

The Prevalence of Polycystic Ovarian Syndrome, Metabolic Abnormalities and Its Association With Obesity in Adolescents: A Cross-Sectional Study in an Urban Population in Iran

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Abstract- The diagnosis of polycystic ovary syndrome (PCOS) and metabolic syndrome (MS) in adolescents is clinically challenging. It is on the rise as consistent with the increasing trends in obesity rates. This study aimed to investigate the prevalence of PCOS in adolescents by the National Institutes of Health (NIH) criteria and compare the prevalence of insulin resistance (IR) and metabolic syndrome (MS) between obese (OB) and non-obese (NOB) adolescents with PCOS. This was cross-sectional research with multi-stage cluster random sampling. Participants were 15-18-year-old girls from high schools in Semnan, Iran. The ones who had a history of menstrual dysfunction underwent clinical and hormonal tests. From among a total of 900 participants, 74 girls (8.2%) had a history of menstrual dysfunction. The prevalence of PCOS was 6.44% by NIH criteria. The prevalence of abnormal glucose metabolism, MS, and IR in girls with PCOS were 8(13.7%), 6(10.3%), 24(41.4%), respectively. The OB-PCOS group with a mean BMI of 28.21 ± 1.26 kg/m² had a significantly greater prevalence of MS, high BP, waist circumference ≥ 88 cm, and higher IR than NOB-PCOS cases with a mean BMI of 20.54 ± 2.97 kg/m². Abnormal glucose metabolism was prevalent in adolescents with PCOS and occurred with equal frequency in OB and NOB PCOS groups. Obesity could worsen IR, MS, and some of the components of Mets in PCOS adolescents.

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder that influences about 6%-8% of reproductive-aged women worldwide (1).

Its characteristics include menstrual irregularity, hyperandrogenism, and polycystic ovarian morphology and is also associated with insulin resistance, obesity, and components of the metabolic syndrome (MS) (2) endometrial carcinoma, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and possibly cardiovascular disease (3). So its diagnosis is clinically, socially, and financially important.

Three completely different sets of criteria have been suggested for the diagnosis of PCOS in adults. At first,

the National Institutes of Health (NIH) consensus proposed that PCOS was defined as chronic anovulation with clinical and/or biochemical hyperandrogenism (1). Later the Fertility and Embryology Association of Europe and America Fertility Society in Rotterdam conference in 2003 have considered two criteria from the following three criteria for the diagnosis of PCOS. 1-anovulation or oligo-ovulation 2- clinical and/or biochemical hyperandrogenism, 3- polycystic ovaries by ultrasound (4). Finally, the AndrogenExcess (AE) and PCOS Society in 2009 defined PCOS as clinical or biochemical hyperandrogenism with ovarian dysfunction or polycystic ovaries (3). All agree that other relevant endocrine disorders should be ruled out.

There was not an agreement about the best diagnostic

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criteria for PCOS in adults, and none of these diagnostic criteria could be applied to adolescents with certainty (5). But recently, a consensus recommended a guideline about diagnosis and assessment of PCOS. They suggested in adolescents within eight years of menarche, both hyperandrogenism and ovulatory dysfunction are required for the diagnosis of PCOS, and where these two factors are present, ultrasound is not necessary for diagnosis (6).

PCOS prevalence in adolescents has been found between 0.81% to 18.5% (7-9). This difference in different countries is due to the choice of the population under study and the criteria used to define it. Impaired glucose tolerance (IGT), which is associated with insulin resistance and is an important predictor for T2DM, cardiovascular disease, and premature mortality, is shown at an increased level in adolescents with PCOS (10). Some studies showed an increased risk of IGT in PCOS (10,12). However, some other studies did not show that PCOS was related to insulin resistance after matching for BMI (13).

MS, a category of risk factors that increase the risk for cardiovascular disease and diabetes, is also associated with PCOS. Up to 40% of adults with PCOS have MS (11). Most studies showed an increased occurrence of MS in PCOS compared with control subjects (14-16). On the contrary, some studies did not show that the prevalence of MS was significantly different between PCOS and controls when adjusted for obesity (11-12).

