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Glucose Metabolism in Overweight Hispanic Adolescents With and Without Polycystic Ovary Syndrome

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WHAT'S KNOWN ON THIS SUBJECT: There have been a limited number of studies on adolescents with PCOS, and these studies reported on small numbers of subjects. The prevalence of IGT and DM in adolescents with PCOS is unknown, and there is debate about the proper screening tools.

WHAT THIS STUDY ADDS: Using a larger sample of entirely Hispanic overweight adolescents with PCOS, we found a lower prevalence of glucose intolerance IGT and DM than previously reported. QUICKI values, a surrogate marker of insulin resistance, were abnormal for all subjects with IGT.

abstract

OBJECTIVES: About one third of overweight women with polycystic ovary syndrome (PCOS) have either impaired glucose tolerance (IGT) or type 2 diabetes mellitus (DM) by the age of 30. We sought to determine if overweight Hispanic adolescents with PCOS are more likely to be insulin resistant and glucose intolerant than those without PCOS.

METHODS: A retrospective chart review of 101 subjects with PCOS and 40 without PCOS was conducted. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Sensitivity Check Index (QUICKI), and fasting glucose/insulin ratio (FGIR) values were calculated by using fasting glucose and insulin levels. Insulin resistance (IR) was defined as a fasting insulin level of >15 μU/mL, a 2-hour insulin level of >75 μU/mL, a HOMA-IR value of >3.16, a QUICKI value of <0.357, and/or a FGIR value of <7.

RESULTS: Of the 101 overweight subjects with PCOS (BMI: 33.2 $\pm$ 5.9 kg/m^2), 4 had IGT and 2 had DM versus none of the 40 subjects without PCOS (BMI: 32.4 $\pm$ 5.3 kg/m^2). IR was more frequent in the overweight PCOS than in the overweight non-PCOS group (QUICKI: 68.4% vs 14.3%, $P = .014$) and FGIR (47.4% vs 0%, $P = .024$). Of the 6 subjects with glucose intolerance, only the QUICKI value was abnormal in all.

CONCLUSIONS: This retrospective study demonstrated that overweight Hispanic adolescents with PCOS had more IR, IGT and DM than their non-PCOS counterparts. As the QUICKI Index was abnormal in all subjects with IGT and DM, we suggest its use as the first step in deciding which overweight Hispanic adolescents with PCOS should be further tested with an OGTT. *Pediatrics* 2009;124:e496–e502

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KEY WORDS

Hispanic, adolescents, overweight, insulin resistance, glucose intolerance, polycystic ovary syndrome

ABBREVIATIONS

PCOS—polycystic ovary syndrome
IGT—impaired glucose tolerance
DM—diabetes mellitus
HOMA-IR—Homeostasis Model Assessment of Insulin Resistance
QUICKI—Quantitative Insulin Sensitivity Check Index
FGIR—fasting glucose/insulin ratio
IR—insulin resistance
OGTT—oral glucose-tolerance test
FPG—fasting plasma glucose
NFG—normal fasting plasma glucose
IFG—impaired fasting plasma glucose

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women and affects 5% to 10% of females of reproductive age.[1–3] According to the Rotterdam criteria, PCOS is a condition characterized by the presence of 2 of the following 3 criteria: chronic oligoovulation and/or anovulation, clinical or biochemical evidence of hyperandrogenism, and the presence of polycystic ovaries, after excluding other known pathologies (such as congenital adrenal hyperplasia, Cushing's syndrome, or androgen-secreting tumors).[4] The prevalence in adolescent girls and young women has been reported to be 4% to 6%.[5]

PCOS causes significant morbidity, and is one of the most common causes of infertility in reproductive-aged women. This syndrome has been associated with endometrial cancer, hypertension, hyperlipidemia, obesity, acanthosis nigricans, impaired glucose tolerance (IGT), and type 2 diabetes mellitus (DM). It is estimated that women with PCOS have a 5 to 10 times greater chance of being affected with type 2 DM than women without PCOS and that by 30 years of age approximately one third of obese women with PCOS will have either IGT or type 2 DM.[6–8]

