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Prevalence and Predictors of Risk for Type 2 Diabetes Mellitus and Impaired Glucose Tolerance in Polycystic Ovary Syndrome: A Prospective, Controlled Study in 254 Affected Women*

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ABSTRACT

Women with polycystic ovary syndrome (PCOS) are insulin resistant, have insulin secretory defects, and are at high risk for glucose intolerance. We performed this study to determine the prevalence of glucose intolerance and parameters associated with risk for this in PCOS women. Two-hundred and fifty-four PCOS women, aged 14–44 yr, were prospectively evaluated at 2 centers, 1 urban and ethnically diverse (n = 110) and 1 rural and ethnically homogeneous (n = 144). The rural PCOS women were compared to 80 control women of similar weight, ethnicity, and age. A 75-g oral glucose challenge was administered after a 3-day 300-g carbohydrate diet and an overnight fast with 0 and 2 h blood samples for glucose levels. Diabetes was categorized according to WHO criteria. The prevalence of glucose intolerance was 31.1% impaired glucose intolerance (IGT) and 7.5% diabetes. In nonobese PCOS women (body mass index, <27 kg/m^2), 10.3% IGT and 1.5% diabetes were found. The prevalence of glucose intolerance was significantly higher in PCOS *vs.* control women ($\chi^2 = 7.0$; $P = 0.01$; odds ratio = 2.76; 95% confidence interval = 1.23–6.57). Variables most associated with postchallenge glucose levels were fasting glucose levels ($P < 0.0001$), PCOS status ($P = 0.002$), waist/hip ratio ($P = 0.01$), and body mass index ($P = 0.021$). The American Diabetes Association criteria applied to fasting glucose significantly underdiagnosed diabetes compared to the WHO criteria (3.2% *vs.* 7.5%; $\chi^2 = 4.7$; $P = 0.046$; odds ratio = 2.48; 95% confidence interval = 1.01–6.69). We conclude that 1) PCOS women are at significantly increased risk for IGT and type 2 diabetes mellitus at all weights and at a young age; 2) these prevalence rates are similar in 2 different populations of PCOS women, suggesting that PCOS may be a more important risk factor than ethnicity or race for glucose intolerance in young women; and 3) the American Diabetes Association diabetes diagnostic criteria failed to detect a significant number of PCOS women with diabetes by postchallenge glucose values. (*J Clin Endocrinol Metab* **84:** 165–169, 1999)

POLYCYSTIC ovary syndrome (PCOS) is one of the most common endocrine disorders of premenopausal women (1–3). It is the leading cause of oligo- and amenorrhea and of hormonally related infertility (2, 4). The etiology of PCOS remains unknown, and it is diagnosed by its reproductive endocrine abnormalities of hyperandrogenism and chronic anovulation with the exclusion of specific diseases of the ovaries, adrenals, and pituitary (1, 3).

It was first reported in 1980 (5) and subsequently confirmed (6–10) that PCOS women were hyperinsulinemic, suggesting the presence of insulin resistance. We showed that PCOS women have profound insulin resistance independent of obesity (11), that is secondary to a unique, apparently genetic, disorder of insulin action (12–16). Insulin resistance is now recognized as a major risk factor for the development of type 2 diabetes mellitus (17–19). Pancreatic β-cell dysfunction is a second important risk factor (19), an abnormality that is also found in PCOS (20–22). PCOS women would thus be predicted to be at an increased risk for type 2 diabetes mellitus.

We began to prospectively assess glucose tolerance in PCOS women in 1983 as part of our research studies on insulin action in the disorder. We were the first to report in a series of 46 PCOS women (23) that there appeared to be an increased risk for impaired glucose tolerance (IGT) and type 2 diabetes mellitus in obese PCOS women. However, we did not compare the prevalence of glucose intolerance to that in a control group in that study (23). The metabolic abnormalities occurred at an early age (18–36 yr) (23).

To assess the prevalence of glucose intolerance and to determine parameters associated with increased risk, we examined our entire clinical experience in 254 PCOS women studied prospectively at 2 centers, Mt. Sinai School of Medicine (New York, NY) and Pennsylvania State University

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College of Medicine (Hershey, PA). We also evaluated the utility of the new American Diabetes Association (ADA) diabetes diagnostic criteria based on fasting glucose values (24) for detecting this disorder in PCOS women. We report here for the first time that not only is the prevalence of IGT and undiagnosed diabetes significantly increased in PCOS compared to control women, but also that a substantial number of nonobese PCOS women have these disorders.