So considering the number of controversies in these fields, we decided to do a community-based study in the urban population of Semnan, a city in the center of Iran, in order to diagnose PCOS in adolescents by NIH criteria and compare the prevalence of IR and MS between the obese and non-obese adolescents with PCOS.

Materials and Methods

The cluster sampling method was used to select and collect the participants; girls aged 14-18 years who studied at high schools in Semnan from July 2015 to December 2016. The sample size was calculated 900 using the Cochran formula ($n = \frac{NZ^2pq}{Nd^2 + Z^2pq}$) considering the design effect of 2.4, $P=0.5$, $Z=1.96$, and $N=9,700$.

The study was approved by the Research Council and Ethical Committee of Semnan University of Medical Sciences. Approved written informed consent and personal medical histories were obtained from each student by using a validated questionnaire. Unmarried girls with irregular menstrual cycles at intervals more than 45 days, or with a history of eight or fewer menses

annually that had attained menarche more than two years, underwent examination and blood testing then.

Weight in kgs, waist circumference, height in meters, and blood pressure (mm Hg) was measured using standard methods. Height and weight were measured without shoes, and with the participants wearing light clothes, height was measured using a wall-mounted ruler with the participants standing with head and with feet together, shoulder, heels, and buttocks touching the wall. Waist circumference was measured to the nearest 0.1 cm using an inelastic but flexible measuring tape; it was taken between the iliac crest and the costal margin in the mid axillary line around the gluteal area. Hirsutism was calculated by Ferriman-Gallwey (F-G) methods. The score of ≥ 8 over 9 body parts was considered positive (17). Any patient receiving metformin, a second-generation antipsychotic medication or dyslipidemia drugs or taking any medication known to influence glucose metabolism or BP at the time of the first visit, or had abnormal TSH and prolactin was excluded from the analysis.

After 10 hours of fasting during the 3rd-5th days of a normal menstrual cycle or menstruation happening after the daily administration of 10mg of medroxyprogesterone for a week, 5 ml of the blood sample was obtained and stored at -800 C for measuring hormonal and biochemical parameters. Leutinizing hormone (LH), follicle-stimulating hormone(FSH), 17-hydroxy progesterone (17-OHP), serum prolactin (PRL), thyroid-stimulating hormone (TSH), total testosterone, DHEAS, and insulin were assessed by enzyme-linked immunosorbent using commercially available kits (DiaPlus, Inc, Canadian). Biochemical hyperandrogenism was defined by total testosterone >80 ng/dl. Blood glucose was estimated by the glucose oxidation method.

The lipid profile was measured by a commercially available enzymatic colorimetric technique (Pars Azmoon, Tehran, Iran) adapted to a Selectra autoanalyzer.

MS was defined according to the Adult Treatment Panel III (ATP III) criteria as the co-occurrence of three or more of the following risk factors (18):

- 1) Central obesity: waist circumference ≥ 88 cm
- 2) High blood pressure [systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg]
- 3) Fasting plasma glucose ≥ 100 mg/dl
- 4) Fasting serum triglycerides ≥ 150 mg/dl
- 5) Fasting high density cholesterol (HDL-C) <50 mg/dl

Glucose abnormalities were assessed according to the

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2011 American Diabetes Association (ADA) criteria (19). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin concentration ($\mu\text{U/mL}$) multiplied by fasting glucose concentration (mg/dL) divided by 405(20).

According to Hosseinpanah *et al.*, in the Iranian population (21), HOMA-IR ≥ 2.3 was taken as laboratory evidence of IR. We also divided the PCOS cases into two groups: obese (OB; BMI ≥ 25) and non-obese: (NOB; BMI < 25) and compared them in terms of frequencies IFG, IGT, IR, MS, and its components.

Statistical analysis

Data were analyzed by using the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL), using Student's *t*-test to compare the mean of numerical variables of the groups and Pearson's Chi-square to test the independence of categorical variables. Mean and Standard deviations (SD) were calculated for continuous variables. Categorical variables were summarized by absolute frequencies and percentages, *P* less than 0.05 was considered statistically significant in all statistical tests. The results are presented as mean \pm standard deviation.

