism and menstrual irregularities. Obesity and family history were more frequent in PCOS adolescents. Concordant clinical and biochemical hyperandrogenism was confirmed in only half of PCOS patients. PCOS patients may be at higher risk of metabolic syndrome **.**

Keywords: Adolescents, Diagnosis Guidelines, Hirsutism, Obesity, PCOS, Testosterone.

INTRODUCTION

Polycystic ovarian syndrome (PCOS), is a disorder characterized by hyperandrogenism as well as prolonged anovulation or oligo-ovulation. According to the diagnostic criteria, the prevalence of the condition ranges from 6% to 20% among women of reproductive age [(1)]. The vast majority of the available clinical data reports observations and results for adult women [(2).] While the Rotterdam criteria are recognized for women of reproductive age, identifying PCOS in teenage girls is hampered by the similarity between normal pubertal development and the disorder's clinical symptoms [(3)].

The diagnostic criteria for PCOS in adolescents are disputed, partly due to the possibility that

the pathological characteristics used to diagnose PCOS in adult women are typical pubertal physiological occurrences. In this context, the Amsterdam criteria propose that all three Rotterdam criterion features should be present in adolescents in order to diagnose PCOS [4]. The Endocrine Society recommend the adoption of National Institutes of Health (NIH) criteria for the diagnosis of PCOS in teenagers, including hyperandrogenism and prolonged anovulatory menstrual periods [5]. Since there was insufficient evidence to corroborate the NIH criteria for teenagers, the Pediatric Endocrine Society approved the criteria of chronic hyperandrogenism and oligo-anovulatory cycles on the basis of adequate criteria [6]. The evidence-based international Consortium of Pediatric Endocrinology (ICPE) diagnosis criteria (Table 1) sought to promote accurate and prompt diagnosis, maximize consistent management, and improve health outcomes for adolescents and women with PCOS [7]. To minimize misdiagnosed or delayed, under-, or overdiagnosis, the most significant modification to the Adolescent Consensus Recommendations for PCOS diagnosis was the deletion of certain unneeded procedures, specifically ovarian ultrasound imaging and blood anti Müllerian hormone (AMH) level [6]. In Iraq, there are few research documenting the prevalence of PCOS among teenagers none of which used the updated guidelines. This research aims to use the revised consensus criteria for diagnosing PCOS in teenagers with hyperandrogenism or monthly irregularities.

Table No. 1: International Consortium of Pediatric Endocrinology diagnostic criteria of PCOS in adolescents [2].

Required	Optional	Not recommended	Comments
1-Irregular menses/ oligomenorrhea **2-Evidence of hyperandrogenism:** **a- Biochemical** **b. Clinical (e.g., progressive hirsutism)**	1. PCOM 2. Severe acne	1-Obesity 2-Insulin resistance 3-Hyperinsulinemia 4-Biomarkers (e.g., AMH, T/DHT ratio) 5-Acanthosis nigricans	1-Must generally be 2 years post-menarche 2- Must rule out other disorders of hyperandrogenism (e.g., NC-CAH, Cushing syndrome)

Abbreviations: AMH, anti Müllerian hormone; T, testosterone, DHT, dihydrotestosterone; NC-CAH, non-classical congenital adrenal hyperplasia.

PATIENT AND METHODS

This is a cross sections study conducted in Al-Zahraa Teaching Hospital for gynecology and obstetrics in Al Najaf city – Iraq during the period between 01-9-2021 and 01-06-22. The study was approved by the ethical committees in the Faculty of Medicine, University of Kufa; informed verbal consents were given by all participants.

A total of 60 patients visited the Dermatology clinic in Al-Sader Teaching Hospital and the outpatient clinic of Al-Zahraa Teaching Hospital with clinical features of hyperandrogenism or menstrual abnormalities. Inclusion criteria included: age 13-19, marital status, menstrual irregularities 2 years after menarche and clinical features of hyperandrogenism (hirsutism and/or acne). Exclusion criteria included: abnormal thyroid function test and abnormal cortisol levels.

