Association Between Polycystic Ovarian Syndrome, Overweight, and Metabolic Syndrome in Adolescents

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Abstract

Purpose: Polycystic syndrome (PCOS) is associated with multiple metabolic abnormalities. Studies in the adolescent population are still limited and the results have been much different. The aim of this study was to investigate the association between PCOS, overweight, and metabolic syndrome in adolescents.

Methods: 30 PCOS adolescents were randomly selected from a PCOS population with NIH 1990 criteria and 71 adolescents from the normal adolescents. Anthropometric, hormonal and metabolic parameters were evaluated in four sub-groups including obese and non-obese PCOS and obese and non-obese normal adolescents.

Results: The prevalence of overweight and metabolic syndrome in adolescents with PCOS was 52% and 33.3% respectively vs 22.4% (P = 0.005) and 11.26% in control (normal) adolescents (P = 0.0001). Among all subjects, including obese and non-obese adolescents with or without PCOS, the prevalence of insulin resistance, hypercholesterolemia, central obesity, and metabolic syndrome was higher in obese PCOS with 61.5%, 46.2%, 53.8%, and 69.2%, respectively.

Conclusions: Obesity and IR are important risk factors for metabolic syndrome in PCOS. Considering the long-term health risks, it is necessary to identify metabolic disorders in adolescents with PCOS as early as possible.

Key Words: Metabolic abnormalities, Polycystic ovary syndrome, Adolescents

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that affects 6–8% of women worldwide. PCOS is associated with metabolic abnormalities, such as dyslipidemia, obesity, and glucose intolerance, which are also components of the metabolic syndrome (MS). The prevalence of MS in adult premenopausal women with PCOS is approximately 40%. There is a growing appreciation that adolescents are at increasing risk for type 2 diabetes mellitus and MS since the prevalence of obesity is increasing in this population. Data of 12- to 19-year-old adolescents included in the National Health and Nutrition Examination Survey from 1999 to 2002 (NHANES 99-02) demonstrated that the prevalence of the metabolic syndrome in all teens varied from 2.0% to 9.4% of teens in the United States, depending on the definition used. In obese teens, these prevalence rates varied from 12.4% to 44.2%.

Since adolescents with PCOS are insulin resistant as are their adult counterparts, they would be predicted to be at increased risk for the MS as well. In one study using a national database, adolescents with PCOS were found to be at increased risk for MS in comparison with controls. However, PCOS status could not be accurately ascertained in the control subjects, MS prevalence in an adolescent PCOS cohort was found to be at least 3-fold greater than normal adolescents when adjusted for body mass index (BMI). There is intriguing evidence that this increased risk may be conferred not only by IR but also by hyperandrogenemia, which is a risk factor for MS independent of obesity and insulin resistance.

In our first study for evaluating the prevalence of PCOS in adolescents in an Iranian population, the findings showed lower rate of PCOS and obesity among this group (2.9% and 8% respectively). Although the prevalence of PCOS in that study was the same as the other studies in Iranian adolescents, the prevalence of PCOS in Iranian women is greater and similar to worldwide reports (i.e., 7.1–14%). The aim of this study was to investigate the association between PCOS, overweight and metabolic syndrome in adolescents of Zanjan, Iran.

Methods

In the previous study in 2009, 50 (2.9%) PCOSs were diagnosed among 1882 high school adolescents (14–18 years old) of Zanjan city. NIH 1990 criteria was used for diagnosis and just by clinical criteria including: oligo- and/or anovulation (i.e. ≤8 menstrual periods in a year or menstrual cycles more than 35 days in length) and clinical hyperandrogenism (i.e. hirsutism with modified Ferriman-Gallwey scores ≥ 8 with or without acne). Then this
group was evaluated by one endocrinologist and after ruling out other etiologies (e.g., congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing syndrome), they were enrolled in the PCOS group.

In the present study, six months after the first study, all the PCOS group members were invited to participate, i.e., from which 40 of them referred to us. In addition, we randomly selected 80 adolescents from the normal adolescents of the previous study (total of 120 adolescents). In the new study, all the population was reevaluated confirming the previous diagnosis; all of the normal adolescents had regular menses (an average length of the cycles between 22 and 41 days; none or a single cycle with a length of <22 to >41 days during the past year) without hirsutism.