A small prospective study of adolescents with PCOS found that 8 of 27 patients had diagnostic criteria for IGT (a glucose level of >140 but <200 mg/dL in a 2-hour oral glucose-tolerance test [OGTT]), and 1 of 27 patients had DM (a glucose level of >200 mg/dL in a 2-hour OGTT).[9] However, had fasting plasma glucose (FPG) been used, only 2 of the 8 patients would have had impaired glucose and the patient with diabetes would have been missed.[9] In this study, the normal FPG (NFG) level used was ≤110 mg/dL. The definition of an NFG level has since been revised downward by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association, and the NFG is now <100 mg/dL and the range for impaired FPG (IFG) level is now 100 to 125 mg/dL (5.6–6.9 mmol/L).[10] These authors concluded that screening for glucose intolerance should be part of the routine management of PCOS using the 2-hour glucose level from the OGTT.

It is generally accepted that insulin resistance (IR) precedes the development of type 2 diabetes and possibly is an independent risk factor for cardiovascular disease.[11,12] The presence of hyperinsulinemia has been demonstrated in obese as well as in normal weight women affected with PCOS, and it has been suggested that adolescents with PCOS should be screened for IR.[13–16] The gold standard to measure insulin sensitivity is the hyperinsulinemic-euglycemic clamp, first described by DeFronzo et al[17] in 1979. The minimal model analysis of a frequently sampled intravenous glucose-tolerance test is an alternative to the clamp technique.[18] These 2 methods are costly, labor intensive, and impractical in the clinical setting, leading researchers to develop surrogates for insulin sensitivity derived from fasting levels of glucose and insulin. Among the most commonly used methods are the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR),[19] the Quantitative Insulin Sensitivity Check Index (QUICKI),[20] and the fasting glucose/insulin ratio (FGIR),[21] which have been validated in numerous studies, both in children[22–26] and in adults.[27–30]

At least half of the women with PCOS are overweight or obese.[31] There is still a controversy over whether the metabolic differences seen in patients with PCOS are secondary to the syndrome itself or the associated obesity. One study in women with PCOS concluded that women with PCOS had significant IR that was independent of obesity.[32] Similarly, in adolescents a small study noted that the fasting insulin was twofold higher and the FGIR was lower in the PCOS group when compared with the control group.[33]

Hispanic women have a higher lifetime risk for developing diabetes, and it manifests at a younger age than in other ethnic groups or in a non-Hispanic white population.[34] The purpose of this study was to determine if obese Hispanic adolescents with PCOS have a greater degree of IR and glucose intolerance than their obese Hispanic adolescent counterparts without PCOS. We hypothesized that the obese patients with PCOS would have (1) higher fasting and 2-hour post-glucose challenge insulin levels, (2) higher indices of IR as measured by the HOMA-IR, QUICKI, and FGIR, and (3) higher fasting and 2-hour glucose levels after glucose challenge than obese Hispanic patients without PCOS.

MATERIALS AND METHODS

A retrospective chart review was approved by the Western institutional review board. We reviewed charts of postmenarchal female patients ages 10 to 21 years from the log of patients with "overweight status" and PCOS ($N = 190$) seen at the adolescent medicine clinic at Miami Children's Hospital by the 3 investigators. The principal investigator extracted the following data: age, ethnicity, weight, height, BMI, menstrual history, presence of hirsutism, acne, and acanthosis nigricans. The laboratory values included free and total testosterone, insulin, and glucose levels (fasting and 2-hour levels from the OGTT). From the total sample of 190 patients, we excluded non-Hispanic patients ($n = 15$) and lean patients with PCOS ($n = 34$) for a total study sample of 141 subjects from Mexico, Central and South America, and the Caribbean region.

Data Analysis

Definitions

Obese was defined as gender-specific and age-specific BMI that exceeds the 95th percentile.[35] Overweight was defined as gender-specific and age-specific BMI that exceeds the 85th percentile but is less than the 95th percentile.[35] PCOS was defined according to the Rotterdam criteria.[4] Glucose tolerance was based on the recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association.[10]

Fasting levels were defined as follows: FPG $<$ 100 mg/dL (5.6 mmol/L) as NFG; FPG between 100 and 125 mg/dL (5.6–6.9 mmol/L) as IFG; and FPG $\geq$ 126 mg/dL (7.0 mmol/L) as provisional diagnosis of DM. Two-hour glucose levels after the oral glucose challenge were defined as: a 2-hour postload glucose level of $<$140 mg/dL (7.8 mmol/L) as NGT; a 2-hour postload glucose level between 140 and 199 mg/dL (7.8–11.1 mmol/L) as IGT; and a 2-hour postload glucose level of $\geq$200 mg/dL (11.1 mmol/L) as a provisional diagnosis of DM.