All patients were individually interviewed and detailed history was taken followed by clinical

examination. Menstrual irregularities were defined as: 1) primary amenorrhea, when there is no menarche by 15 years of age or more than three years after breast development onset; 2) secondary amenorrhea, when period is absent for more than 90 days after menarche; and 3) Oligomenorrhea, when the patient had less than 8 periods per year 3-5 years post menarche or less than 9 periods per year after 6 years of menarche.

By using the modified Ferriman-Gallwey scoring system (mFG), hirsutism was looked for in the following areas: upper lip, chin, neck, chest, periumbilical, upper back, and around nipples (2). Reviewing acne in their faces, shoulders, and backs, patients were judged positive when they had at least 10 instances of moderate to severe inflammatory acne which was resistant to topical therapy at any one location(2).

The diagnosis of PCOS was validated by using recommendations tailored specifically to adolescents and derived from the ICPE 2017 Consensus Statement. The following criteria were used to validate the diagnosis:

1) The presence of chronic clinical or biochemical hyperandrogenism in adolescents who are at least two years beyond menarche.
2) The presence of persistent irregular menstruation in adolescents who are at least two years past menarche.
3) The exclusion of other potential reasons for these findings. (2, 6).

On physical examination, blood pressure, height, and weight of the patient were taken.

Body mass index (BMI) was measured for each participant according to the following equation BMI= weight (kg)/ hight^2(m). Following the WHO classification of BMI for children and adolescent less than 19 years old and using the BMI for age-specific for girls, the following categories were applied(8): Underweight <15th percentile, Normal weight ≥15th to < 85th percentile, Overweight ≥ 85th to <97th percentile, and Obesity ≥ 97th percentile.

All enrolled patients were sent for the following tests conducted in the Al-Zahraa Teaching Hospital and Al-Sader General Hospital labs: Total testosterone: a value of 1µg was considered elevated, Dehydroepiandrosterone (DHEA), luteinizing hormone (LH), thyroid stimulating hormone (TSH), Prolactin up to 20 ng/ ml was considered normal. Furthermore, all included participants had normal TSH, cortisol, and prolactin levels. For patients with confirmed PCOS diagnosis, tests of oral glucose tolerance test (OGTT), and Lipid profile were performed.

The Statistical Package for Social Sciences software for windows version 25 (IBM Corp., Armonk, N.Y., USA) and Excel (Microsoft office 2019) were used to conduct the analysis. Besides, the statistical comparisons were performed by using the Chi-square test to assess proportions of nominal/ ordinal variables in different groups; student t-test and ANOVA were used to compare continuous variables as well. P values of <0.05 were considered statistically significant.

RESULTS

The mean age of the participants was 16.27 years ± 1.89 years with a mean BMI of 20.73 ± 5.83. Referring to the BMI chart for adolescent girls, 8 (13.3%) of the participants were overweight and 9 (15%) were obese.

During history taking, a quarter of the participants reported PCOS in their first-degree relative (mother and /or sister) as shown in Table 2. Menstrual irregularity was reported by 20 (33.3%) of the participants, 17(85%) had menstrual disturbances and 3(15%) complained of secondary amenorrhea 2 years after menarche.

By clinical examination, hyperandrogenism features were observed in 21(35%) of the participants. All had an mFG score of hirsutisms ≥4, and 23 (38.3%) had more than 10 acne lesions in the face, upper arms and back.

Following the international consensus criteria for diagnosing PCOS in adolescents, the simultaneous presence of menstrual irregularities and hyperandrogenism (whether clinical and/or biochemical) was confirmed in 14 (23%) participants, as shown in Figure 1. Seven out of these 14 patients had both clinical and biochemical hyperandrogenism.

