0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(12):4546–4556

doi: 10.1210/jc.2007-1549

POSITION STATEMENT: Glucose Intolerance in Polycystic Ovary Syndrome—A Position Statement of the Androgen Excess Society

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Objectives: Women with polycystic ovarian syndrome (PCOS) are at increased risk for developing glucose intolerance and type 2 diabetes mellitus (DM). Recommendations for the timing and method of screening have varied. The purpose of this statement is to determine the optimal screening method, timing of screening, and treatment modalities for impaired glucose tolerance (IGT) among women with PCOS.

Participants: The expert panel was appointed by the Androgen Excess Society (AES) to review the literature and make recommendations based on the available evidence. Meetings were open, and there was no funding for the panel.

Evidence: A systematic review was conducted of the published, peer-reviewed medical literature using MEDLINE to identify studies that addressed the prevalence, risk factors, testing, and treatment for IGT in both adults and adolescents with PCOS. Unpublished data were not considered.

Consensus Process: The panel held meetings to review the literature and draft the statement as a committee. The AES board members reviewed and critiqued the manuscript, and changes were made based on their comments.

Conclusions: The panel recommends that all patients with PCOS be screened for IGT with a 2-h oral glucose tolerance test. A few members of the AES board recommend alternatively screening women with PCOS for IGT and type 2 DM using an oral glucose tolerance test only in patients with a body mass index of 30 kg/m^2 or greater or in lean patients with additional risk factors. Patients with normal glucose tolerance should be rescreened at least once every 2 yr, or more frequently if additional risk factors are identified. Those with IGT should be screened annually for development of type 2 DM. PCOS patients with IGT should be treated with intensive lifestyle modification and weight loss and considered for treatment with insulin-sensitizing agents. **(*J Clin Endocrinol Metab* 92: 4546–4556, 2007)**

THE POLYCYSTIC ovarian syndrome (PCOS) is a common endocrinopathy, affecting approximately 5–10% of women of reproductive age (1–4). In its classical form, the syndrome is characterized by oligo- or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovarian morphology on ultrasonography (5). Although much remains unknown regarding the underlying pathophysiology of PCOS, a form of insulin resistance intrinsic to the syndrome appears to play a central role in its development. Among many women with PCOS, the observed insulin resistance is partially explained by excess adiposity; however, it is increasingly recognized that even lean women with PCOS have increased insulin resistance compared with normal controls (6).

Given the significant metabolic burden of insulin resistance seen in women with PCOS, affected women may have an increased risk of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM). IGT is a known risk factor for type 2 DM and the development of cardiovascular disease (7). Because IGT is often asymptomatic, the screening of women with PCOS for IGT has been recommended; however, recommendations have varied regarding the timing and method of screening for IGT (8, 9). Because patients with PCOS are at high risk for developing IGT, the early identification of affected patients and institution of lifestyle changes or pharmacological treatments may help delay the progression to type 2 DM. The following consensus recommendations attempt to determine the optimal screening method, timing of screening, and treatment modalities for IGT among women with PCOS based on the currently available medical literature.

Abbreviations: ADA, American Diabetes Association; AES, Androgen Excess Society; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; IDPP, Indian Diabetes Prevention Program; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MeSH, Medical Subject Headings; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; WHO, World Health Organization.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Process

A systematic review was conducted of the published, peer-reviewed medical literature to identify studies assessing the prevalence and risk factors for IGT in patients with PCOS, as well as the testing and treatment of IGT in both adults and adolescents using MEDLINE databases.

To review the natural history of PCOS and IGT, MEDLINE was searched from 1966 through 2007. Medical Subject Headings (MeSH) used included polycystic ovary syndrome

(which includes polycystic ovarian disease) or ovarian hyperandrogenism and diabetes, IGT, β-cell dysfunction, gestational diabetes, or metabolic syndrome. Additional references identified from these initial articles were also considered.

To examine risk factors for IGT in PCOS, the MEDLINE MeSH headings used were PCOS or ovarian hyperandrogenism, and glucose intolerance and risk factors, with the following limitations: major topic (PCOS) and English and humans. Cross-referenced studies were also reviewed.

To review the measurements of IGT, MEDLINE was searched using the terms IGT and measure. PCOS or ovarian hyperandrogenism were added in a subsequent search. Furthermore, the MeSH heading glucose intolerance with the subheading diagnosis was searched by itself and combined with the MeSH heading polycystic ovary syndrome. Supplementary references were obtained from initial citations.

