Primary Amenorrhea as a Manifestation of Polycystic Ovarian Syndrome in Adolescents

A Unique Subgroup?

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Objective: To compare clinical and metabolic features of adolescents having primary amenorrhea (PA) and polycystic ovarian syndrome (PCOS) with those having oligomenorrhea or secondary amenorrhea (OM/SA) and PCOS.

Design: Retrospective case-control study.

Setting: Endocrine Gynecology Clinic at The Hospital for Sick Children, Toronto, Ontario, Canada.

Patients: Girls and young women aged 14 to 18 years having PA and PCOS (n=9) seen during a 2½-year period were compared with control subjects having OM/SA and PCOS (n=18) randomly selected during the same period.

Intervention: Medical record review was performed to assess clinical, biochemical, and ultrasonographic measures, as well as response to a progesterone challenge.

Main Outcome Measures: Differences in response to the progesterone challenge, hyperandrogenism, and the presence of features of the metabolic syndrome.

Results: Compared with adolescents having OM/SA, adolescents having PA demonstrated older age at pubarche, higher androstenedione levels, greater prevalence of family history of obesity, a tendency toward no withdrawal bleeding in response to the progesterone challenge, and more features associated with the metabolic syndrome (acanthosis nigricans, higher diastolic blood pressure, and lower high-density lipoprotein cholesterol level). No significant correlation was demonstrated between response to the progesterone challenge, metabolic features, and androstenedione levels.

Conclusion: Adolescents with PA and PCOS exhibit increased features of the metabolic syndrome and higher androstenedione levels and may represent a more severe spectrum of a common condition.


POLYCYSTIC OVARIAN SYNDROME (PCOS) is a heterogeneous condition with a spectrum of clinical and biochemical features, including symptoms of anovulation, hyperandrogenism, and polycystic ovaries. Obesity is a feature in 35% to 50% of cases. There is evidence that insulin resistance, hyperinsulinism, and typical features of the metabolic syndrome (MS) are associated with the development of PCOS and its late metabolic implications.

Many of the features appear during early adolescence as secondary amenorrhea (SA) or oligomenorrhea (OM) and as symptoms of hyperandrogenism such as acne and hirsutism. Primary amenorrhea (PA) is an uncommon manifestation of PCOS. Literature regarding PA and PCOS is scant. The reported percentage of PA as an initial feature in PCOS among small cohorts has varied between 1.4% and 14%. Nduwayo et al described 9 patients with PCOS and PA, all of whom had signs of hyperandrogenism. Dramus et al noted that most obese adolescents with PCOS had PA or prolonged SA, while girls of normal weight had OM. To our knowledge, no studies have compared specific clinical and biochemical features in adolescents with PA and PCOS vs those with OM/SA and PCOS.

We hypothesized that adolescents with PCOS and PA may represent a more severe spectrum of the PCOS disorder and exhibit a greater degree of hyperandrogenemia and metabolic disturbances. The objective of this study was to compare the clinical, biochemical, and radiologic features of adolescents having PA and PCOS with those having OM/SA and PCOS.
TABLE 1. Clinical Characteristics of Subjects With Polycystic Ovarian Syndrome and Primary Amenorrhea (PA) vs Oligomenorrhea or Secondary Amenorrhea (OM/SA)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With PA (n=9)</th>
<th>Control Subjects With OM/SA (n=18)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>15.6 (1.0)</td>
<td>15.8 (1.1)</td>
<td>.65</td>
</tr>
<tr>
<td>Family history, % (No. of patients/total No. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirsutism</td>
<td>50 (3/6)</td>
<td>25 (3/12)</td>
<td>.34</td>
</tr>
<tr>
<td>Menstrual abnormalities</td>
<td>0 (0/8)</td>
<td>27 (4/15)</td>
<td>.26</td>
</tr>
<tr>
<td>Obesity</td>
<td>67 (6/9)</td>
<td>22 (4/18)</td>
<td>.04</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>67 (6/9)</td>
<td>100 (18/18)</td>
<td>.68</td>
</tr>
<tr>
<td>Age at pubarche, mean (SD), y</td>
<td>11.2 (2.1)</td>
<td>9.8 (1.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Age at thelarche, mean (SD), y</td>
<td>11.2 (1.7)</td>
<td>10.0 (1.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Body mass index z score, mean (SD)</td>
<td>2.1 (0.4)</td>
<td>1.5 (1.0)</td>
<td>.08</td>
</tr>
<tr>
<td>Age at menarche, mean (SD), y</td>
<td>. . .</td>
<td>12.2 (1.2)</td>
<td>. .</td>
</tr>
<tr>
<td>Cycle length, mean (SD), d</td>
<td>. . .</td>
<td>4.6 (1.6)</td>
<td>. .</td>
</tr>
<tr>
<td>Acanthosis nigricans, % (No.)</td>
<td>67 (6)</td>
<td>22 (4)</td>
<td>.04</td>
</tr>
<tr>
<td>Hirsutism, % (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>28 (5)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>33 (3)</td>
<td>33 (6)</td>
<td>.26</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 (3)</td>
<td>28 (5)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>33 (3)</td>
<td>11 (2)</td>
<td></td>
</tr>
<tr>
<td>Acne, % (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>22 (2)</td>
<td>36 (6)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>33 (3)</td>
<td>28 (5)</td>
<td>.80</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 (3)</td>
<td>17 (3)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>11 (1)</td>
<td>22 (4)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure percentile, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>74.2 (20.6)</td>
<td>69.5 (30.1)</td>
<td>.43</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.3 (16.0)</td>
<td>70.8 (17.8)</td>
<td>.04</td>
</tr>
<tr>
<td>Metabolic syndrome, % (No. of patients/total No. of patients)</td>
<td>38 (3/8)</td>
<td>19 (3/16)</td>
<td>.36</td>
</tr>
</tbody>
</table>