Table No.2: Study group demographics and characteristics

Characteristic			
Age (year)	**mean ±(SD)**	16.27	(1.89)
BMI (Kg/m^2)	**mean ±(SD)**	20.73	(5.83)
BMI groups			
Underweight	**No (%)**	26	(43.3)
Normal weight	**No (%)**	17	(28.3)
Overweight	**No (%)**	8	(13.3)
Obese	**No (%)**	9	(15)
Family history of PCOS	**No (%)**	15	(25)
Menstrual irregularities	**No (%)**	20	(33.3)
Menstrual disturbances	**No (%)**	17	(85)
Secondary amenorrhea	**No (%)**	3	(15)
Clinical Hyperandrogenism	**No (%)**	21	(35)
Hirsutism	**No (%)**	21	(35)
Acne	**No (%)**	23	(38.3)

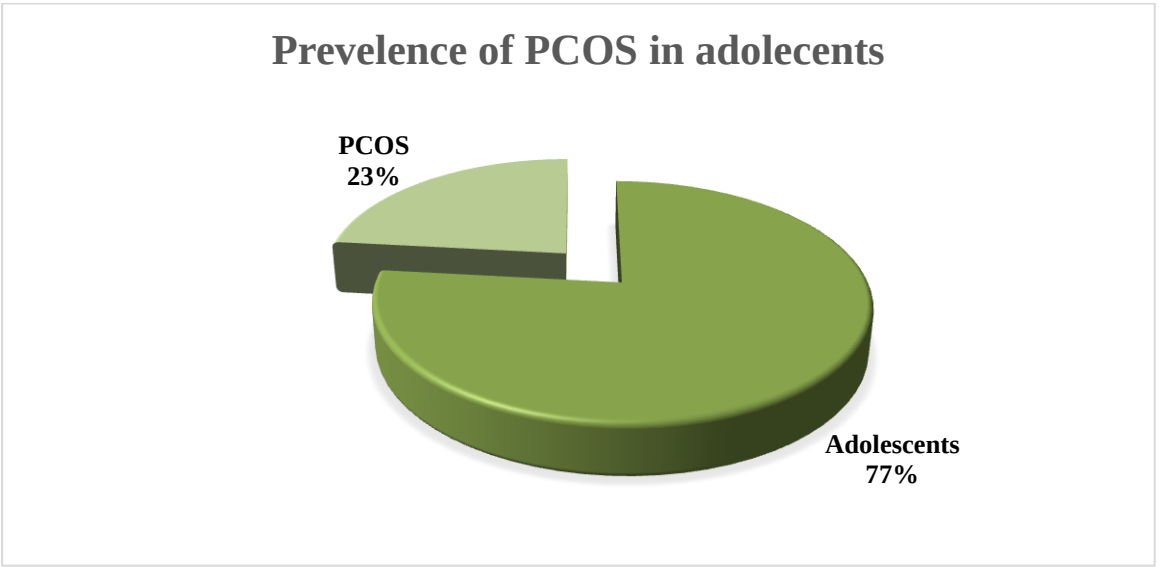

Figure No.1: The prevalence of PCOS in the study group.

Menstrual irregularity was significantly higher in PCOS patients (P<0.001). The menstrual disturbance was the most common irregularity reported by PCOS patients (78.6%) and only 3 (21.4%) had secondary amenorrhea. Yet, six (13%) of those who did not have confirmed PCOS complained of menstrual disturbance but none had secondary amenorrhea, Table 3.

Although hirsutism was significantly observed in PCOS patients, it was also seen in approximately a quarter of the non PCOS group. Similarly, acne was observed in approximately one-third of non-PCOS participants. Total serum androgen and LH were significantly higher in PCOS patients 10(71.4%), but high testosterone levels were also seen in 11(23.9%) of non PCOS patients.

Elevated serum testosterone was seen in 14 out of 21 (66.7%) patients with clinical hyperandrogenism (hirsutism with or without acne). In patients diagnosed NS= not significant with PCOS, seven out of 14 (50%) had both clinical and biochemical hyperandrogenism. The association between testosterone elevation was more significant with hirsutism (P<0.001) than in acne (P=0.001). No significant association was observed between testosterone and menstrual irregularity, as shown in Figure 2.