Indices of IR were defined as follows: fasting insulin level of $>$15 μU/mL was considered to be indicative of IR (over time the laboratories have changed the cut off values for insulin levels. Because this is a retrospective study, some of the subjects were tested as far back as 5 years when the cutoff value was 15 μU/mL. Therefore, we used the fasting insulin level of $>$15 μU/mL to define IR); 2-hour insulin level after oral glucose challenge: $>$75 μU/mL was considered to be indicative of IR; HOMA-IR: was calculated by using the formula (plasma glucose [mmol/L] $\times$ insulin [μU/mL]/22.5. A level of $>$3.16 indicated IR. This cutoff value was taken from the study by Keskin et al,[36] because it assessed IR in a population of obese adolescents; QUICKI: was calculated by using the formula (1/Log fasting insulin [μU/mL] + Log fasting glucose [mg/dL]). A value of $<$0.357 was used to define IR on the basis of a study by Hrebícek et al[30] in which "adult patients with a QUICKI index of $<$0.357 (which is at the lower limit of 95% confidence limits in healthy persons) represented a group with typical manifestations of metabolic syndrome." A similar value was found in a study by Gunczler and Lanes[37] in moderately obese children and adolescents; FGIR was calculated as the ratio of glucose expressed in mg/dL to insulin expressed as μU/mL. We used a value of $<$7 to define IR.[22,37]

TABLE 1 Demographic Data

	PCOS	Non-PCOS	*P*
Overall group, *N*	101	40	
Age, mean (SD), y	15.3 (1.8)	14.6 (2.3)	.072
Menarche, mean (SD), y	11.3 (1.6)	11.4 (1.4)	.861
Gynecological age, mean (SD), y	4.0 (2.1)	3.2 (2.5)	.088
Weight, mean (SD), kg	85.6 (18.2)	82.5 (16.1)	.338
Height, mean (SD), cm	160.4 (7.3)	159.1 (6.1)	.341
BMI, mean (SD), kg/m^2	33.2 (5.9)	32.4 (5.3)	.501
Overweight (BMI: 85th–95th percentile), *N*	22	10	
Age, mean (SD), y	15.5 (1.6)	14.9 (1.7)	.387
Menarche, mean (SD), y	11.5 (1.4)	11.8 (0.6)	.327
Gynecological age, mean (SD), y	3.9 (1.8)	3.0 (1.7)	.186
Weight, mean (SD), kg	68.8 (6.9)	66.9 (5.3)	.456
Height, mean (SD), cm	161.4 (6.1)	158.2 (4.3)	.145
BMI, mean (SD), kg/m^2	26.3 (1.6)	26.7 (1.3)	.542
Obese (BMI: $>$95th percentile), *N*	79	30	
Age, mean (SD), y	15.2 (1.8)	14.5 (2.5)	.173
Menarche, mean (SD), y	11.3 (1.6)	11.2 (1.6)	.865
Gynecological age, mean (SD), y	4.0 (2.2)	3.3 (2.8)	.201
Weight, mean (SD), kg	90.3 (17.6)	87.7 (15.2)	.463
Height, mean (SD), cm	160.1 (7.6)	159.4 (6.7)	.682
BMI, mean (SD), kg/m^2	35.1 (5.2)	34.3 (4.7)	.517

Statistical Analyses

All data were expressed as mean $\pm$ SD and frequencies (%). Categorical data were analyzed with the χ^2 test, whereas the differences between groups were analyzed by using the Student's *t* test for continuous data. A 2-tailed *P* value of $<$.05 was considered statistically significant. SPSS 15.0 (SPSS Inc, Chicago, IL) was used for statistical analysis.[38]

RESULTS

The overall sample consisted of overweight subjects with PCOS ($n = 101$) and overweight subjects without PCOS ($n = 40$). We further subdivided the 2 groups by BMI into overweight (BMI: 85th–95th percentile) and obese (BMI: $>$95th percentile) subgroups. As shown in Table 1, there were no demographic differences between these 4 subgroups.