To review treatments for IGT, MEDLINE was searched using the terms: type 2 diabetes prevention; PCOS and diabetes prevention; ovarian hyperandrogenism and diabetes prevention; and IGT prevention, and IGT treatment with the limits (clinical trial, metaanalysis, or randomized-controlled trial). During evaluation, particular emphasis was placed on identifying prospective randomized, controlled studies that enrolled at least 100 subjects, included women as part of their study population, involved an intervention and follow-up period of at least 1 yr, and clearly defined the prevalence of glucose intolerance at baseline and the end of the study period.

To examine the development, measurement, and treatment of IGT in adolescents, MEDLINE was searched using the terms PCOS, glucose intolerance, and adolescents, and ovarian hyperandrogenism and glucose intolerance. Insulin resistance was also used as a search term, but only studies that assessed IGT were reviewed.

Unpublished data or data published only in abstract form were not included in the review.

Development of IGT and Type 2 DM

Insulin resistance is present in both lean and obese women with PCOS compared with their body mass index (BMI) and age-matched counterparts. A seminal study conducted by Dunaif *et al.* (6) evaluated insulin sensitivity using the hyperinsulinemic-euglycemic clamp technique in lean and obese women with and without PCOS. In this study women with PCOS were more insulin resistant than women without the disorder, at equivalent degrees of obesity. Insulin resistance has been identified as a major risk factor for the development of type 2 DM, and likely contributes to the high prevalence of glucose intolerance in women with PCOS.

Prevalence of glucose intolerance in women with PCOS

In two of the largest studies (>100 women) to date that documented the prevalence of IGT and type 2 DM in women with PCOS, it is estimated that IGT is present in 31–35% of women with PCOS (10, 11). In addition, type 2 DM, classified according to the World Health Organization (WHO) criteria, is present in 7.5–10% of women with PCOS. Compared with the prevalence of IGT (1.6%) and DM (2.2%) found in U.S. women of similar age in the Third National Health and Nutrition Survey (12), the rates in women with PCOS are considerably higher. In addition, IGT and type 2 DM are also highly prevalent among adolescents with PCOS. In one study, IGT was present in eight of 27 (29.6%), and type 2 DM was present in two of 27 (7.4%) adolescent girls with PCOS (13).

The majority of U.S. studies evaluating the prevalence of glucose intolerance in PCOS primarily included obese women, which aggravates their risk for glucose intolerance. Studies on the prevalence of glucose intolerance are limited in Europe where women with PCOS are substantially leaner. However, it has been shown that glycemic abnormalities are not restricted to Caucasian women with PCOS. A high prevalence of abnormal glucose tolerance has been documented in Chinese (20.5%) and Thai (20.3%) women with PCOS (14, 15). Current studies also support abnormal glucose homeostasis in Japanese women with PCOS (16, 17), although one study (17) suggests that obesity may have a stronger effect than the existence of PCOS. In Indian populations, women with PCOS appear to have worse glucose tolerance than Caucasian populations (18).

Conversion rates to IGT and type 2 DM

The conversion from IGT to frank diabetes is also substantially enhanced in women with PCOS. In an uncontrolled study, Norman *et al.* (19) assessed 77 Australian women with PCOS. During an average 6.2-yr follow-up, five of 54 (9.3%) women with normal glucose tolerance (NGT) at baseline developed IGT, and another four women (7.4%) progressed from normoglycemia to type 2 DM. Among the 13 women with IGT at baseline, seven of them (5.4%) developed DM at follow-up. Furthermore, BMI at baseline appeared to be an independent predictor of worsening glycemic control.

The enhanced rate of deterioration in glucose tolerance was corroborated by Legro *et al.* (20), who assessed the changes in glucose tolerance over time in 71 U.S. women with PCOS and 23 control women who had baseline NGT. The mean follow-up period was approximately 3 yr. In this study, of 35 women with PCOS with NGT at baseline, 17 converted to IGT, equivalent to a NGT to IGT conversion rate of 16% per year. In addition, in this study the conversion rate from IGT to DM among PCOS women was 2% per year. Conversely, seven women with PCOS who had abnormal glucose tolerance at baseline reverted in their WHO glucose tolerance category. The conversion rate from NGT to IGT in the control women is less prominent. Of 23 control women who had NGT at baseline, only five converted to IGT, which is less than half the rate of women with PCOS. There are little data on conversion rates from European countries.

Development of gestational DM (GDM)

Besides converting to IGT or type 2 DM, women with PCOS are also at high risk for developing GDM. Polycystic ovarian morphology is a common finding among women with a history of GDM (21, 22). In a metaanalysis of 720 women with PCOS and 4505 controls, PCOS women have a 2.94 times [confidence interval (CI) for odds ratio 1.70–5.08] higher risk of developing GDM than control women (23).