Patients with PCOS had GTT and lipid profiles that were within the normal range while those with polycystic ovary syndromes had a mean systolic blood pressure of 100.128.1 and a mean diastolic blood pressure of 70.47.3 respectively, which was not substantially different from the SBP107.6 mmHg 12.8 and DBP 71.4 mmHg 9.8 of those in the non-PCOS group, Figure 3. However, there were eight (13.3%) participants who had their diastolic blood pressure 90mm Hg, and only one (7%) was diagnosed with PCOS.

Similarly, no significant difference was seen between the mean fasting blood sugar between PCOS (95.6 mg/dL ±7.5) and non-PCOS patients (94.1mg/dL ±9.4). Yet, 24 (40%) of the participants had an FBS ≥100 mg/dL; one of whom also showed acanthosis nigricans on the physical examination and six (39%) only were diagnosed with PCOS. The number of obese patients in the PCOS group was higher than those on the non-PCOS group (21.4% vs 13%); statistically, that was not significant, Figure 3 and Table 3. Patients with incomplete criteria for PCOS diagnosis were a high-risk group.

Table No. 3: Demographics and characteristics of PCOS patients in comparison to non-PCOS.

	PCOS (n=14)	No PCOS (n=46)	
Variables	Frequency %	Frequency %	P value
Age mean ±(SD)	17.361.598	15.931.855	0.412 NS
BMI mean ±(SD)	22.715.269	20.135.909	0.528 NS
BMI groups			0.618 NS
Underweight	4(28.60%)	22(47.8%)	
Normal weight	5(35.70%)	12(26.1%)	
Overweight	2(14.30%)	6(13.0%)	
Obese	3(21.4%)	6(13.0%)	
Family history of PCOS			0.236 NS
Positive	5(35.70%)	10(21.70%)	
Negative	9(64.30%)	36(78.30%)	
Hirsutism			<0.001
mFG≥4	11(78.6%)	10(21.70%)	
mFG<4	3(21.40%)	36(78.30%)	
Acne			0.004
>10 lesion	10(71.40%)	13(28.3%)	
≤ 10 lesions	4(28.60%)	33(71.70%)	
Total testosterone			0.002
High	10(71.4%)	11(23.9%)	
Normal range	4(28.6%)	3576.1%)	
Menstrual irregularities			<0.001
No irregularities	0(0.00%)	40(87%)	
Menstrual disturbances	11(78.60%)	6(13%)	
Secondary amenorrhea	3(21.40%)	00	
Serum LH			0.002
High	10(71.4%)	11(23.9%)	
Normal range	4(28.6%)	35(76.1%)	

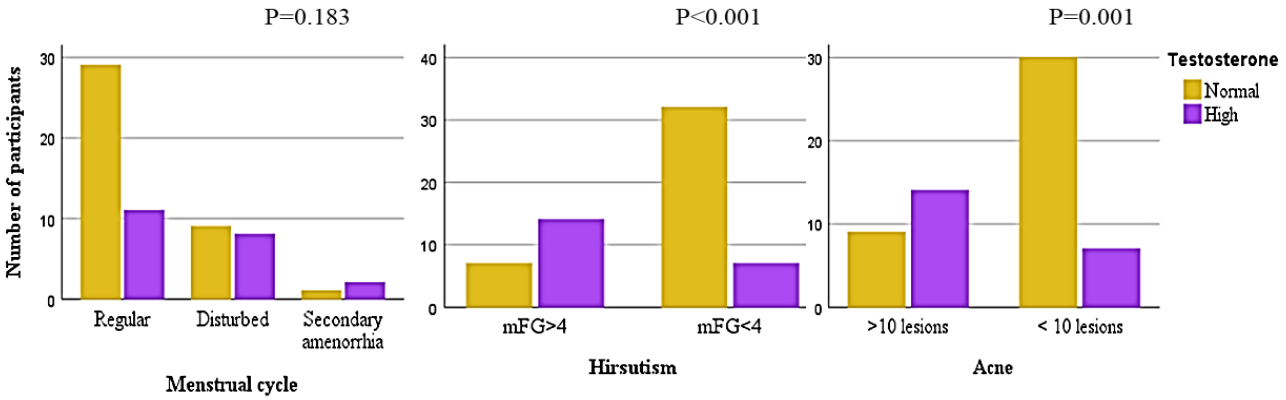

Figure No.2: Association between serum total testosterone and menstrual cycle, hirsutism, and acne.