Abbreviation: Ellipses, not applicable.

aFisher exact test for discrete variables expressed as percentages and nonparametric Kruskal-Wallis test for continuous variables expressed as mean (SD).

METHODS

DEFINITIONS

Primary amenorrhea was defined as no menstrual bleeding by age 16 years or older or no menarche at least 4 years after initiation of secondary sexual signs. Oligomenorrhea was defined as fewer than 9 menses per year. Secondary amenorrhea was defined as no menses for 6 months.8 To decrease the possible confounder of physiologic anovulatory cycles occurring after menarche, OM and SA were only considered if present at least 2 years after menarche. Polycystic ovarian syndrome was defined according to the revised 2003 Rotterdam ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group statement.13 Metabolic syndrome was defined according to criteria by Weiss et al.16

STUDY POPULATION

This was a case-control study. All medical records of adolescents referred to the Endocrine Gynecology Clinic at The Hospital for Sick Children, Toronto, Ontario, Canada, from November 1, 2003, to May 31, 2006, with PA were reviewed. Inclusion criteria for the cases included PA and PCOS. Investigations to rule out other causes of PA included prolactin level, thyroid function, evaluation of the hypothalamic-pituitary-ovarian axis, ultrasonography to detect structural genitourinary anomalies, and screening for congenital adrenal hyperplasia and Cushing syndrome. The control group (2 controls for every PA case) included adolescents with OM/SA and PCOS who were seen during the same 21⁄2-year period. This group was randomly collected as the first 2 patients seen at the clinic during the same month as each patient with PA.

DATA COLLECTION

Data collected included the following: (1) Demographic characteristics (age, race/ethnicity, and family history). (2) Coexisting medical illness and medications. (3) Clinical and physical findings (acne, obesity, hirsutism, elevated blood pressure,
and acanthosis nigricans). (4) Laboratory results (lipid profile, the levels of fasting and 2-hour glucose following an oral glucose tolerance test, and the levels of insulin, androstenedione [Diagnostic Products, Los Angeles, California], 17-hydroxyprogesterone [Diagnostic Products], estradiol [DiaSorin Diagnostics, Saluggia, Italy], free testosterone [Coat-A-Count, Diagnostic Products], dehydroepiandrosterone sulfate [Immune, Diagnostic Products], serum gonadotropins [luteinizing hormone and follicle-stimulating hormone], and testosterone [Chemiluminescence Immunoassay; Bayer Corporation, West Haven, Connecticut]). (5) Ultrasonographic variables based on 2003 Rotterdam ESHRE/ASRM–Sponsored PCOS Consensus Group criteria for PCOS.15 (6) Withdrawal bleeding in response to progesterone challenge (PC). The study was approved by the Institutional Ethics Review Board of The Hospital for Sick Children.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using commercially available software (SAS version 9.1; SAS Institute Inc, Cary, North Carolina). The nonparametric Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables were used to evaluate differences between the PA and OM/SA groups. Spearman rank correlation was performed to evaluate associations between variables. $P \leq .05$ was considered significant.

**RESULTS**

There were 9 subjects aged 14 to 18 years with PA and PCOS, matched to 18 subjects with OM/SA. Subjects represented various racial/ethnic backgrounds. Adolescents with PA and PCOS had statistically significantly increased family history of obesity and more features associated with MS (acanthosis nigricans, higher diastolic blood pressure, and lower high-density lipoprotein cholesterol level) ($P = .04$ for all) (Table 1 and Table 2). The association between MS and obesity was statistically significant ($P = .002$).

Subjects with PA had pubarche and thelarche later than subjects with OM/SA; however, both were within the normal range. Features of hyperandrogenism were similar in the 2 groups. There was no significant difference in the hormonal profiles except for androstenedione levels (Figure).

