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Comparison of Clinical and Biochemical Parameters in Adolescent Girls with Polycystic Ovary Syndrome in Different Clinical Settings

Kansra AR* and Marquart K

Division of Pediatric Endocrinology, Department of Pediatrics, Medical College of Wisconsin, WI, USA

Abstract

Objective: The aim of this study is to identify different polycystic ovary syndrome (PCOS) phenotypes in adolescent girls presenting to different clinical subspecialties and assess the metabolic syndrome (MS) among these phenotypes.

Design: Retrospective chart review of Adolescent girls with PCOS seen in Pediatric Endocrine (PEndo), Pediatric Adolescent Medicine (PAMed) clinics.

Main outcome measure: Compare the clinical and laboratory hallmarks for PCOS and evaluate for MS among adolescent populations presenting in sub-specialty clinics.

Results: One hundred and sixty two charts from PEndo, PAMed clinics on post-menarchal girls with PCOS diagnosis were reviewed. Adolescent girls presented in PEndo clinic have distinct PCOS phenotype that showed statistically significant free testosterone (FT) (p=0.0257) with possibly more hirsutism. In addition 17 hydroxyprogesterone (17 OHP) levels were higher (p=0.0257) in patients from PEndo clinic as compared to other clinic. To quantify the risk of MS, we regrouped patients having body mass index (BMI)>90 percentile from both the clinics and divided them in hyper-androgenemia (HA) if FT ≥ 4.0 pg/mL and non-HA phenotype. 35.9% (28/78) met the criteria for MS in HA phenotype. When compared, HA phenotype had higher rate of MS as compared to non- HA (35.9% Vs 0.1%).

Conclusion: Adolescent girls with PCOS presenting in the sub-specialty clinics are likely to have different phenotypes. HA phenotype had increased rate of MS syndrome. Understanding the heterogeneous nature of this disorder will address specific health needs of an individual patient and help us tailor appropriate medical therapy.

Keywords: Polycystic ovary syndrome; Adolescence; Hirsutism; Hyperandrogenemia

Introduction

PCOS is the most common endocrine disorder in women of reproductive age with a prevalence of 5-10% [1]. PCOS is a diagnosis that is being made more commonly in adolescent girls; not surprisingly, mirroring the increasing rate of obesity in this population [2]. The exact mechanism affecting ovarian steroid genesis in PCOS is still unclear. Insulin resistance is a common feature of PCOS that has been observed both in obese and lean patients [3,4]. Hyper insulinemia has been recognized as a contributory factor for ovarian disruption due to increased production of ovarian androgens [5-7]. Since obesity is commonly seen with this disorder; this further worsens the insulin resistance state in PCOS patients.

The heterogeneous nature of PCOS has led to difficulty building consensus for standard diagnostic criteria [8]. Three widely accepted clinical and biochemical features of the disorder include: oligomenorrhea, clinical or biochemical evidence of excess androgen levels, and evidence of polycystic ovaries on pelvic ultrasound. National Institute of Health (NIH) (1990) suggested the presence of oligomenorrhea with clinical or biochemical HA are essential for the diagnosis [9]. Rotterdam (2003) expanded the diagnostic criteria for PCOS by adding the ultrasound diagnostic criterion and recommended that at least two out of the three criteria should be met [10]. Finally, the Androgen Excess Society (2006) recommended that to define PCOS patients must have clinical and/or biochemical HA with either oligomenorrhea and/or polycystic ovaries [11].

The difficulty of PCOS diagnosis extends to the adolescent group; perhaps more so as many of the typical hallmarks of early puberty mimic PCOS. For example, the oligomenorrhea seen in PCOS is commonly seen for the first few years after menarche. Another similar includes the androgen excess which most commonly manifests as acne [12,13]. Relying on pelvic ultrasound in adolescence for PCOS diagnosis is also challenging due to the variability in the ovarian appearance and volume in adolescent girls during puberty [14-18].

The heterogeneous nature of this disorder leads patients to present to different clinical sub-specialties likely determined by the predominant bothersome symptom [19]. There is a significant variability in the evaluation and treatment approach that is observed in these clinics [20,21].

Overall patients with PCOS are at a risk for metabolic syndrome (MS); whether the occurrence of MS is simply due to increased rate of obesity Vs HA is debated [22-27]. Limited data has suggested the lack of association between elevated testosterone levels and MS in adolescent girls with PCOS [28]. The recognition and timely treatment of MS is important since this increases the risk for cardiovascular disease in future [29,30].