Table 2 lists the means and SDs of the absolute values of each of the laboratory tests extracted from the database. Also included are the 3 calculated indices for IR. The fasting insulin level was significantly higher in the overweight PCOS subgroup compared with the overweight non-PCOS subgroup. In addition, the HOMA and QUICKI indices indicated significantly greater IR in the overweight PCOS versus the overweight non-PCOS subgroup. The differences in the obese subgroups did not reach statistical significance.

Table 3 shows the percentage of subjects in each of the 3 categories of FPG and 2-hour oral glucose tolerance. Abnormal glucose tolerance (IGT and DM) was found only in the PCOS groups. Table 4 demonstrates that the only

TABLE 2 Laboratory Values in Overweight Hispanic Adolescents With PCOS Versus Overweight Hispanic Adolescents Without PCOS

	PCOS	Non-PCOS	*P*
Overweight ($N = 32$), *n*	22	10	
Total testosterone, mean (SD), ng/dL	47.3 (22.0)	33.7 (20.4)	.139
Free testosterone, mean (SD), pg/mL[a]	5.2 (3.3)	1.9 (2.1)	.016
FPG, mean (SD), mg/dL	85.9 (14.5)	81.3 (6.9)	.345
2-h glucose, mean (SD), mg/dL	105.9 (60.9)	78.2 (4.3)	.392
Fasting insulin, mean (SD), μU/mL[a]	11.5 (5.4)	6.1 (3.2)	.022
2-h insulin, mean (SD), μU/mL	69.6 (43.5)	31.5 (17.1)	.119
HOMA, mean (SD)[a]	2.42 (1.14)	1.26 (0.69)	.019
QUICKI, mean (SD)[a]	0.343 (0.032)	0.381 (0.040)	.020
FGIR, mean (SD)	10.5 (9.3)	17.1 (10.4)	.135
Obese ($N = 109$), *n*	79	30	
Total testosterone, mean (SD), ng/dL[b]	55.1 (26.6)	28.7 (14.3)	.000
Free testosterone, mean (SD), pg/mL[b]	9.4 (6.4)	3.4 (2.5)	.000
FPG, mean (SD), mg/dL	84.3 (19.7)	82.5 (6.2)	.614
2-h glucose, mean (SD), mg/dL	102.5 (20.5)	100.2 (16.7)	.663
Fasting insulin, mean (SD), μU/mL	19.0 (12.3)	15.8 (10.0)	.244
2-h insulin, mean (SD), μU/mL	119.6 (97.2)	88 (59.2)	.228
HOMA, mean (SD)	4.16 (3.88)	3.21 (2.14)	.233
QUICKI, mean (SD)	0.324 (0.033)	0.331 (0.028)	.317
FGIR, mean (SD)	6.5 (5.5)	7.1 (4.2)	.592

[a] $P < .05$.
[b] $P < .001$.

TABLE 3 Frequency of IGT and DM in Overweight Hispanic Adolescents With PCOS Versus Overweight Hispanic Adolescents Without PCOS

	PCOS, *n* (%)	Non-PCOS, *n* (%)	*P*
Overweight			
FPG			.601
NFG	19 (90.5)	10 (100.0)	
IFG	1 (4.8)	0 (0.0)	
DM	1 (4.8)	0 (0.0)	
2-h OGTT			.657
NGT	9 (81.8)	4 (100.0)	
IGT	1 (9.1)	0 (0.0)	
DM	1 (9.1)	0 (0.0)	
Obese			
FPG			.531
NFG	76 (98.7)	30 (100.0)	
IFG	0 (0.0)	0 (0.0)	
DM	1 (1.3)	0 (0.0)	
2-h OGTT			.263
NGT	47 (94.0)	20 (100.0)	
IGT	3 (6.0)	0 (0.0)	
DM	0 (0.0)	0 (0.0)	

NGT indicates normal glucose tolerance.

marker of IR consistently abnormal in all 6 subjects with glucose intolerance (IGT and DM) was the QUICKI at the cutoff value of <0.357.