This risk estimate was recently confirmed by a large database study performed using a multiethnic population in the Northern California Kaiser Permanente program (24).

Mechanisms of glucose intolerance in PCOS

Several mechanisms have been postulated to account for the predisposition to the development of type 2 DM among women with PCOS. Dunaif *et al.* (6, 25) demonstrated that women with PCOS are insulin resistant, independent of obesity. Although the nature of insulin resistance in PCOS is currently unclear, defects in insulin receptor or post-receptor signal transduction (25), altered adipocyte lipolysis (26, 27), decreased glucose transporter 4 in adipocytes (28), and impaired release of a D-chiro-inositol mediator (29–31) have all been implicated. Furthermore, many women with PCOS exhibit β-cell dysfunction (32–35), rendering insulin response to a glucose load insufficient for the degree of insulin resistance in PCOS.

Current Controversies in Screening for Glucose Intolerance

Given the presence of significant insulin resistance in the syndrome, several organizations have made recommendations regarding screening for glucose intolerance in patients with PCOS (Table 1).

A number of risk factors, including family history, advanced age, increased BMI, and a history of GDM, has increased the risk of glucose intolerance in patients with PCOS. Legro *et al.* (11) prospectively studied 254 women with PCOS using the oral glucose tolerance test (OGTT) and showed that PCOS women with a first-degree relative with DM were at an increased risk for developing glucose intolerance. In a smaller study of 122 women with PCOS, Ehrmann *et al.* (10) found that those with type 2 DM were 2.6 times more likely to have a first-degree relative with type 2 DM than patients with NGT. In a separate study evaluating a population of 408 premenopausal women with PCOS, Ehrmann *et al.* (36) also found a family history of type 2 DM in a first-degree relative to be associated with a significantly higher risk for IGT and type 2 DM in women with PCOS.

In addition to evaluating family history as a risk factor, Legro *et al.* (11) also showed an increased risk for IGT in women with advanced age, increased BMI, and increased waist to hip ratios, which are identical risk factors for the general population in developing IGT. This was corroborated in a cross-sectional study of 91 women with PCOS by Trolle and Lauszus (37), who found women who were older and had a higher BMI were more likely to have elevated fasting glucose levels. In women with a history of GDM, Koivunen *et al.* (38) found an increased prevalence of an abnormal OGTT as well as a higher prevalence of PCOS (39.4 *vs.* 16.7%; $P = 0.03$) when compared with controls.

There remains some controversy in the practicality of screening all patients with PCOS for IGT. Due to the time-consuming nature of the OGTT, Mohlig *et al.* (39) investigated the use of decision tree modeling in 118 women with PCOS to determine whether the number of patients with PCOS who should undergo the OGTT could be decreased. The best decision tree used the homeostasis assessment model for estimating insulin resistance, the proinsulin to insulin ratio, proinsulin, 17-OH progesterone, and the ratio of LH to FSH. The sensitivity of this tree was 100% and the specificity was 74%, and it cut down on the number of OGTTs by about 60%. The most suitable decision tree using medical history and clinical parameters only used BMI (>25.7 kg/m^2), waist circumference (>76 cm), and waist to hip ratio (>0.77). Applying the clinical data tree alone to a stratified screening algorithm reduced the number of OGTTs in patients with PCOS by about 25%. This decision tree yielded a sensitivity for the detection of IGT of 100%, with a specificity of 32.3%. Thus, the use of this decision tree correctly identified all women with IGT. However, the widespread application of this tree needs to be confirmed by larger studies.

Measurement of Glucose Intolerance

Presently, the only clinical method of identifying individuals with IGT is by an OGTT, typically performed as a 2-h OGTT (40). The WHO describes this test as a measure of venous plasma glucose 2 h after a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water (41). The most current recommendations for diagnosing IGT from the WHO and American Diabetes Association (ADA) slightly

TABLE 1. Screening for glucose intolerance in patients with PCOS—organization recommendations

Organization	Recommendations
American Association of Clinical Endocrinologists	Women with PCOS should have glucose levels measured. An oral glucose challenge may be considered, particularly in obese women with PCOS and those with a family history of type 2 DM (75).
American College of Obstetrics and Gynecology	Screening for glucose intolerance should be performed in all patients with PCOS with a fasting glucose level followed by a 2-h glucose level obtained after a 75-g glucose load (76).
ADA	Screening for DM should be performed in asymptomatic individuals under the age of 45 yr if they are overweight (BMI 25 kg/m^2) and have additional risk factors, which include PCOS. The recommended screening test is the fasting plasma glucose; an OGTT may be considered in patients with IFG to define better the risk of diabetes (77).
American Society of Reproductive Medicine and the European Society of Human Reproduction and Endocrinology PCOS Consensus Workshop Group	Obese women with PCOS should be screened for the metabolic syndrome, including screening for glucose intolerance with an OGTT. Screening should be considered for nonobese PCOS women with PCOS if there are additional risk factors for insulin resistance, such as a family history of insulin resistance (78).