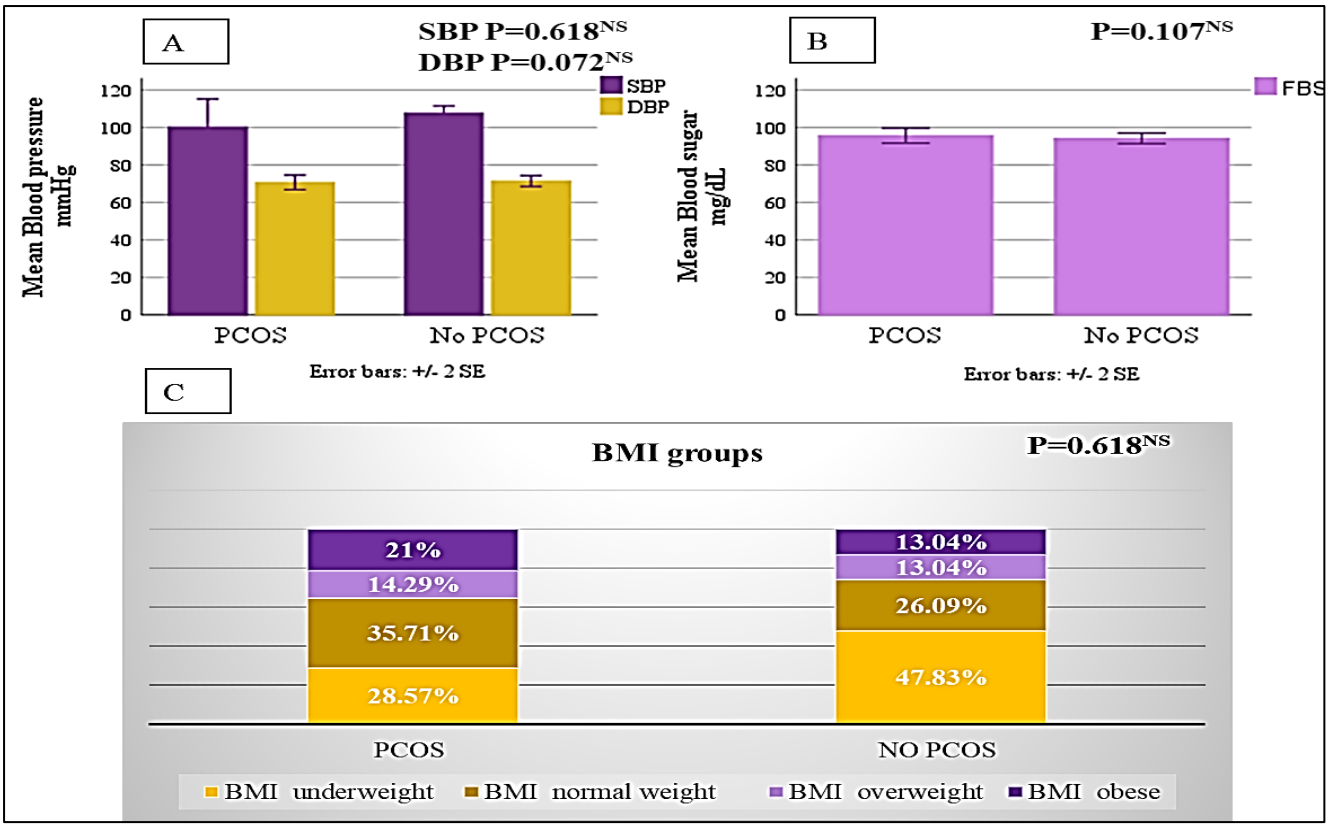

Figure No.3: Risk factors of metabolic syndrome, A) Blood pressure systolic (SBP) and diastolic (DBP); B) fasting blood sugar (FBS); C) BMI categories in PCOS patients in comparison to the rest of the sample.