Ultrasonography findings were similar between the 2 groups. A subset of subjects underwent PC. All 6 in the OM/SA group exhibited a large amount of withdrawal bleeding; only 2 of 5 in the PA group responded to PC ($P = .06$). No association was detected between response to PC, androstenedione levels, and ultrasonography findings.

**COMMENT**

We hypothesized that the group of adolescents having PCOS and PA would exhibit a greater degree of hyperandrogenism and metabolic dysfunction compared with adolescents having PCOS and OM/SA. The prevalence of MS among youth in the United States varies between 4.2% and 8.4% in the general population but rises to 28% to 39% among obese adolescents (body mass index, $>95th$
The incidence of the MS was similar in the present study, at 25% among the cohort. In contrast, Covelli et al reported MS rates of 11% in overweight girls and 63% in obese girls with PCOS. Differences in the results may be accounted for by differences in the number of subjects, duration of symptoms, degree of obesity among the subjects assessed, or definitions used of the MS and PCOS during adolescence. Although the PA group did not have a higher prevalence of MS compared with the OM/SA group, the PA group demonstrated more acanthosis nigricans, higher diastolic blood pressure, slightly elevated fasting insulin levels, slightly higher body mass index z score, and lower high-density lipoprotein cholesterol levels. Together, this suggests that adolescents with PCOS and PA may have a higher risk for features of MS than those with PCOS and OM/SA. Further prospective study among larger numbers of adolescent patients is warranted. Adult women with PCOS have higher rates of MS and type 2 diabetes mellitus and increased risk factors for cardiovascular disease, linked to the role of hyperinsulinism in the pathogenesis of PCOS, and it would be valuable to identify young women at greatest risk for these comorbidities.21

The PA group had higher androstenedione levels compared with the OM/SA group. Higher serum androstenedione levels have been previously described in adolescents with PCOS, related to the hypothesis of isolated functional ovarian hyperandrogenism as being causative.2,12,13 We did not find evidence of a history of premature adrenarche or elevation of dehydroepiandrosterone sulfate levels, which have been reported in patients with PCOS.21 Although hyperandrogenism is a core feature of PCOS, most adolescents with PCOS exhibit elevated estrogen levels with thickened endometrial lining, anovulatory cycles, and OM or SA.24 Hyperandrogenism has been suggested as a rare cause of negative withdrawal response to PC due to a persistently decidualized endometrium induced by a prolonged anovulatory state.25 Our study results support this assumption because the adolescents with PA had laboratory evidence of higher serum androstenedione levels and lack of response to PC.

This study has some limitations. First, the study included a small number of subjects and a retrospective nature of evaluation, leading to potential bias in recall of puberty onset. However, all patients attended a specialized clinic and likely had heightened concerns about puberty, potentially improving the accuracy of patient recall. Second, PCOS can be difficult to diagnose in this age group because girls may indeed have acne, irregular bleeding, and physiologic anovulatory cycles following menarche.25,26 By including those with OM/SA for comparison at least 2 years after menarche, we minimized this potential confounder. Third, the use of the free testosterone assay, rather than the calculated free androgen index, may underestimate the degree of hyperandrogenemia. The free testosterone assay has been criticized for representing only 20% to 60% of the free testosterone measured by equilibrium dialysis.27

Although the link between PA and PCOS has been mentioned briefly in the literature, PCOS is rarely listed as a differential diagnosis for PA. Although PCOS is becoming more prevalent in parallel with rising obesity rates, studies8–14 have not evaluated the clinical features of this subgroup of patients with PA-PCOS. We conclude that adolescents with PA-PCOS are similar in many respects to those with OM/SA, but they demonstrate more features of MS and have higher androstenedione levels and lower frequency of response to PC. Accordingly, this may indicate elevated androgen levels or enhanced sensitivity to androgen with persistent decidualization of the endometrium. Further studies in a larger cohort of patients to determine the frequency of this finding are warranted. Finally, it is important for health care providers to recognize that PA may be due to PCOS so that appropriate investigative and management strategies may be undertaken.

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Author Contributions: Drs Rachmiel and Hamilton had complete access to all data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rachmiel, Kives, and Hamilton. Acquisition of data: Rachmiel. Analysis and interpretation of data: Rachmiel, Atenafu, and Hamilton. Drafting of the manuscript: Rachmiel and Hamilton. Critical revision of the manuscript for important intellectual content: Kives, Atenafu, and Hamilton. Administrative, technical, and material support: Rachmiel. Supervision: Kives and Hamilton.

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REFERENCES


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20. Coviello AD, Legro RS, Dunaii 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(2):492-497.


**Announcement**

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Pediatrics and Adolescent Medicine* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archpediatrics.com.