differ (Table 2). The WHO criteria recommend first measuring a fasting plasma glucose level, followed by a 2-h OGTT only in individuals with impaired fasting glucose (IFG), *i.e.* fasting plasma glucose level between 110 and 125 mg/dl (6.1–6.9 mmol/liter). IGT is then defined as a 2-h fasting glucose equal to or more than 140 mg/dl and less than 199 mg/dl (7.8–11.0 mmol/liter) (40). The ADA also defines IGT as a 2-h plasma glucose of 140–199 mg/dl (7.8–11.0 mmol/liter) but does not require a fasting glucose before the performance of the OGTT (9).

Both the ADA and the WHO recommend using fasting plasma glucose as the initial screening test for DM because it is more convenient to patients, less costly, more reproducible, and easier to administer than the 2-h OGTT (9, 40). Despite these disadvantages, the 2-h OGTT is more sensitive and moderately more specific in diagnosing DM compared with fasting plasma glucose (9). In addition to providing information on both β-cell secretion and peripheral insulin action, the OGTT provides a better assessment of IGT than homeostatic techniques such as fasting glucose to insulin ratio, fasting insulin, and homeostatic model assessment (42). Reproducibility of the 2-h OGTT can be enhanced by paying attention to the carbohydrate intake of the last meal before a 2-h OGTT because low-carbohydrate intake may falsely result in a diagnosis of IGT (43, 44), and by ensuring that the 2-h sample is collected within 120 ± 5 min (40).

Several studies have shown that the fasting plasma glucose and the OGTT do not identify the same group of patients (45–48). The Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe (DECODE) study (45) demonstrated in a group of 1517 individuals with newly diagnosed DM that 40% met the criteria by fasting plasma glucose only, 31% met the criteria by a 2-h OGTT only, and 28% met both criteria. Therefore, nearly one third of individuals with DM would have been missed using fasting plasma glucose only. In a study of 5023 Pima Indians, Gabir *et al.* (48) reported that IGT was more common than IFG (15 *vs.* 5%). In fact, IGT, measured by an OGTT, is typically more common in women, whereas IFG, measured by fasting plasma glucose, is more common in men (40). In women with PCOS, Legro *et al.* (11) revealed that the majority of PCOS women with IGT have normal fasting glucose levels. In the PCOS population studied, fasting plasma glucose measurements by ADA criteria failed to diagnose 58% of women with DM diagnosed by a 2-h OGTT. Therefore, in PCOS, measurement of fasting blood glucose misses even more persons with IGT and DM than in the general population.

IGT is a strong predictor for DM, as well as risk of cardiovascular disease and premature mortality (7, 48–51). A 7-yr cohort study reported that IGT, but not IFG, is a risk factor for cardiovascular disease (5). In the Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe study (45), hazard ratios (95% CI) for DM diagnosed by a fasting plasma glucose were 1.6 (1.4–1.8) for all-cause mortality, 1.6 (1.3–1.9) for cardiovascular mortality, and 1.6 (1.4–1.9) for noncardiovascular mortality, respectively. The corresponding hazard ratios for DM by a 2-h OGTT were 2.0 (1.7–2.3), 1.9 (1.5–2.4), and 2.1 (1.7–2.5). In terms of prevention, the ADA acknowledges that although the efficacy of interventions for primary prevention of type 2 DM has been well recognized in individuals with IGT, there are presently no data regarding individuals with IFG who do not also have IGT (9). Data are also nonexistent regarding primary prevention of premature mortality and cardiovascular disease in individuals with IFG only (40).

The OGTT is a simple test and can be performed in an office laboratory setting. Based on current evidence and because the majority of women with PCOS have normal fasting plasma glucose, the 2-h OGTT is the best screening measure for glucose intolerance and diagnosis of type 2 DM in women with PCOS.

Prevention and Treatment of Glucose Intolerance in PCOS

A systematic review of the published peer-reviewed medical literature did not reveal high-quality, prospective, randomized-controlled trials addressing the prevention and treatment of IGT specifically in women with PCOS. Consequently, recommendations regarding the roles of lifestyle modification and pharmacological therapy in the prevention of type 2 DM in PCOS are primarily derived from studies involving broader subject populations.