Results

The mean (\pm SD) age of the participants was 15.72 \pm (1.13) years. Among a total of 900 participants, 74 ones (8.2%) had a history of menstrual dysfunction who underwent clinical examination, biochemical, and hormonal tests. 58 out of the 900 (6.44%) girls were diagnosed to have PCOS by NIH criteria. Table 1 shows mean values for demographic, anthropometric, and biochemical findings in all girls and PCOS groups. 16 (27.5%) of PCOS patients had hirsutism, and 54 (93.1%) of them had a total testosterone level > 80 ng/dl. Abnormal glucose metabolism was present in 12 out of 74 (16.21%) subjects: 6 (8.10%) impaired fasting glucose(IFG) (fasting blood sugar ≥ 100 mg /dl), 6 (8.1%) impaired glucose tolerance (IGT) (2 h post 75 g plasma glucose value ≥ 140 mg /dl).The fasting plasma glucose levels were abnormal in 2 (3.4%) of PCOS girls, and 6 (10.3%) of them had IGT.10 out of 74 (13.5%) girls and 6(10.3%) of those with PCOS had MS. 31out of 74 (41.89%) girls with menstrual disorders and 24out of 58(41.4%) girls with PCOS had IR.22 out of 58(37.93%) PCOS cases with mean BMI 28.21 \pm 1.26 kg/m² were obese. The NOB subjects had a mean BMI of 20.54 \pm 2.97 kg/m².

Table 1. Mean (\pm SD) of values for anthropometric and biochemical characteristics in all girls (who had menstrual dysfunction) and PCOS group

Characteristics	All (n=74)	PCOS(n=58)
Age (years)	15.72 \pm 1.13	15.96 \pm 0.91
BMI(kg/m ²)	22.29 \pm 4.71	23.45 \pm 4.48
Weight (Kg)	59 \pm 14.85	63.46 \pm 15.13
Height (cm)	164 \pm 6.87	163.21 \pm 6.98
WC (cm)	79 \pm 12.34	81.92 \pm 13.23
HC (cm)	94.50 \pm 12.30	99.25 \pm 12.93
SBP (mmHg)	102.07 \pm 16.92	106.66 \pm 12.11
DBP (mmHg)	72.80 \pm 1.26	74.15 \pm 10.78
FSH (mIU/mL)	3.95 \pm 1.14	4.02 \pm 1.24
LH (mIU/mL)	8.70 \pm 6.87	10.94 \pm 7.18
TSH (mU/L)	2.5 \pm 1.35	2.65 \pm 1.32
17-OHP (ng/mL)	470 \pm 185.5	468.62 \pm 184
PRL (ng/mL)	12.20 \pm 6.83	12.42 \pm 7.01
Insulin ($\mu\text{U/mL}$)	10 \pm 3.30	10.82 \pm 3.58
Testosterone (ng/mL)	120 \pm 80.2	157.24 \pm 75.64
DHEAS (g/mol)	2.80 \pm 1.46	3.17 \pm 1.43
TG (mg/dL)	103 \pm 41.67	111.59 \pm 39.13
HDL (mg/dL)	48 \pm 0.16	47.24 \pm 9.22
LDL (mg/dL)	95 \pm 23.53	99.13 \pm 22.95
FBS (mg/dL)	84.50 \pm 10.21	85.37 \pm 9.39
1hpp (mg/dL)	95.50 \pm 24.02	125.14 \pm 28.72
2hpp (mg/dL)	123 \pm 29.29	103.02 \pm 23.94
HOMA -IR	2.13 \pm 0.76	2.24 \pm 0.78

Notes: PCOS, polycystic ovarian syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; HC, hip circumference; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; 2hpp, two hours postprandial sugar; 1hpp, one hour postprandial; FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance

The OB-PCOS group had a significantly greater prevalence of MS, high BP, waist circumference (≥ 88), and higher IR than NOB-PCOS cases. There was not a

significant difference in the prevalence of TG and HDL levels, IFG, and IGT between the two groups (Table 2).