***Corresponding author:** Alvina R Kansra, Children's Hospital and Health System, Section of Pediatric Endocrinology, Diabetes and Metabolism, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226, USA, Tel: 4142666750; E-mail: akansra@mcw.edu

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Similar to PCOS, diagnostic criteria for MS in adolescent population are not clear. Recently the International Diabetes Federation (IDF) has launched new criteria to identify adolescent with MS (Table 1). According to these criteria consider MS in a child or adolescent patient if their BMI>90 centile and they meet 2 out of the 4 criteria shown in Table 1 [31].

The focus of our study is to identify the different PCOS phenotypes in adolescent age patients based upon the clinical and biochemical features and to assess MS among these phenotypes.

Methods and Materials

After receiving the approval of the Institutional Review Board (IRB) at Children's Hospital of Wisconsin (CHW), we performed a retrospective chart review of 162 patients with PCOS from the pediatric specialty clinics; PEndo (103/162), PAMed (45/162) and Downtown Health Center (DHC) (14/162) at CHW. Subjects between the ages of 12-19 years were identified based upon the ICD-9 diagnostic code for PCOS using NIH 1990 criteria (chronic anovulation characterized by oligomenorrhea, primary or secondary amenorrhea, clinical or biochemical evidence of HA). Data was collected on patients presenting to PEndo and PAMed clinics from 2003-2009 and DHC 2008-2010. Since DHC is a part of PAMed clinic, the data from these 2 offices was combined. Subjects were included if they were at least two years from menarche. Exclusion criteria for all participants included: (1) any biochemical evidence of hyperprolactinemia, late onset congenital adrenal hyperplasia, or thyroid disease (2) history of type 1 or type 2 diabetes mellitus (3) any medication known to affect sex hormone, carbohydrate metabolism or lipid profile.

Chart review was conducted and the following were captured: age at presentation, body mass index (BMI), blood pressure (BP), menstrual pattern, clinical (hirsutism) and biochemical markers including free testosterone, DHEAS, 17 OHP, androstenedione, fasting glucose, HbA1c, prolactin, TSH, Follicular stimulating hormone (FSH), Luteinizing hormone(LH), and lipid profile. Other clinical parameters such as family history of type 2-diabetes (T2DM) and premature adrenarche were also collected.

Statistical Analysis

This retrospective study included subjects from two groups, P Endo and PAMed clinics. Descriptive statistics were performed on the various variables. The two sample t-test and chi-square test were used to determine the statistical difference in the two groups for the continuous and categorical variables, respectively. P-values were further adjusted using the stepdown Sidak method due to multiple testing. All data management and analyses were carried out using the Statistical Analysis System, version 9.2 (SAS Institute, Cary, NC, USA). A two-tailed p-value<0.05 was considered statistically significant. Data are expressed as mean ± s.d.

Results

Table 2 and Figure 1 summarizes the clinical, and biochemical profile in all groups. 162 patients (56% Caucasian, 22% African American 16% Hispanic and 6% other ethnicity) post-menarchal adolescent girls with menstrual abnormalities and hirsutism presented to the PEndo and PAMed clinics. One hundred and three (63.6%) adolescent girls were seen in the PEndo and 59 (36.4%) in PAMed clinics. Eighty-five percent of girls were overweight with a BMI ≥ 85%; 68% were obese with a BMI ≥ 95% in all groups. Adolescent girls presented to PEndo clinic were noted to have increased biochemical evidence of HA as compared with PAMed clinics patients.

The results of our chart review did not show any significant difference in age of diagnosis, BMI, menstrual irregularities, total testosterone, HbA1c, lipid profile, prolactin, LH, FSH or DHEAS

Obesity	>90th percentile
Triglycerides	>150 mg/dL (1.7 mmol/L)
HDL-cholesterol	<50 mg/dL (1.29 mmol/L)
Blood pressure	>130 mm Hg systolic or 85 mm Hg diastolic
Glucose	>100 mg/dL (5.6 mmol/L)

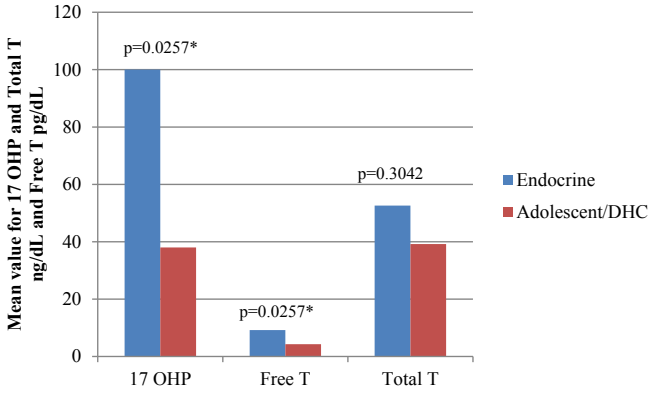
According to IDF definition, consider MS if patient has BMI >90% plus two out of the four criteria.