Lifestyle modification

The characteristics and results of five studies evaluating the role of lifestyle modification, including dietary modification and regular moderate activity, in preventing the development of type 2 DM among high-risk individuals are outlined in Table 3. Of note, there were significant variations

TABLE 2. Current WHO and ADA criteria for defining hyperglycemia

	WHO (2006)	ADA (2007)
2-h glucose/OGTT		
NGT	<140 mg/dl (7.8 mmol/liter)	<140 mg/dl (7.8 mmol/liter)
IGT	FG < 126 mg/dl (7.0 mmol/liter) if measured and 2-h glucose ≥ 140 mg/dl (7.8 mmol/liter) and < 200 mg/dl (11.1 mmol/liter)	140 mg/dl (7.8 mmol/liter) to 199 mg/dl (11.0 mmol/liter)
Diabetes	=200 mg/dl (11.1 mmol/liter)	≥200 mg (11.1 mmol/liter)
FG		
Normal FG	<110 mg/dl (6.1 mmol/liter)	<100 mg/dl (5.6 mmol/liter)
IFG	110 mg/dl (6.1 mmol/liter) to 125 mg/dl (6.9 mmol/liter)	100 mg/dl (5.6 mmol/liter) to 125 mg/dl (6.9 mmol/liter)
Diabetes	=126 mg/dl (7.0 mmol/liter)	≥126 mg/dl (7.0 mmol/liter)

FG, Fasting glucose.

TABLE 3. Summary of randomized, controlled trials evaluating the role of lifestyle modification in preventing progression to DM among high-risk populations

Study	Knowler *et al.* (52)	Pan *et al.* (54)	Ramachandran *et al.* (55)	Tuomilehto *et al.* (53)	Wein *et al.* (56)	Wing *et al.* (57)
No. of randomized subjects	3234[a]	577[b]	531[a]	522	200	154[b]
Inclusion criteria	Males and females, BMI $\geq$ 24 kg/m^2 (22 kg/m^2 in Asians), IFG and IGT	Males and females, IGT	Males and females, IGT	Males and females, BMI $>$ 25 kg/m^2, ages 40–65 yr, IGT	Women with history of GDM, IGT	Males and females, 30–100% over ideal body weight, 40–55 yr, parent with DM
IGT/DM definition	ADA 1997	WHO 1985	WHO 1999	WHO 1985	WHO 1985	WHO
Follow-up duration (yr)	2.8	6	3	3.2	4.25	2
Age (yr)	50	45	45–46	55	25	46
BMI (kg/m^2)	34	26	25–26	31	38–40	36
Intervention	Diet and exercise, >7% weight loss, 16-lesson curriculum	Diet and exercise, small group support sessions	Diet and exercise	Diet and exercise, >5% weight loss	Diet alone	Diet and exercise
Dietary education	Hypocaloric, low-fat diet	Hypocaloric diet to induce 0.5–1.0 kg/month weight loss in BMI $\geq$ 25 kg/m^2	Hypocaloric, low-fat, high-fiber diet	Low-fat, high-fiber diet, sessions with nutritionist	Standard dietary advice, nutrition telephone follow-up every 3 months	Hypocaloric, low-fat diet, multidisciplinary nutrition sessions
Exercise education	Moderate activity (150 min/wk)	Increase physical activity 1–2 U/d	Moderate (30 min/d) exercise	Moderate (30 min/d) exercise, supervised circuit resistance training		1500 kcal/wk moderate activity
Control intervention	Standard lifestyle modification (single education session)	General information regarding DM and IGT		General verbal and written diet and exercise information	Standard dietary advice	Provided self-help manual
Diabetes incidence intervention	4.8/100 person/yr	9.6/100 person/yr, 46.0%	39.3%	27/265, 3.2/100 person/yr, 10.2%	26.8%	5/32, 15.6%
Diabetes incidence controls	11/100 person/yr	15.7/100 person/yr, 67.7%	55.0%	59/257, 7.8/100 person/yr, 23.0%	28.1%	2/31, 6.5%
RRR (95% CI)	58% (48–66%)	38%	28.5% (20.5–37.3%)	58%	NS	NS
Hazard ratio (95% CI)				0.4 (0.3–0.7)		

NS, Nonsignificant; RRR, relative risk reduction.
[a] Included a group randomized to treatment with medication.
[b] Included groups randomized to diet alone and exercise alone.

in the reported effects of lifestyle modification on the conversion of IGT to DM among high-risk populations.