The frequency of IR among overweight (BMI: 85th–95th percentile) and obese (BMI: >95th percentile) Hispanic adolescents with PCOS versus those without PCOS is shown in Table 5. IR was more frequent in the overweight PCOS than in the overweight non-PCOS subgroup: QUICKI (68.4% vs 14.3%; $P = .014$) and FGIR (47.4% vs 0%; $P = .024$). The differences in the obese subgroups did not reach statistical significance.

DISCUSSION

To our knowledge, this is the first study to report the prevalence of IR, IGT, and DM in a sample of overweight, exclusively Hispanic adolescents with PCOS.

Adult women with PCOS are more likely to have IR, hyperinsulinemia, IGT, and DM[6–8] than women without PCOS. In 2007, the Androgen Excess Society position statement recommended that all patients with PCOS should be screened for IGT with a 2-hour OGTT, and those with IGT should be screened annually for development of type 2 DM.[39] Recommendations for screening adolescents are less clear. Few studies mention the prevalence of IR and IGT in adolescents.[8,9,40] We can infer the prevalence of type 2 DM in adolescents with PCOS from a study by Palmert et al[9] who reported 1 of 27 (3.7%) subjects met criteria for the provisional diagnosis of diabetes from a 2-hour OGTT. The prevalence in our study was much lower with only 2 of 101 (2%) adolescents with PCOS having type 2 DM. The prevalence of IGT (6.6%) in our sample was also much lower than that reported by Silfen et al[40] (27.2%) and Palmert et al[9] (29.6%), but like them we noted that the FPG test failed to predict the majority of the subjects with IGT. In our study, the prevalence of impaired glucose went from 1% using the FPG test to 6.6% with the 2-hour OGTT, reinforcing the recommendation that overweight adolescents with PCOS be screened for glucose intolerance with the 2-hour OGTT.[9] The lower prevalence of IGT and type 2 DM in our sample compared with that reported by the other 2 authors could be a result of our larger sample size. In addition, there may be a referral bias. The

TABLE 4 IR Indices and Glucose and Insulin Levels of the 6 Subjects With Glucose Abnormalities

Subject No.	Diagnosis	BMI, kg/m^2	FPG, mg/dL	2-h Glucose From OGTT, mg/dL	Fasting Insulin, μU/mL	2-h Insulin During OGTT, μU/mL	HOMA	QUICKI	FGIR
1	DM	27.45	143	266	5.0	22	1.76	0.350	28.60
2	IGT	25.34	100	171	16.0	154	3.95	0.312	6.25
3	IGT	34.41	82	153	8.0	83	1.62	0.355	10.25
4	DM	39.19	244	—	49.0	—	29.50	0.245	4.98
5	IGT	31.83	91	142	25.1	530	5.64	0.298	3.63
6	IGT	36.07	83	146	17.7	185	3.62	0.316	4.69

TABLE 5 Frequency of IR in Overweight Hispanic Adolescents With PCOS Versus Overweight Hispanic Adolescents Without PCOS

	PCOS, *n* (%)	Non-PCOS, *n* (%)	*P*
Overweight (BMI: 85th–95th percentile)			
Fasting insulin			.264
Normal, <15 μU/mL	16 (84.2)	7 (100.0)	
Abnormal, >15 μU/mL	3 (15.8)	0 (0.0)	
2-h insulin			.159
Normal, <75 μU/mL	7 (63.6)	4 (100.0)	
Abnormal, >75 μU/mL	4 (36.4)	0 (0.0)	
HOMA-IR			.187
Insulin sensitive, <3.16	15 (78.9)	7 (100.0)	
Insulin resistant, >3.16	4 (21.1)	0 (0.0)	
QUICKI[a]			.014
Insulin sensitive, >0.357	6 (31.6)	6 (85.7)	
Insulin resistant, <0.357	13 (68.4)	1 (14.3)	
FGIR[a]			.024
Insulin sensitive, >7	10 (52.6)	7 (100.0)	
Insulin resistant, <7	9 (47.4)	0 (0.0)	
Obese (BMI: >95th percentile)			
Fasting insulin			.467
Normal, <15 μU/mL	31 (43.7)	14 (51.9)	
Abnormal, >15 μU/mL	40 (56.3)	13 (48.1)	
2-h insulin			.159
Normal, <75 μU/mL	16 (34.8)	9 (56.3)	
Abnormal, >75 μU/mL	30 (65.2)	7 (43.8)	
HOMA			.074
Insulin sensitive, <3.16	33 (46.5)	18 (66.7)	
Insulin resistant, >3.16	38 (53.5)	9 (33.3)	
QUICKI			.780
Insulin sensitive, >0.357	9 (12.7)	4 (14.8)	
Insulin resistant, <0.357	62 (87.3)	23 (85.2)	
FGIR			.361
Insulin sensitive, >7	22 (31.0)	11 (40.7)	
Insulin resistant, <7	49 (69.0)	16 (59.3)	