Table 1: IDF criteria for MS for Adolescent age group.

Variables	Reference range	Total patients	Pediatric Endocrine	Pediatric Adolescent/ DHC	Unadjusted (adjusted) p-value
		N (%)	n (%)		
Number (%)		162	103	59	
Age		15.2 ± 1.74	14.94 ± 1.5	15.5 ± 1.9	
Race					
AA		36(22.4)	19(18.5)	17 (29.3)	
Hispanic/Latino		25(15.5)	15(14.6)	10 (17.2)	
White		90(55.9)	65(63.1)	25 (43.1)	NS
other		10(6.2)	4(3.8)	7 (10.4)	
BMI	above 85%	125 (85)	86 (87.8)	39 (79.6)	
	above 95%	99 (67.8)	69 (70.4)	30 (62.5)	
Oligomenorrhea			78 (84.78)	46 (83.64)	
Hirsutism			65 (67.01)	28 (47.46)	0.016 (0.3099)
F/H of type 2 diabetes			54 (39)	22 (52.38)	
Premature adrenarche			5(5.43)	3 (6.12)	
HDL	>50 mg/dL	45.8 ± 13.6	45.3 ± 13.7	46.9 ± 13.5	
Triglycerides	<150 mg/dL	124.5 ± 78.5	122.0 ± 69.4	129.8 ± 95.8	NS
LDL	<130 mg/dL	101.9 ± 27.3	105.1 ± 28.2	94.9 ± 24	
Total cholesterol	<200 mg/dL	178.3 ± 77.2	175 ± 35.6	165.6 ± 30.1	
17 hydroxy progesterone	16-283 ng/dL	80.8 ± 65.8	100.2 ± 70.0	38.2 ± 21.7	<0.001 (0.0257)*
DHEAS	37-307 mcg/dL		64	36	NS
Free testosterone	0.5-3.9 pg/mL	7.7 ± 6.0	9.2 ± 6.4	4.3 ± 3.1	<0.001 (0.0257)*
Total testosterone	<41 ng/dL	48.5 ± 29.1	52.6 ± 30.5	39.2 ± 23.4	0.011 (0.3042)
LH	10.7 ± 11.8 mIU/mL	135	90	45	
FSH	5.0 ± 2.6 mIU/mL	136	89	47	
LH/FSH ratio		2.2 ± 2.2	2.1 ± 1.6	2.4 ± 3.1	NS
TSH	0.50-4.50 uIU/mL	2.2 ± 1.8	2.4 ± 2.1	1.8 ± 1.2	
Prolactin	3.8-23.2 ng/mL	10.8 ± 6.6	10.4 ± 5.3	11.5 ± 8.3	
HbA1c		5.4 ± 0.6	5.4 ± 0.6	5.3 ± 0.6	

Comparison between the two groups was analyzed by chi-square test.
Significance defined as p<0.05 for p-value
*Due to multiple variables p value was further adjusted and was significant for free testosterone and 17 hydroxyporgesterone levels only.

Table 2: Comparison between the clinical and biochemical characteristics in the two clinical populations.



Adjusted P-value was significant for 17 hydroxyprogesterone (17 OHP) and free testosterone (FT) levels.
*Significant p<0.05

Figure 1: Comparison between the biochemical characteristics in the two clinical populations.

levels. Patients seen in the PEndo clinic were found to have increased free testosterone and 17-OHP levels and were statistically significant for both adjusted and unadjusted p value (p=0.0257, p<0.001). The adjusted p value for hirsutism was not clinically significant (p= 0.3099) however the unadjusted p value (p=0.016) was significant.

To further measure the risk of MS, presence of abnormal MS criteria's were assessed in HA (FT ≥ 4.0 pg/mL) and non-HA phenotypes having BMI above 90%. Due to the retrospective nature of our study; only 78/162 (48%) patients (70 PEndo and 8 PAMed) in HA phenotype and 20/162 (12%) patients (6 PEndo and 14 PAMed) in non-HA phenotype had complete data to meet the criteria for MS diagnosis. 35.9% (28/78) were identified having MS in HA phenotype. When compared, 35.9% of HA and 0.1% of non-HA phenotypes were shown to have MS.