Two large intervention studies, the Diabetes Prevention Program (DPP) (52) and the Finnish Diabetes Prevention Study (53), demonstrated strikingly similar reductions (58% relative risk reduction) in the conversion rate to DM among overweight men and women with IGT randomized to treatment with intensive lifestyle modification compared with controls. Importantly, the study populations had mean BMI measurements more than 30 kg/m^2, and the goal of both lifestyle treatment programs was a 5–7% reduction in body weight. The specific interventions involved in the DPP included a hypocaloric low-fat diet and a minimum of 150-min moderate intensity physical activity a week.

Studies by Pan *et al.* (54) and Ramachandran *et al.* (55) also demonstrated a significant but less dramatic relative risk reduction (28–38%) in the conversion rate from IGT to diabetes with intensive lifestyle modification. The discrepancies among the reported differences in risk reduction with lifestyle modification may be partially explained by differences in the study populations. The mean BMI measurements in the studies by Pan *et al.* (54) and Ramachandran *et al.* (55) were 25–26 kg/m^2, lower than the mean BMI measurements in the DPP and Finnish Diabetes Prevention Study.

A study by Wein *et al.* (56) involving 200 women with a history of GDM and current IGT demonstrated a small but nonsignificant reduction in the diabetes conversion rate; however, the study intervention included dietary modification alone. Finally, one smaller study by Wing *et al.* (57) failed to show a significant difference in the development of diabetes with diet alone, exercise alone, or a combined intervention in overweight subjects with a family history of diabetes.

Little is known regarding the role of exercise in preventing the development of IGT and DM in nonobese women with PCOS.

Pharmacological intervention

Pharmacological therapies, including insulin-sensitizing agents, have also been shown to decrease the conversion rate to overt DM among subjects with IGT, and randomized-controlled trials evaluating pharmacotherapy that met the specified criteria are outlined in Table 4. Treatment with medications from a variety of different drug classes, including the biguanide, metformin (52, 55), thiazolidinediones (58,

59), the α-glucosidase inhibitor, acarbose (60), and the lipoprotein lipase inhibitor, orlistat (61, 62), has prevented the development of DM among high-risk populations with IGT.

In addition to intensive lifestyle modification, the DPP evaluated the role of the insulin-sensitizing agent metformin in the prevention of DM (52). In the DPP, the treatment arm randomized to receive metformin 850 mg twice daily demonstrated a 31% reduction in the relative risk of developing DM compared with placebo treatment. Notably, the risk reduction in the metformin treatment arm was less robust than the response reported in the group receiving intensive lifestyle modification (31 *vs.* 58%, respectively). Although the DPP represents a large, well-designed control trial evaluating the efficacy of lifestyle modification and pharmacotherapy in preventing DM, there were several limitations to the study. First, there was no treatment arm in the DPP that evaluated the combined effect of intensive lifestyle modification and metformin therapy in high-risk individuals. Second, some experts have suggested that treatment with metformin may merely mask the development of DM as opposed to preventing the disease. In response to this debate, the DPP Research Group published follow-up results reporting repeat OGTTs in a subset of subjects who received metformin therapy after a washout period of 1–2 wk (63). Although the reported incidence of DM increased in the metformin treatment group after the washout period, the incidence of DM in the metformin arm was still reduced by 25% compared with the placebo group.

Similar to the DPP, the Indian Diabetes Prevention Program (IDPP) evaluated the role of lifestyle modification and metformin in the prevention of DM among overweight Asian Indian men and women with IGT (55). The IDPP results revealed significant, 28.5 and 26.4%, relative risk reductions for the development of DM with intensive lifestyle modification and metformin treatment, respectively. Although both lifestyle modification and metformin therapy reduced the incidence of DM in the IDPP, there was no added benefit from the combination lifestyle modification and metformin compared with either treatment alone. As outlined previously, the less robust reduction in DM risk reported with lifestyle modification in the IDPP compared with the DPP may be explained by differences in subject BMIs at baseline between the two studies (25.7 ± 3.3 kg/m^2 in the IDPP compared with 33.9 ± 6.8 kg/m^2 in the DPP).

Similar to metformin, the thiazolidinediones improve insulin sensitivity and may prevent or delay the development of DM in high-risk individuals. Randomized, placebo-controlled trials involving the prevention of DM using thiazolidinediones demonstrated a 62–89% relative risk reduction with this class of medications (58, 59). Unfortunately, these studies did not compare treatment with thiazolidinediones with intensive lifestyle modification or other medications. The DPP initially contained a treatment arm that was randomized to receive the thiazolidinedione, troglitazone; however, given concerns of hepatotoxicity, the troglitazone arm was discontinued in 1998 (64). Before its discontinuation, the incidence of DM among the 585 subjects receiving troglitazone for a mean duration of 0.9 yr was statistically lower than the incidence in both the placebo and metformin groups. Furthermore, there was no statistical difference in the progression rate to DM between the troglitazone and intensive lifestyle modification treatment arms. Despite these findings, longer term studies are needed to compare the efficacy of thiazolidinediones and other insulin-sensitizing agents and lifestyle modification in preventing DM.