DISCUSSION

Gynecology, Endocrine, and Pediatric Societies have focused on PCOS in adolescents for a decade. The Pediatric Endocrine Society developed a consensus guideline for PCOS diagnosis and care in 2017 with the aim of early diagnosis, effective management, and lifestyle change at a younger age [(2)]. This is the first Iraqi research to use consensus PCOS diagnostic criteria in teenagers.

In this cross-sectional study, PCOS prevalence according to consensus guideline diagnostic criteria was 23%. The prevalence of PCOS in adolescents varies greatly according to the study design and diagnosing criteria implied. The true prevalence of polycystic ovary syndrome (PCOS) according to the diagnostic criteria established by the National Institutes of Health was closer to 2 per 200 teens in a major community-based population research that had been undertaken previously in the United States [(9)]. In a different study, Ybarra et al carried out on 49 obese Brazilian teens found that the prevalence of PCOS according to the Rotterdam criteria was 26.4%. Based on a questionnaire assessing PCOS symptoms, an Iranian screening study conducted on schoolgirls calculated the prevalence of PCOS to be 3% [(10)]. A total of 149,477 people took part in the research that was compiled and analyzed in a metanalysis carried out by Naz et al. The prevalence of polycystic ovary syndrome in adolescent females was found to be 11.04% (95% confidence interval: 6.84-16.09%) when using the Rotterdam criteria, 3.09% (95% confidence interval: 0.28-9.54%) when using the National Institutes of Health criteria, and 8.03% (95% confidence interval: 6.24-10.01%) when using the Androgen Excess and Polycystic Ovary Syndrome Society

criteria (11). Although regional and ethnic factors affect the prevalence of PCOS, differences due to variable diagnostic criteria highlight the risk of under-diagnosis, delayed and/ or poor diagnosis [3].

The association between childhood obesity and early onset of puberty in girls is well established and results in aberrant (neuro) endocrine activity during adolescence, which may predispose to PCOS [12]. Findings from the present research did not support a link between PCOS and being overweight or obese. Christensen et al. found similar results in a larger trial that included both newly and previously diagnosed PCOS adolescents, showing that when all individuals with PCOS were evaluated, the link between excess body weight and PCOS was greatly decreased. They also noticed that the correlation was strongest when only confirmed instances of PCOS were analyzed, indicating that overweight women are more likely to seek medical attention than their normal-weight counterparts [9]. When doing research based on a diagnosis, it's possible that a large number of persons with a lower body mass who don't have PCOS are contributing to an overestimation of the significance of the connection between body mass and PCOS [9].

PCOS has been recognized for a long time as a familial condition. Environmental, ethnic, and genetic factors are contributors to the etiopathology of this condition [13]. In the current study, 25% of the participants had a positive family history of PCOS and 35.7% of those diagnosed with PCOS had a first-degree relative with PCOS, although, that was statically not significant due to the small sample size. An astonishing cross-sectional study of 80 sons of women with polycystic ovary syndrome (PCOS) discovered that in addition to the expected hyperinsulinemia and hypercholesterolemia, they also displayed early-onset obesity, which was detected as early as infancy. The prevalence of hyperinsulinemia and insulin resistance among adult sons was also significantly higher than predicted by their body mass index [14, 15].