Subjects and Methods

Subjects

We prospectively studied 254 PCOS women, aged 14–44 yr, and 80 control women, aged 18–40 yr, from 1983–1998. One hundred and ten PCOS women were studied at the Mt. Sinai School of Medicine (Mt. Sinai) between 1983 and 1991. One hundred and forty-four PCOS women and all control women were studied at the Pennsylvania State University College of Medicine (Penn State) in Hershey, PA from 1992 to 1998. The studies were approved by the institutional review boards of Mt. Sinai and Penn State, and the subjects gave written informed consent.

All women were in good health and, for at least 1 month before study, were not taking any medication (except for oral contraceptive agents that were stopped for 3 months before study) known to affect sex hormone or carbohydrate metabolism. The diagnosis of PCOS was made by the presence of chronic anovulation in association with elevated circulating androgen levels (1, 15, 23). Nonclassical adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate tests before the diagnosis of PCOS was made (1, 23). No PCOS patient had diagnosed diabetes mellitus. The control women had menses every 27–32 days and were not hirsute. To control for conditions altering insulin action, control women did not engage in regular aerobic exercise, nor did they have a history of hypertension, a personal history of diabetes, or a first degree relative with diabetes (25–27).

PCOS women were recruited from the practices of the authors, attending physicians at the medical centers, and advertisements. Control women were recruited through advertisements. Ethnicity was recorded for 108 Mt. Sinai women: 51 were non-Hispanic white, 6 were Asian Indian, 39 were Caribbean-Hispanic, and 12 were African-American. The ethnicity of the PCOS women at Penn State was 138 non-Hispanic white, 3 Caribbean-Hispanic, and 3 African-American. The ethnicity of the control women was 70 non-Hispanic white, 7 Caribbean-Hispanic, and 3 African-American. A history of diabetes in first degree relatives was recorded for 28 Mt. Sinai PCOS women and all Penn State subjects.

Protocol

An oral glucose tolerance test was performed between 0800–1000 h after a 3-day 300-g carbohydrate diet and an overnight fast of 10–14 h. A waist/hip girth ratio was determined as previously reported (12) on 63 Mt. Sinai PCOS women, 127 Penn State PCOS women, and 75 control women. Eighty women at Mt. Sinai (all subjects before 1988) were administered a 40 g/m^2 body surface area oral glucose challenge (23). Thirty subjects at Mt. Sinai and all subjects at Penn State were administered a 75-g oral glucose challenge. Blood was obtained for glucose determinations at 0 and 2 h. Insulin levels were also determined in these samples, but are not reported here because the RIA used has been changed several times over the years. An additional blood sample was obtained at 0 h for testosterone (T), nonsex hormone-binding globulin-bound testosterone (uT), and dehydroepiandrosterone sulfate (DHEAS) levels in all Penn State subjects. Some of the oral glucose tolerance test data have been reported as part of our previous studies of insulin action in PCOS (11, 14, 22, 23, 28, 29). Data for 123 Penn State PCOS women have not been previously reported. This is the first report of the cumulative prevalence of glucose intolerance in our population of PCOS women since 1987 (23).

Assays

Plasma glucose levels were determined by the glucose oxidase technique (22, 23, 29). Levels of T, uT, and DHEAS were determined as previously reported (29).

Data analysis

Glucose tolerance was assessed by WHO criteria (30). Categorical data were analyzed using χ^2, odds ratio (OR), and exact 95% confidence intervals (CI). Continuous data were compared between PCOS and control groups using unpaired *t* tests and are reported as the mean ± 1 SD. $P \leq 0.05$ was considered statistically significant.

Among all PCOS women, no differences in 2-h glucose values according oral glucose challenge [40 g/m^2 *vs.* 75 g; 132 ± 42 *vs.* 138 ± 44 mg/ml, respectively ($P = 0.32$); 7.3 ± 2.3 *vs.* 7.7 ± 2.4 mmol/L] were found. Thus, PCOS women from the two study sites were combined to examine diabetes diagnostic categories based on postchallenge glucose levels using WHO criteria (30) compared to those determined according to the 1997 ADA criteria based on fasting glucose values [normal fasting glucose, <110 mg/dL (<6.1 mmol/L); impaired fasting glucose, 110–125 mg/dL (6.1–6.9 mmol/L); diabetes ≥126 mg/dL (7.0 mmol/L)] (24).