Prevention of glucose intolerance in PCOS

Although there are no published prospective, randomized-controlled trials that evaluate the prevention or treatment of IGT specifically in women with PCOS, several small studies do address the potential role of insulin-sensitizing agents in this high-risk population. Unluhizarci *et al.* (65) reported the impact of treatment with metformin 500 mg twice daily for 3 months on IGT in 17 adult women with PCOS (mean age 24.4 ± 1.4 yr; mean BMI 29.7 ± 1.4 kg/m^2). At baseline, five (31.6%) of the women demonstrated IGT. Of these, two patients (40%) showed NGT after treatment with metformin. In a study by Arslanian *et al.* (66), 15 obese adolescents with PCOS and IGT (mean age 14.0 ± 0.8 yr; mean BMI 38.1 ± 1.6 kg/m^2) were treated with metformin 850 mg twice daily for 3 months. At the end of the relatively brief treatment period, approximately one half (n = 8) of the adolescents had reverted back to NGT on repeat testing. In a study by Dereli *et al.* (67), 40 women with PCOS, a BMI less than 27 kg/m^2, and IGT were randomized to treatment with rosiglitazone with either 2 (n = 20) or 4 mg daily (n = 20) for 8 months. In addition to decreases in free testosterone levels and improvements in ovulatory dysfunction in both treatment groups, 19 (95%) and 15 (75%) of the women receiving rosiglitazone 4 and 2 mg daily, respectively, had reverted to NGT after 8-month treatment.

Finally, using a retrospective study design, Sharma and Nestler (68) evaluated the role of metformin in preventing the progression of glucose intolerance in PCOS. At baseline, 11 (22%) of the 50 nondiabetic women with PCOS had evidence of IGT according to an OGTT. After a mean treatment period of 2.4 yr, approximately half (n = 6) the women with IGT at baseline had reverted to NGT with metformin therapy. Furthermore, while receiving metformin (average treatment period of 3.6 yr), only two (5.1%) of the 39 women with NGT at baseline had converted to IGT, representing an annual conversion rate of 1.6%. None of the women with IGT at baseline converted to overt DM during treatment with metformin. When compared with the 16% annual conversion rate from NGT to IGT among drug-naive PCOS women reported by Legro *et al.* (20), treatment with metformin appeared to lead to an 8-fold decrease in the annual conversion rate. Despite the limitations of these four studies, including small sample size, lack of control groups, and the question of whether glucose intolerance was prevented or merely being masked, their results support the potential role of insulin-sensitizing agents in the prevention of IGT and DM in PCOS. However, well-designed, prospective, randomized-controlled trials are needed to evaluate more fully the specific roles of lifestyle modification and insulin-sensitizing agents in the prevention of IGT and its progression to type 2 DM among women with PCOS.

TABLE 4. Summary of randomized, controlled trials evaluating the role of pharmacotherapy in preventing progression to DM among high-risk populations