All the girls were at least 1 year post menarche at the time of evaluation. The exclusion criteria were hypothyroidism, hyperprolactinemia, use of any medications known to affect sex hormone, glucose or lipid metabolism for at least a month and oral contraceptives for 3 months before entering of the study. Taking these measures, 10 and 9 participants were excluded from the PCOS group and normal group respectively. Based on the previous survey, obesity was defined by BMI ≥85th percentile. Then the study participants were divided into four sub-groups including obese and non-obese PCOS and obese and non-obese normal adolescent.

The study protocol was approved by the Institutional Review Board of the Zanjan University of Medical Sciences. Written informed consent was obtained from all participants and/or their parent or legal care-taker before their participation in the study.

**Study Protocols**

All subjects who were enrolled in the study had a medical history and underwent physical examination, including height, weight waist and hip circumference, blood pressure, modified Ferriman-Gallwey scores, and acne scores. All measurements were done by observers trained with the same standard protocols (allowing for comparison with other studies)\textsuperscript{17,18}; waist circumference was measured midway between the lowest rib and the iliac crest with the subject standing at the end of gentle expiration, and hip circumference at the greater trochanters. Weight was measured in kilograms and height was measured to the nearest 0.5 cm. BMI was calculated. Blood pressure was measured twice with mercury sphygmomanometer with subjects sitting quietly for at least 5 minutes; the readings were averaged as the final value. Ferriman-Gallwey scores were assessed by at least two observers.

Since our study group consisted of virginal girls, we could not perform trans-vaginal ultrasound. So trans-abdominal ultrasound examination was obtained to evaluate the ovaries using a Toshiba Sonolayer SSA-220A (Toshiba, Tokyo, Japan) with a mechanical 6-MHz probe. Adolescents with regularly menstruation were scanned in the early follicular phase (cycle days 3–5), while those with oligomenorrhea or amenorrhea were scanned between days 3 and 5 of spontaneous or progestin-induced withdrawal bleeding. The polycystic-appearing ovary (PAO) was defined according to the presence of increased ovarian size and/or at least 12 follicular cysts measuring 2 to 9 mm.

After a 10-hour overnight fast, blood samples were taken from adolescents between the first and fifth day of the menstrual period/withdrawal bleeding in order to measure prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), free testosterone (FT), dehydroepiandrosterone-sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), thyroid stimulating hormone (TSH), and lipid profile.

The cutoff values for abnormal serum lipid levels were based on the National Cholesterol Education Program Pediatric Panel Report.\textsuperscript{19} Hypertriglyceridemia, hypercholesterolemia, low levels of high-density lipoprotein (HDL-C), and high levels of low-density lipoprotein (LDL-C) were defined by serum concentrations of triglycerides ≥150 mg/dL, total cholesterol ≥170 mg/dL, HDL-C ≤35 mg/dL, and LDL-C ≥110 mg/dL. The homeostasis model analysis insulin resistance (HOMA-IR = fasting glucose mmol/L × fasting insulin µU/mL/(22.5) index was used for estimating insulin action. Cutoff value of 16 µU/mL was used for hyperinsulinemia based on a study in an independent cohort of 748 children and adolescents.\textsuperscript{20} MS was defined by International Diabetes Federation criteria for MS in children and adolescents,\textsuperscript{21,22} if they had central obesity (waist circumference ≥80 cm) plus two or more of the following four factors: (1) increased concentration of triglyceride (TG) ≥150 mg/dL; (2) reduced concentration of HDL-C <35 mg/dL; (3) raised blood pressure: systolic pressure ≥130 mm Hg or diastolic pressure ≥85 mm Hg or treatment of previously diagnosed hypertension; and (4) increased fasting glucose level ≥100 mg/dL.

**Assays**

The serum levels of FSH, LH, PRL, TSH, and insulin (Monobind, Lake Forest, CA) in serum were measured by enzyme-linked immunosorbent assay (ELISA) (Stat Fax 2100, Awareness Technologies, Los Angeles, CA). Serum FT, DHEAS, 17-OHP, and androstenedione were measured using an ELISA and commercial kits (IBL, Hamburg). Serum glucose, HDL cholesterol, total cholesterol, and TG were measured using an enzymatic calorimetric method with an autoanalyzer (Mindray BS-Clinical Chemistry Analyzer, Guangzhou Shihai Medical Equipment Co, Guangdong, China).