A multiple regression analysis was preformed to determine which variables predicted postchallenge glucose values (31). To control for the potential confounding effects of a family history of diabetes and ethnicity, we included only Penn State non-Hispanic white control and PCOS women without a first degree relative with diabetes in this analysis. The candidate predictive variables were status (PCOS *vs.* control), age, body mass index (BMI), waist/hip ratio, and fasting glucose values. Androgen values were not considered as candidate predictive variables, because they were used to make the diagnosis of PCOS. The criterion for a predictive variable to remain in the model was $P \leq 0.15$. All analyses were performed using the SAS statistical software package (SAS Institute, Inc., Cary, NC) or Epi Info version 6 (Centers for Disease Control and Prevention, Atlanta, GA).

Results

Prevalence of glucose intolerance

The clinical and biochemical characteristics of the subjects are summarized in Table 1. Seventy-eight percent of PCOS women were overweight (BMI, ≥25 kg/m^2), and 73% were obese (BMI, ≥27 kg/m^2). Overall, 38.6% (98 of 254) of the

TABLE 1. Clinical and biochemical characteristics

	PCOS women, Mt Sinai (n = 110)	PCOS women, Penn State (n = 144)	Control women, Penn State (n = 80)
Age (yr)	27 ± 5 (18–40)	28 ± 6 (14–44)	30 ± 7 (18–40)
BMI (kg/m^2)	29.9 ± 8.1 (17.6–55.5)	35.9 ± 8.0 (18.9–56.6)	32.7 ± 8.8 (19.4–55.0)
Waist/hip ratios	0.84 ± 0.09 (0.68–1.18)	0.83 ± 0.09 (0.46–1.17)	0.78 ± 0.07 (0.41–0.93)
Fasting glucose (mg/dL)	89 ± 12 (48–129)	92 ± 20 (68–210)	86 ± 9 (56–116)
2-h Glucose (mg/dL)	132 ± 40 (59–284)	139 ± 46 (71–356)	110 ± 28 (56–182)
T (ng/dL)	[a]	83 ± 38 (28–330)	37 ± 16 (15–93)
uT (ng/dL)	[a]	32 ± 22 (9–211)	9 ± 6 (2–27)
DHEAS (ng/mL)	[a]	2327 ± 1230 (632–8092)	1689 ± 756 (553–3632)

Values are the mean ± SD followed by the range in *parentheses*.

[a] Values for androgens for Mt. Sinai women are not reported, as different androgen assays were used. To convert values for glucose to mmol/L, multiply by 0.05551; to convert values of T and uT to nmol/L, multiply by 0.03467; to convert DHEAS values to mmol/L, multiply by 0.002714.

PCOS women had either IGT (31.1%) or diabetes (7.5%) by WHO criteria (Fig. 1). The prevalence was 30.0% IGT and 7.3% diabetes in the urban, ethnically diverse population of Mt. Sinai and 31.9% IGT and 7.6% diabetes in the rural, predominantly non-Hispanic white population of Penn State. There was no significant difference in the overall prevalence of glucose intolerance according to study site ($\chi^2 = 0.14$; $P = 0.71$) despite the fact that there were significantly more nonobese PCOS women (BMI, $\leq$27 kg/m^2) at Mt. Sinai than at Penn State ($\chi^2 = 25.2$; $P < 0.001$; Table 2). The Mt. Sinai population did contain substantially more members of high risk ethnic/racial groups (Caribbean-Hispanic, 36% Mt. Sinai *vs.* 2% Penn State; African-American, 11% Mt. Sinai *vs.* 2% Penn State). There was no difference in prevalence by oral glucose load (data not shown). Fourteen percent of the control women had IGT, and none had diabetes. In the combined population of nonobese PCOS women (BMI, <27 kg/m^2), 10.3% had IGT, and 1.5% had diabetes (Table 2). The youngest PCOS woman in the study (14 yr old) had IGT (Table 3). Although IGT and diabetes were detected in nonobese and/or young PCOS women, the prevalence of both significantly increased with BMI (by stratified Cochran-Armitage trend test, $P < 0.0001$; Table 2) and with age (by stratified Cochran-Armitage trend test, $P < 0.002$; Table 3) while controlling for the site where the PCOS woman was studied.