Table 2. Prevalence of metabolic syndrome and its components, IGT and Insulin resistance in all girls and PCOS cases separately in obese (BMI ≥ 25) and non-obese (BMI < 25) subgroups in term of count (%)

Variables	All (74)	PCOS (n=58)	PCOS-OB (n=22)	PCOS-NOB (n=36)	P*
BMI(kg/m ²)	22.2 \pm 4.7	23.45 \pm 4.48	28.21 \pm 1.26	20.54 \pm 2.97	<0.001**
Metabolic syndrome	8(10.8%)	6(10.3%)	6(27.3%)	0(0.0%)	0.001
BP \geq 130/85 mmHg	7(9.4%)	8 (13.8%)	8(36.4%)	0(0.0%)	<0.001
TG \geq 150mg/dL	12(16.21%)	10 (17.2%)	6(27.3%)	4(11.1%)	0.114
HDL $<$ 50mg/dL	33(44.5%)	34 (58.6%)	14(63.6%)	20(55.6%)	0.544
WC \geq 88 cm	21(28.37%)	20 (34.5%)	17 (77.3%)	3(8.3%)	<0.001
FBS \geq 100mg/dL	4(5.4%)	2(3.4%)	1(4.5%)	1(2.8%)	0.720
IGT	6(8.1%)	6(10.3%)	0(0.0%)	6(16.7%)	0.073
Insulin resistance	31(41.89%)	24(41.4%)	15(68.2%)	9(25%)	0.001

Notes:PCOS: Polycystic ovary syndrome, BMI: Body Mass Index, BP: Blood Pressure, TG: Triglyceride, HDL: High-Density Lipoprotein, WC: Waist circumference, IFG: Fasting blood sugar ≥ 100 , IGT; impaired glucose tolerance IR: Insuline resistance(HOMA-IR ≥ 2.3 (

* Comparison between PCOS-obese (OB) and PCOS- non-obese (NOB) cases (Two-sample test of proportion), ** Two-sample *t*-test Data are presented as Mean \pm Standard deviation

Discussion

To our knowledge, this is a large urban community-based study in Iran, estimating the prevalence of PCOS in adolescents with NIH criteria and comparing the prevalence of MS, IGT, and IR in OB and NOB-PCOS girls.

In this large study, the prevalence of PCOS was 6.44% by NIH criteria. In one study in Iran, the rate of clinical PCOS was 3% (8). In other countries, this prevalence is also different. Hickey *et al.*, in a prospective cohort study, showed that 18.5% of post-menarchial girls would have fulfilled the Rotterdam criteria for PCOS (9).

This difference is due to the choice of the population under study, the criteria used to define it, and the methods used to define the criteria. In this study, 8.3% of total girls and 100% of girls with PCOS had irregular menses. In Hicky *et al.*, study fifty-one percent of girls showed menstrual irregularity (9). Rossi in 2008 found that 100% of adolescents diagnosed with PCOS showed menstrual irregularity (11).

There is proof that greater menstrual irregularity is associated with a more intensive PCOS phenotype and higher androgen levels (4).

In our study, 27.5% of girls with PCOS had hirsutism. The prevalence of hirsutism is different in other studies. Roe in 2013 and Rossi in 2008 in two separate studies showed that 65% and 87.5% of adolescents had hirsutism, respectively (11,16). However, in Hicky's study 8.2% of girls with PCOS had hirsutism according to an F-G score

of ≥ 5 (9). This might be because hirsutism develops in a longer period of time in the presence of increased androgens, so the prevalence of hirsutism in adolescent time is less than adulthood. Considering the low reliability of these clinical symptoms of hyperandrogenism, increased serum androgen levels provide the best index of androgen excess in the adolescent. Elevated free testosterone (T) is the most common abnormal biochemical finding, although total testosterone and DHEAS may also be elevated (22). In this study, 93.1% of girls with PCOS had an increased level of total testosterone (TT). In Rossi's study, a total of 90% of the subjects with PCOS had an elevated TT or free androgen index FAI (11). In this study, 37.93% of adolescents with PCOS were overweight or obese.