**Statistical Analysis**

All data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL). The normality of the distribution of all continuous variables were assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean and standard deviation. Means between groups were compared with the t test and medians between them were compared with the Mann-Whitney U test. The Pearson chi-square test was used to analyze the differences between the groups and obtain an odds ratio. Statistical significance was set at $P < 0.05$. 
Results

The participants of this study, i.e., 30 adolescents in PCOS group and 71 adolescents in the normal group, were comparable in age (17.73 ± 1.01 vs 17.69 ± 1.29, respectively). However, PCOS adolescents had greater BMI (P = 0.007) and greater level of FT (P = 0.001). Table 1 shows the demographic and hormonal features of adolescents with or without PCOS. Majority of the PCOS adolescents had polycystic-appearing ovaries on pelvic sonography in comparison to those without PCOS (63.3% vs 7%; P = 0.0001).

Adolescents with PCOS displayed significantly greater waist circumference, TG, and cholesterol levels, but there were no significant differences in fasting glucose, HOMA-IR, and HDL levels between the PCOS and the control groups. The prevalence of MS in PCOS group was greater than the normal group (33.3% vs 11.26% respectively; P = 0.038). See Table 2.

The metabolic parameters between the four sub-groups of this study, including obese and non-obese PCOS and obese and non-obese normal adolescents are demonstrated in Table 3. There were no significant differences between the non-obese adolescents either with or without PCOS regarding metabolic parameters. Based on Table 3, it can be concluded that the frequency of impaired MS parameters such as hypercholesterolemia, hypertriglyceridemia, and raised BP were significantly more in obese adolescents with PCOS.

The prevalence of MS in obese adolescents with PCOS was greater than the adolescents without PCOS (69.2% vs 10.2 OR 19.8, 95% CI: 4.6—84.6) and also non-obese adolescents with PCOS (69.2% vs 5.8 % OR 36, 95% CI: 3.4—373.1).

Discussion

In our study the prevalence of MS in PCOS group was 33.3%, almost two-fold greater than the normal adolescents and 69.2% in obese PCOS, i.e. six-fold greater than the normal group. PCOS group had greater BMI and FT level which are two important risk factors for MS and cardiovascular disease in future. The prevalence of MS increased with BMI in the NHANES III population with both the Cook and the de Ferranti criteria23 and has been estimated to be as high as 50% in a study of severely obese adolescents. Both BMI and waist circumference have been shown to be predictive of metabolic cardiovascular risk factors in children and adolescents.24

Visceral adiposity is associated with IR, the primary pathophysiological mechanism thought to be responsible for the metabolic disturbances of MS.25–27 During the past decades, the increasing prevalence of MS in children and adolescents has coincided with the rise in obesity, just as in adults.28 Based on the current studies, the prevalence of obesity in PCOS is currently about 70%, 20% greater than 15 years ago.29 In 1999–2000, the prevalence of overweight was 14.8% among a representative sample of American females aged 2—19 years old, and in 2003—2004 the prevalence was 16.4%.30

In our first study, the prevalence of PCOS and obesity in adolescents were 2.9% and 8% respectively, which were lower than the other studies’ populations. In this study, the NIH 1990 criteria were used for diagnosis of PCOS. It should be mentioned that specialized criteria for the diagnosis of PCOS in adolescents have not been accepted to date so instead the diagnostic criteria for adults are used in most clinical practices.