Penn State controlled study

We examined the prevalence of glucose intolerance in non-Hispanic white Penn State PCOS women without a first degree relative with diabetes (n = 100) compared to that in non-Hispanic white control women (n = 70) to adjust for confounding effects of ethnicity and family history of diabetes. These PCOS women were significantly younger than control women (27 ± 6 *vs.* 30 ± 6 yr old, respectively; $P = 0.001$), with no significant difference in BMI (35.6 ± 8.4 *vs.* 33.2 ± 8.9 kg/m^2, respectively; $P = 0.08$). They had a significantly higher prevalence of glucose intolerance (30.0% IGT; 4.0% diabetes) compared to control women (15.7% IGT; 0% diabetes; $\chi^2 = 7.0$; $P = 0.01$; OR = 2.76; 95% CI = 1.23–6.57). To assess the impact of a family history of diabetes, we compared the prevalence of glucose intolerance in non-Hispanic white PCOS women from Penn State and found that it was borderline significantly higher in PCOS women with a first degree relative with diabetes (52.6% first degree relative with diabetes *vs.* 34% no first degree relative with diabetes; $\chi^2 = 4.0$; $P = 0.053$; OR = 2.44; 95% CI = 0.94–4.94).

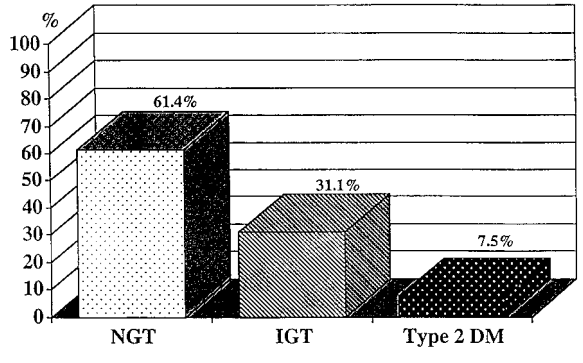

FIG. 1. Combined prevalence of glucose intolerance by WHO criteria in 254 PCOS women. NGT, Normal glucose tolerance; Type 2 DM, type 2 diabetes mellitus.

TABLE 2. Prevalence of glucose intolerance by BMI

BMI (kg/m^2)	Total no.	NGT [% (no.)]	IGT [% (no.)]	Type 2 diabetes [% (no.)]
Mt. Sinai				
15.0 to <20.0	8	100 (8)	0 (0)	0 (0)
20.0 to <25.0	33	94 (31)	3 (1)	3 (1)
25.0 to <30.0	18	44 (8)	50 (9)	6 (1)
30.0 to <35.0	22	41 (9)	45 (10)	14 (3)
35.0 to <40.0	17	53 (9)	41 (7)	6 (1)
40.0 to <45.0	6	17 (1)	66 (4)	17 (1)
45.0 to <50.0	5	40 (2)	40 (2)	20 (1)
≥50.0	1	100 (1)	0 (0)	0 (0)
Penn State				
15.0 to <20.0	3	67 (2)	33 (1)	0 (0)
20.0 to <25.0	13	92 (12)	8 (1)	0 (0)
25.0 to <30.0	13	77 (10)	23 (3)	0 (0)
30.0 to <35.0	40	55 (22)	32 (13)	13 (5)
35.0 to <40.0	27	63 (17)	26 (7)	11 (3)
40.0 to <45.0	27	52 (14)	37 (10)	11 (3)
45.0 to <50.0	16	44 (7)	56 (9)	0 (0)
≥50.0	5	60 (3)	40 (2)	0 (0)

NGT, Normal glucose tolerance; IGT, impaired glucose tolerance.

TABLE 3. Prevalence of glucose intolerance by age in PCOS

Age (yr)	Total no.	NGT [% (no.)]	IGT [% (no.)]	Type 2 diabetes [% (no.)]
14.0 to <20.0	16	88 (14)	13 (2)	0 (0)
20.0 to <25.0	72	69 (50)	31 (22)	0 (0)
25.0 to <30.0	73	67 (49)	23 (17)	10 (7)
30.0 to <35.0	61	44 (27)	46 (28)	10 (6)
35.0 to <40.0	28	54 (15)	25 (7)	21 (6)
40.0 to <45.0	4	25 (1)	75 (3)	0 (0)

NGT, Normal glucose tolerance; IGT, impaired glucose tolerance.