Excessive body weight is prevalent in both adolescents and adults with PCOS. Some studies show the prevalence of obesity in PCOS to be over 50% (15). While a large number of adolescents with PCOS are obese, obesity possibly does not completely account for all metabolic features associated with PCOS. We observed that 16.21% of girls with menstrual dysfunction and 13.7% of girls with PCOS had IFG or IGT, suggesting that young age does not provide protection from the metabolic disturbances commonly seen in adults with PCOS.

Several studies of adolescents with PCOS have reported the incidence of IGT to be 11.8% to 25% (10-12). They also showed that adolescents with PCOS, just like adults, run a high risk of IGT and DM (10,12).

However, Hart *et al.*, found that PCOS was not associated with insulin resistance after controlling BMI (13).

We found that IGT was the most common glucose abnormality, occurring without any significant difference between obese and non-obese adolescents with PCOS, a finding which was in line with the result of the other studies (10,12).

In this study, 10.3% of girls with PCOS had MS. Several studies of adolescents with PCOS have reported the incidence of MS to be 6.6% to 37 % (13-15).

The variety of prevalence rates can be accounted for by the fact that there is no universal criterion available to diagnose MS in children and adolescents concerning its components and cutoff points. We showed that the OB-PCOS group had a significantly greater prevalence of MS, hypertension, waist circumference (≥ 88), and higher IR than NOB-PCOS cases. In our study, all cases of MS were seen in the OB group, just like the other two studies (12,14). We did not find any significant difference in the prevalence of TG and HDL levels, IFG, and IGT between the two groups.

Most studies showed an increased incidence of MS in PCOS girls compared with control subjects (12,14-15). Coviello *et al.*, in 2006, found that 37% of girls with PCOS had MS compared with 5% of controls and that this difference could not be justified by obesity alone. In their study, none of the girls of normal body mass index (BMI) had MS, whereas 11% of overweight and 63% of obese girls with PCOS had MS compared with 0 and 32% of control girls, respectively (14). Huang *et al.*, also in South China, showed that the adolescents with PCOS had more metabolic abnormalities than their age- and BMI controlled non-PCOS group and obesity could exacerbate insulin resistance, hyperinsulinemia, and MS in PCOS adolescent. Although there was no significant difference in pre-diabetes and hypercholesterolemia between the obese and non-obese groups (12). In Rahmanpour's study, including obese and non-obese adolescents with or without PCOS, the prevalence of IR, hypercholesterolemia, central obesity, and MS was also higher in obese PCOS than non-obese adolescents with PCOS (15).

On the contrary, some studies indicated that using adult criteria for PCOS diagnosis for adolescent girls did not recognize girls at risk of the MS reliably; in fact, an elevated BMI was the most potent indicator of metabolic syndrome risk factors (13). Rossi *et al.*, also in a cohort study, showed that obese adolescents have a high prevalence of Mets, but PCOS doesn't enhance the further risk for MS (11). Recently Fazleen *et al.*, in a systematic review and meta-analysis, confirmed the

hypothesis that the risk of MS is far greater in adolescents with PCOS compared to the normal population, and it is essential to screen PCOS at an early age to prevent MS and its complications which lead to morbidity and mortality later in life (22). The increasingly frequent occurrence of MS in children and adolescents has happened simultaneously with the rise in obesity as it has in adults (23,24). Weiss *et al.*, in 2004, also showed that the prevalence of MS was high (50%) in severely obese adolescents. They also observed that the prevalence of MS increased with the severity of obesity and IR (24).

In this large study, the prevalence of PCOS was 6.44% according to NIH criteria. Abnormal glucose metabolism was prevalent in adolescents with PCOS. Obesity could worsen IR, MS, and some components of MS. So it is necessary to monitor PCOS adolescents at an early age regardless of their BMI for OGTT and obese PCOS girls for MS to avert MS and its complications, which result in morbidity and mortality later in life.

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