Table 1
Endocrine Characteristic of PCOS and Control Adolescents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCOS adolescent (n = 30)</th>
<th>Normal adolescent (n = 71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>17.73 ± 1.01</td>
<td>17.69 ± 1.29</td>
<td>0.87</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 ± 3.09</td>
<td>21.06 ± 2.85</td>
<td>0.007**</td>
</tr>
<tr>
<td>BMI &gt; 85° percentile</td>
<td>13 (43.30%)</td>
<td>12 (16.90%)</td>
<td>0.005***</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.05 ± 7.92</td>
<td>54.18 ± 8.08</td>
<td>0.006*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.9 ± 5.32</td>
<td>158.13 ± 5.03</td>
<td>0.49</td>
</tr>
<tr>
<td>Freet (ng/dl)</td>
<td>1.81 ± 1.33</td>
<td>1.07 ± 0.72</td>
<td>0.001**</td>
</tr>
<tr>
<td>DHEAS (ng/dl)</td>
<td>2.51 ± 1.26</td>
<td>2.25 ± 1.33</td>
<td>0.061**</td>
</tr>
<tr>
<td>FSH IU/L</td>
<td>5.86 ± 1.86</td>
<td>6.53 ± 2.27</td>
<td>0.152</td>
</tr>
<tr>
<td>LH IU/L</td>
<td>9.03 ± 6.4</td>
<td>5.79 ± 6.73</td>
<td>0.545</td>
</tr>
<tr>
<td>PAO</td>
<td>19 (63.3%)</td>
<td>5 (7%)</td>
<td>0.0001***</td>
</tr>
</tbody>
</table>

Abbreviation: PAO, polycystic-appearing ovaries
Data are presented as mean ± standard deviation or percent (%), and number
* t test
** Mann-Whitney U test
*** Chi-square test

Table 2
Metabolic Characteristic of PCOS and Control Adolescents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCOS adolescent (n = 30)</th>
<th>Normal adolescent (n = 71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>74.3 ± 7.26</td>
<td>70.31 ± 7.91</td>
<td>0.02*</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>108.17 ± 12.06</td>
<td>103.1 ± 12.22</td>
<td>0.059</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>76.67 ± 11.24</td>
<td>78.03 ± 11.43</td>
<td>0.02*</td>
</tr>
<tr>
<td>Fasting HDL (mg/dl)</td>
<td>35.5 ± 12.54</td>
<td>35.18 ± 4.32</td>
<td>0.94</td>
</tr>
<tr>
<td>Fasting triglyceride (mg/dl)</td>
<td>108.23 ± 59.88</td>
<td>98.55 ± 40.87</td>
<td>0.043**</td>
</tr>
<tr>
<td>Fasting cholesterol (mg/dl)</td>
<td>154.43 ± 26.42</td>
<td>142.58 ± 25.53</td>
<td>0.037**</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>96.6 ± 12.32</td>
<td>94.39 ± 8.21</td>
<td>0.565</td>
</tr>
<tr>
<td>Fasting insulin (µIU/liter)</td>
<td>10.42 ± 6.45</td>
<td>8.93 ± 5.65</td>
<td>0.222</td>
</tr>
<tr>
<td>HOMA - IR</td>
<td>2.56 ± 1.9</td>
<td>2.13 ± 1.5</td>
<td>0.25</td>
</tr>
<tr>
<td>MS</td>
<td>10 (33.3%)</td>
<td>8 (11.26%)</td>
<td>0.038***</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or as percent, and number
* t test
** Mann-Whitney U test
*** Chi-square test

Table 3
Prevalence of Various Metabolic Abnormalities in Obese and Non-Obese Adolescents with and without PCOS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-obese PCOS</th>
<th>Obese PCOS</th>
<th>Obese control adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 30</td>
<td>N = 13</td>
<td>N = 59</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>IFG</td>
<td>2 (11.8)</td>
<td>6 (46.2)</td>
<td>16 (27.1)</td>
</tr>
<tr>
<td>IR</td>
<td>4 (21.5)</td>
<td>8 (61.5)</td>
<td>12 (20.3)</td>
</tr>
<tr>
<td>HIN</td>
<td>0</td>
<td>7 (53.8)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4 (23.5)</td>
<td>6 (46.2)</td>
<td>8 (13.5)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>1 (5.8)</td>
<td>5 (38.5)</td>
<td>6 (10.1)</td>
</tr>
<tr>
<td>Low HDL</td>
<td>15 (88.2)</td>
<td>12 (92.3)</td>
<td>56 (94.9)</td>
</tr>
<tr>
<td>Central obesity</td>
<td>1 (5.9)</td>
<td>7 (53.8)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Raised BP</td>
<td>1 (5.9)</td>
<td>5 (38.5)</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>MS</td>
<td>1 (5.8)</td>
<td>9 (69.2)</td>
<td>6 (10.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IFG, impaired fasting glycemia; HIN, hyperinsulinemia; IR, insulin resistance; MS, metabolic syndrome
Data are presented as % or number
* Chi-square test, in comparison of the obese-PCOS with three others
At present, the 2003 Rotterdam criteria are more widely accepted than the NIH criteria, but the former tends to expand rather than replace the latter because all women diagnosed by the NIH 1990 criteria would also meet the Rotterdam criteria. The risk of metabolic disturbances may vary among different phenotypes of PCOS based on the Rotterdam criteria. In other studies, adults with PCOS, defined by NIH criteria had more severe metabolic abnormalities than those defined by Rotterdam criteria. The difference in prevalence of obesity and androgen excess may attribute to the characteristic.