Predictors of glucose intolerance

Of the 170 non-Hispanic white women without a first degree relative with diabetes mellitus, 154 (88 PCOS women and 66 controls) had complete data for all candidate variables and were analyzed via the multiple regression model. There were no significant interactions of status (PCOS *vs.* control) with the other variables. The variables remaining in the final model were fasting glucose ($P < 0.0001$), PCOS status ($P = 0.002$), waist/hip ratio ($P = 0.01$), BMI ($P = 0.02$), and age ($P = 0.14$; Table 4). The model accounted for 50% (r^2) of the total variation. The impact of these variables on postchallenge glucose values in PCOS is summarized in Table 4.

Comparison of diabetes diagnostic criteria

The majority of PCOS women with glucose intolerance had normal fasting glucose levels by ADA criteria (Fig. 2). Using the ADA criteria, 3.2% of PCOS women would be classified as having diabetes, whereas 7.5% would be classified as having diabetes by WHO criteria, a difference of 4.3%. Thus, 11 of 19 (58%) PCOS women with diabetes diagnosed by WHO criteria would have been missed using ADA criteria. No PCOS women had diabetes by fasting glucose values who did not have it by postchallenge glucose. The WHO criteria diagnosed significantly more diabetes in

TABLE 4. Impact of variables associated with 2-h postchallenge glucose values from multiple regression model

Factor	Unit change	Effect on 2-h postchallenge glucose (mg/dL)	95% CI (mg/dL)	*P* value
Fasting glucose	1 mg/dL	1.6	1.2–2.0	<0.0001
Status (PCOS *vs.* control)	PCOS	13.8	5.2–22.5	0.002
Waist/hip ratio	0.1 U	6.2	1.3–11.1	0.014
BMI	1 kg/m^2	0.6	0.1–1.1	0.021
Age	1 yr	0.5	−0.2 to 1.2	0.144

PCOS women than the ADA criteria (χ^2 = 4.7; P = 0.046; OR = 2.48; 95% CI = 1.01–6.69). According to the ADA criteria, 4.7% of PCOS women had impaired fasting glucose, whereas 31.1% had IGT by postchallenge glucose values.

Discussion

This is the first controlled study of glucose tolerance in PCOS, and we document that these women are at significantly increased risk for IGT and type 2 diabetes mellitus compared to concurrently studied age-, weight-, and ethnicity-comparable reproductively normal women. We originally reported that only obese PCOS women had glucose intolerance (23). We now find that nonobese PCOS women may also have glucose intolerance (10.3% IGT; 1.5% diabetes). The prevalence rates of glucose intolerance in PCOS (31.1% IGT; 7.5% undiagnosed diabetes) are substantially higher than those found in a major population-based study (Second National Health and Nutrition Survey) (32) of U.S. women of similar age (7.8% IGT; 1.0% undiagnosed diabetes). The prevalence rate of IGT is also higher than that in another profoundly insulin-resistant group of reproductive-age women, Latino women with a history of gestational diabetes mellitus (26%) (33).

The prevalence rates of IGT and diabetes were well above those reported among U.S. Hispanic and African-American women of similar age (34) and did not differ in the two groups of PCOS women studied, one an urban, ethnically mixed group and one a rural, ethnically homogeneous group. A preliminary report by Ehrmann and colleagues (35) found similar prevalence rates in an ethnically mixed PCOS population from the Chicago area. These observations suggest that PCOS is a more important risk factor for glucose intolerance in young women than race or ethnicity (34, 36), although we were unable to test this hypothesis statistically.

The ADA has recently recommended that fasting glucose criteria be used for the diagnosis of diabetes in asymptomatic individuals (24). Fasting glucose levels were poor predictors, however, of diabetes in PCOS, and few women with IGT had impaired fasting glucose values. Using ADA criteria, only 3.2% of PCOS women would have been classified as having diabetes, whereas 7.5% had diabetes by WHO criteria, a difference of 4.3%. In the Third National Health and Nutrition Survey (37), the difference between the criteria in an older cohort was −2.0% with ADA criteria. In the insulin-resistant San Antonio Heart Study population, the ADA criteria missed 27.3% of diabetes detected by postchallenge glucose values (38), whereas in our PCOS population the ADA criteria missed 58% of diabetes.