Discussion

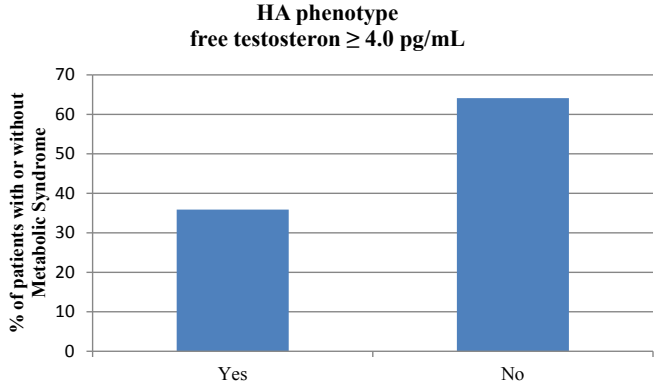
The results of our study indicate that the adolescent girls with PCOS presenting in various subspecialty clinics have different phenotype. Patients were similar in having abnormal menstrual cycles and increased BMI across all subspecialty clinics; however their androgen levels were significantly different. Our study demonstrated that the PCOS phenotype that presented in the PEndo clinic had higher degree of biochemical HA (increased free testosterone levels, Table 2 and Figure 1). While there was no difference in the hirsutism between the two clinical populations, a positive correlation between the high free testosterone levels, hirsutism [32] and increased frequency of hirsutism in PEndo clinic as compared to other clinics has been reported in the literature [16]. Although hirsutism is an important sign of underlying androgen excess [33], however its visual scoring system has limitations and demonstrates a significant inter- and intra-observer variability [34]. This may explain that there may a lack of documentation on hirsutism in PEndo clinic patients even though they had higher free testosterone levels. 17-OHP levels were also higher in the patients from PEndo clinic. Elevated 17-OHP levels are a typical hallmark of CAH; however, the levels in our patients were not suggestive for having late onset CAH and also a relationship between elevated 17-OHP in PCOS subjects at baseline and in response to the human chorionic gonadotropin has been reported previously [35].

An association between MS and PCOS has been established a while ago. Since obesity and HA are common feature associated with PCOS; and both them are linked with MS [22-27]. Majority of the studies have shown that HA is associated with MS in PCOS patients [22,23,27] and the data against that relationship is meager [28]. Our retrospective analysis further strengthens a significant relationship between HA with MS. It is important that the patients with PCOS get evaluated for MS since there is an increased risk of having glucose intolerance, dyslipidemia and, Type 2-diabetes, increases the risk of developing cardiovascular disease [29,30].

Due to the significant increase in the prevalence of PCOS disorder in the adolescent age group and heterogeneous nature of this disorder, adolescent girls with this disorder tend to present with different symptoms, leading them to different clinics [19]. Adolescent girls with PCOS are typically referred from the primary care physician office to either PEndo or PAMed clinics. This may explain some of the differences that we observed in our data.

Variability in the management of PCOS in different clinical settings has been reported; therefore it is important to recognize the different PCOS phenotypes to outline a specific medical therapy that will target to alleviate symptoms individually [20,21].

Our study highlights that different phenotypes of PCOS are commonly seen in various subspecialty clinics. HA seems to be a risk factor for MS. Recognizing adolescent girls with PCOS, screening and treating them earlier for metabolic syndrome would prevent future cardiovascular complications (Figures 2 and 3).



Only 35.9% (28/78) met the diagnosis of MS based upon the IDF criteria

Figure 2: Presence of Metabolic syndrome in Hyperandrogenmic phenotype (HA) with BMI>90% using IDF criteria.

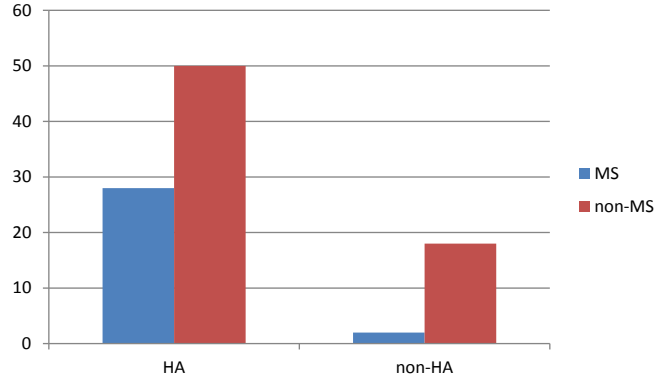


Figure 3: Comparison of Metabolic syndrome (MS) in HA and non-HA phenotypes in patients with BMI>90%.

Limitations to this study are retrospective chart review design, variability in documentation as well as lack of uniform initial laboratory evaluation since patients presented in the different clinical settings.

In conclusion adolescent girls with PCOS may present to different clinics due to the heterogeneous nature of the disease. It is important not only to treat them earlier for menstrual irregularities and hirsutism but also screen them for co-morbidities to prevent future cardiovascular disease. If feasible, development of multidisplinary clinic to address the complex nature of this syndrome may have better health outcome in this population. A multidisplinary approach would help in outlining a specific medical therapy that will target to alleviate symptoms individually.

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