In our present study, obesity and PCOS alone were attributed to lower risk of MS and the PCOS group with normal weight had lower prevalence of IR. In previous studies obese PCOS adolescents have been shown to have an increased prevalence of glucose intolerance and IR. According to Diamanti-Kandarakis, hyperandrogenemia should be considered as the primary abnormality in PCOS. So IR and hyperinsulinemia are superimposed upon the pre-existing ovarian dysfunction. This suggests an interaction between hyperandrogenemia and obesity in the expression of the metabolic phenotype in PCOS.

In comparison of the PCOS group with or without overweight, hyperandrogenemia has also been reported to be an independent risk factor for MS in premenopausal women without PCOS and has been associated with hyperinsulinemia, fasting hyperglycemia, and MS in postmenopausal women as well. However, data on metabolic disturbances in adolescents with PCOS are limited and the results seem to vary in studies of different populations.

In a study in South China, the prevalence of insulin resistance, dyslipidemia, and MS in PCOS adolescents with BMI > 85th percentile was 74.4%, 39.5%, and 14% vs 32.9%, 14.1%, and 0%. In comparison PCOS subjects with BMI < 85th percentile, the prevalence of MS in young Korean women with PCOS was 14.5%, nearly 3.5 times greater than in age-matched women in Korean urban population (4.3%). The most frequently occurring component of MS was low HDL cholesterol (45%), and the least frequent was high fasting serum glucose level (0.9%).

In a Turkish study, the insulin resistance ratio in obese adolescent with PCOS was 93.3% vs 46.6% in lean PCOS and 50% in obese controls. Also in another Turkish study, Vural et al found greater frequency of MS and increased carotid artery intima-media thickness in early adulthood in PCOS patients. In their study the prevalence of MS according to WHO guidelines in adolescents with PCOS was 11.6% vs 0% in normal adolescents. Both in our study and in Vural et al, the polycystic ovarian appearance on ultrasound and in normal adolescents was 7% and 9% respectively, which is lower than expected.

There were several limitations with this study. First, since the prevalence of PCOS was low in the previous study, this resulted in a low sample size in our four sub-groups and it made the interpretation of the results difficult. So it is suggested that future studies be conducted with larger sample sizes. Second, it would have been even better if we had used HPL-MS instead of ELISA with commercial kit for evaluating free testosterone.

Conclusions

The most frequently occurring components of MS in obese PCOS group were impaired fasting glycemia and insulin resistance (61.5%), central obesity (53.8%), and hypercholesterolemia (46.2%), respectively.

Our data demonstrated that PCOS and obesity are two separate risk factors for MS in adolescence that together can have augmented effects. Interventions for weight loss such as diet, exercise, novel interventions with insulin sensitizers, and anti-androgens may reduce the risk of developing diabetes and cardiovascular disease in the PCOS adolescents in the future. However, a question still remains regarding which factor is more prevalent: overweight or PCOS? This suggests the need for a much larger prospective study.

Obesity and IR are important risk factors for MS in PCOS adolescents. Considering the long-term health risks, it is necessary to identify metabolic disorders in adolescents with PCOS as early as possible.

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References

12. Coviello AD, Legro RS, Dunaf A: Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J Clin Endocrinol Metab 2006; 91:492
30. Fruzzetti P, Perini D, Lazzarini V, et al: Adolescent girls with polycystic ovary syndrome showing different phenotypes have a different metabolic profile associated with increasing androgen levels. Fertil Steril 2009; 92:626