Clinical hyperandrogenism was observed in 35% of all participants; this was associated with a high level of total serum testosterone in two-thirds of the cases seven of them only were diagnosed with PCOS. In other words, only half of the patients diagnosed with PCOS had concordant clinical and biochemical hyperandrogenism. There is a general agreement by all the concerned societies that the presence of hirsutism is the characteristic of clinical hyperandrogenism in women, while acne and alopecia are not [6]. This is presumably because acne is so common in young people and is not always linked to polycystic ovary syndrome [16]. On the other hand, significant hirsutism, and abnormal hair growth, as indicated by a high FG score, could not be totally obvious for the whole of adolescence. Some studies argue that the FG score has been designed to estimate adult hirsutism and is not optimized for adolescents [16]. For that reason, they consider biochemical confirmation of hyperandrogenism an important confirming diagnosis [16], however, the consensus guideline stressed that either clinical or biochemical would be enough(2). According to the findings of a research that was carried out in the United Kingdom, as puberty progresses, levels of total T and SHBG go up while SHBG levels go down, which results in an increase in the quantity of free T. It has been observed that the median T level is 40.3 ng/dL, while the median SHBG level is 43 nmol/L [17]. In part, the increasing levels of free T during puberty are a result of the decrease in SHBG caused by physiologic hyperinsulinemia [17]. Consequently, adolescents have to be carefully monitored in order to arrive at a diagnosis of polycystic ovary syndrome (PCOS) and to prevent the later development of conditions connected to the cardiovascular system and type 2 diabetes [18].

In the current study, there were no observed differences in the main risk factors of metabolic syndrome such as blood pressure, blood sugar, and obesity between patients with PCOS and other participants, although a quarter of patients with PCOS were morbidly obese. However, evaluation of insulin resistance (HOMA-IR>2.5) might be essential to better identify individuals who are at increased metabolic risk. BMI (BMI 25 kg/m2) and/or waist-to-hip ratio (WHR 0.8) are possible indications of insulin response dysfunction [16].

The diagnosis of hypertension in adolescents is based on age, gender, and height. Systolic and/or diastolic BP above the 95th percentile for age, gender, and height on three or more occasions constitute hypertension. Starting at 12 years of age, pre-hypertension is defined by a blood pressure value greater than 120/80 mmHg, even if it is less than the 90th percentile [19]. Elevated diastolic pressure (90 mm Hg) was observed in eight participants in the current study, and only one was diagnosed with PCOS.

The diagnosis of prediabetes in adolescents is based on one of three test values according to American Diabetes Association (ADA) recommendations, (1) glucose levels of 100 to 125 mg/dL (5.6–6.9 mmol/L) when fasting; glucose levels of 140 to 199 mg/dL (7.8–11.0 mmol/L) during an oral glucose tolerance test; or HbA1C levels between 5.7% and 6.4% [20]. In the current study, 40% of the participants had an FBS of 100mg/dL or more. Six out of 14 PCOS patients were prediabetic; however, no statistical difference was seen between PCOS patients compared to other participants. This highlights the potential risk that patients with incomplete PCOS diagnostic criteria are carrying.

According to the recent recommendations [2], adolescents with PCOS features who do not have all diagnostic criteria may be considered at "increased risk". This represented 77% of our study group, 15% had prehypertension and 39% had prediabetes. This is one of the challenges in diagnosing PCOS in this age group. Despite adhering to the guideline reduces overdiagnosis, the remaining participants carried a potential risk of metabolic syndrome. Those patients are recommended for re-evaluation before full reproductive age, 8 years after menarche particularly those with high-risk factors for metabolic syndrome [16].

There are several limitations to this study. First and due to time constrain, at-risk patients could not be followed up. Secondly, the insulin resistance test (HOMA-IR) which is a better indicator of metabolic syndrome was not available at the centers where the study was conducted and could not be included in the study. Finally, the sample was a small and larger sample, a population-based study will be needed to estimate the actual prevalence of PCOS in adolescents.

CONCLUSIONS

PCOS was diagnosed in 23% of adolescent girls who had features of hyperandrogenism and menstrual irregularities. 21% of PCOS adolescents were obese and 35% had a family history of PCOS. 7% of PCOS adolescents had prehypertension and 42% had prediabetic features. 77% non PCOS participants were considered at risk of PCOS; 15% had prehypertension and 39% had prediabetes; thus, they required a follow up.

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