2-h insulin indicates the 2-hour insulin level during an OGTT.
[a] $P < .05$.

subjects in our study were referred to us for menstrual irregularities and may be more reflective of a community sample, whereas the subjects in the Palmert et al study[9] were from a tertiary center's pediatric endocrine clinic and were possibly a higher-risk group.

It is well known that Hispanics in the United States have a higher prevalence of IGT and type 2 DM than non-Hispanic white people.[41,42] The risk of having glucose intolerance (IGT, diagnosed diabetes, and undiagnosed diabetes) in the United States among those aged 20 to 44 is highest for Mexican Americans (13.6%), followed by Puerto Ricans (10.4%) and Cuban Americans (10%).[41] There is no data for Central and South Americans in the United States. A study by Dunaif et al[43] of Caribbean-Hispanic women with PCOS (of Puerto Rican and Dominican descent) found a prevalence of IGT and DM of 31% (4 of 13) versus 20% (2 of 10) in non-Hispanic white women with PCOS. Because we have a large sample of younger Hispanic adolescents of mixed ethnicity, it may explain the lower prevalence compared with the smaller sample sizes, more homogeneous ethnicity, and older subjects in the other studies cited.[9,40,43]

We found a high prevalence of IR in both PCOS and non-PCOS groups, as would be expected because of their overweight status. For the overall sample, although the levels of insulin and all surrogate markers of IR were higher in our subjects with PCOS than in the subjects without PCOS, they were not statistically different. Surprisingly, when we subdivided the groups into overweight and obese, the differences in the various indices of IR between the PCOS and the non-PCOS group became statistically significant between those in the overweight subgroups (mean BMI: 26 kg/m^2) but not between those in the obese subgroups (mean BMI: 35 kg/m^2). This difference in the overweight PCOS versus overweight non-PCOS group may be explained by the distribution of body fat, as noted in a study by Carmina et al.[44] They reported that although the total fat was similar, overweight patients with PCOS were more likely to have increased "central abdominal fat" (a marker of IR) than patients without PCOS. When their subjects became obese, the distribution of fat became similar in both groups, which could explain why we did not notice a difference in the obese subgroups.

After extracting the characteristics of all 6 patients with glucose-tolerance abnormalities (2 diabetics and 4 with IGT), the only insulin sensitivity index that was abnormal in all of these 6 patients was the QUICKI at a cutoff value of <0.357. The use of the QUICKI in assessing insulin sensitivity in different insulin-resistant states has been validated previously.[45] However, to accept this as a diagnostic tool will require additional study with larger numbers of subjects including both Hispanic and non-Hispanic groups, with all the laboratory testing performed at a single site.

CONCLUSIONS

This retrospective study demonstrates that overweight Hispanic adolescents with PCOS have more IR and glucose intolerance than their counterparts without PCOS, indicating that PCOS status in addition to the elevated BMI increases the risk for IR, IGT, and DM.

Aggressive lifestyle interventions should be a priority in the management of these patients to prevent additional progression to IGT and DM. As the QUICKI for IR was consistently abnormal in all of our subjects with IGT and DM, it should be considered as a useful first step to decide which overweight Hispanic adolescents with PCOS need to be further tested with an OGTT to screen for glucose intolerance.

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