It is not possible at this juncture to recommend that PCOS women undergo formal glucose tolerance testing, because individuals who do not fulfill the ADA fasting glucose criteria for diabetes are at low risk for microvascular disease (24), and the benefit of treating IGT remains to be proven (39). Nevertheless, it is important to recognize that PCOS women are at high risk for type 2 diabetes and for cardiovascular disease because of their increased prevalence of glucose intolerance (33, 35, 39–41).

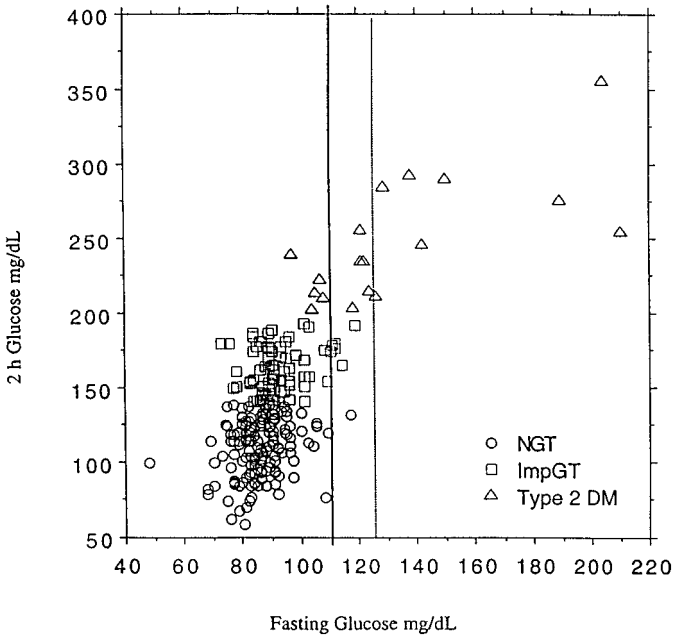

FIG. 2. Scattergram of fasting blood glucose levels *vs.* 2 h postchallenge glucose levels. Points on the graph are coded to reflect the WHO status based on postchallenge glucose levels (n = 254). The *dotted vertical line* is the threshold for impaired fasting glucose (110 mg/dL) by the 1997 ADA criteria, and the *dashed vertical line* (126 mg/dL) is the threshold for diabetes by the same criteria (28). Most PCOS women have normal fasting glucose levels by ADA criteria (28).

It has been suggested that a family history of diabetes worsens insulin secretion and glucose tolerance in PCOS (21). Consistent with this hypothesis, we showed that a first degree relative with diabetes was associated with an increased risk of glucose intolerance in PCOS women. However, the prevalence of glucose intolerance in PCOS, even in those women without a first degree relative with diabetes, was still much greater than that reported in the general U.S. population (32, 34, 36) and was significantly higher than that in control women. The factors associated with glucose intolerance in PCOS, age, BMI, waist/hip ratios, and family history of diabetes, were identical to those in other populations (17, 27, 32, 36). This suggests that the pathogenesis of type 2 diabetes is similar in all of these groups. An underlying genetic defect conferring insulin resistance and perhaps β-cell dysfunction interacts with environmental factors worsening insulin resistance (17–19, 36, 42). β-Cell function worsens, and glucose intolerance supervenes (18, 19, 36, 42).

Only women with the endocrine syndrome of hyperandrogenism and chronic anovulation appear to be insulin resistant and, accordingly, at high risk for glucose intolerance (15, 23, 43). Ovulatory women with the polycystic ovary morphology are not insulin resistant (43). The inclusion of

both ovulatory and anovulatory women may explain the failure of a previous large study of glucose tolerance in hyperandrogenic women to detect glucose intolerance using the National Diabetes Data Group criteria (44). Differences in ethnicity and in the prevalence of obesity among PCOS populations may also have contributed to these discrepant findings (32, 34, 45).

In summary, PCOS women have significantly increased prevalence rates of IGT and undiagnosed diabetes, well above the prevalence in women in the general U.S. population of this age, including racial and ethnic minorities (32, 34). The prevalence rates of glucose intolerance are similar in ethnically diverse populations of PCOS women. Although obesity and age substantially increase risk, IGT and diabetes can occur in young, nonobese PCOS women. Fasting glucose levels are poor predictors of diabetes in PCOS women.

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