Study	Bosch *et al.* (69)	Chaisson *et al.* (60)	Durbin (58)	Gerstein *et al.* (59)	Heymsfield *et al.* (61)	Knowler *et al.* (52)	Ramachandran *et al.* (55)	Torgerson et al. (62)
No. of randomized subjects	5269	1429	172	5269	675, 120 with IGT	3234[a]	531[a]	3305, 694 with IGT
Inclusion criteria	Males and females, ≥ 30 yr, IFG or IGT ± IFG	Males and females, 40–70 yr, BMI 25–40 kg/m^2, IGT	Males and females, IFG and IGT	Males and females, ≥ 30 yr, IFG or IGT ± IFG	Males and females, BMI 30–43 kg/m^2, NGT, IGT, DM	Males and females, ≥ 25 yr, BMI 24 kg/m^2 (22 kg/m^2 in Asians), IFG and IGT	Males and females, IGT	Males and females, BMI ≥ 30 kg/m^2, 30–60 yr, IFG and IGT
IGT/DM definition	WHO	WHO 1985	ADA	WHO	WHO 1985	ADA 1997	WHO 1999	WHO 1994
Follow-up duration (yr)	3.0	3.3	3.0	3.0	2.0	2.8	3.0	4.0
Age (yr)	55	54	54–60	55	44	50	45–46	43
BMI (kg/m^2)	31	31	N/A	31	36	34	25–26	37
Intervention	Ramipril titrated to 15 mg daily	Acarbose 100 mg three times daily	Troglitazone 400 mg daily × 10 months, pioglitazone/rosiglitazone	Rosiglitazone 8 mg daily	Orlistat 120 mg three times daily, hypocaloric diet × 1 yr	Metformin 850 mg twice daily, standard lifestyle modifications	Metformin 500–250 mg twice daily	Orlistat 120 mg three times daily; hypocaloric, low-fat diet; increase exercise by 1 km/d
Control	Placebo	Placebo	Placebo	Placebo	Placebo, hypocaloric diet × 1 yr	Placebo, standard lifestyle modifications	Standard health care advice	Placebo; hypocaloric, low-fat diet; increase exercise by 1 km/d
Diabetes incidence intervention	449/2623, 17.5%	221/682, 32%	1.4/100 person/yr, 3.0%	280/2635, 10.6%	2/67, 3.0%	7.8/100 person/yr	40.5%	6.2%
Diabetes incidence controls	489/2646, 18.5%	285/686, 42%	9.4/100 person/yr, 26.8%	658/2634, 25.0%	4/53, 7.6%	11/100 person/yr	55%	9.2%
RRR (95% CI)	NS	25%	88.9%	62%	47%	31% (17–43%)	26.4% (19.1–35.1%)	37.3%
Hazard ratio (95% CI)	0.91 (0.8–1.03)	0.75		0.38 (0.33–0.44)	$P < 0.04$			0.63 (0.46–0.86)
Adverse events	Cough	Gastrointestinal symptoms	Not formally reported	Heart failure	Not formally reported	Gastrointestinal symptoms	Symptoms of hypoglycemia, gastrointestinal symptoms	Gastrointestinal symptoms

N/A, Not available; NS, nonsignificant, RRR, relative risk reduction.

[a] Included an additional group randomized to intensive lifestyle modification.

Glucose Intolerance in Adolescents with PCOS

Development of IGT in adolescents

Data on glucose intolerance in adolescents with PCOS are limited, and studies are difficult to interpret with confidence, given the small numbers of participants in each study. As in adult women, adolescents with PCOS are at increased risk for developing glucose intolerance and DM compared with their non-PCOS counterparts (11); however, the exact prevalence of IGT in young women with PCOS is less clear. For example, a Canadian study of 22 obese adolescents with PCOS revealed baseline IGT in only one participant (4.5%) (70). In contrast, small studies involving obese adolescents with PCOS in the United States report rates of IGT as high as 33 (13) to 52% (35). These differences may be accounted for by many factors, including, but not limited to, family history, diet, BMI, and exercise habits. Even less is known regarding the risk of IGT in nonobese adolescents with evidence of PCOS or ovarian hyperandrogenism. In two small studies involving a total of 39 nonobese adolescent girls with PCOS by Ibanez *et al*. (71) and Silfen *et al*. (72), none of the nonobese adolescents demonstrated IGT on the OGTT.

Measurements of glucose intolerance in adolescents

As in adults, screening for IGT with a fasting glucose level is not reliable in adolescents, and tests of insulin resistance such as the fasting glucose to insulin ratio and the homeostasis assessment model for estimating insulin resistance are poor predictors of IGT and DM in adolescents with PCOS (13). Therefore, the most reliable screening test for IGT in PCOS adolescents is the 2-h OGTT after a 75-g glucose load, interpreted using ADA guidelines. Although the most appropriate screening interval is not clearly defined, the conversion from NGT to type 2 DM can occur in as little as 5 yr (73), most likely because of the strong correlation of PCOS and insulin resistance.

Treatment of IGT in adolescents

Although the literature regarding treatment of IGT specific to adolescents is sparse, it seems reasonable to use a similar approach to that used in adult women with PCOS. Diet and exercise appear to be the most important aspects of treating IGT and reducing progression to type 2 DM. As demonstrated in the DPP (52), lifestyle intervention comprised of a low-fat diet and 150-min exercise per week reduced the progression from IGT to type 2 DM by 58% compared with placebo and was more successful than metformin therapy, which reduced progression by 31%.

A small randomized-controlled trial comparing metformin to placebo for 12 wk in 22 adolescents with PCOS showed no significant difference in IGT (70). Of note, however, the only subject with baseline IGT was in the metformin group and showed persistence of her IGT at the study end. There were no subjects in the placebo arm with baseline IGT, but one developed IGT by the end of the 12-wk study. Clearly, this study was underpowered, and the duration was not sufficient to detect a true difference. Conversely, the only study evaluating PCOS adolescents with baseline IGT showed that treatment with metformin (850 mg twice daily) resulted in conversion back to NGT in eight of the 15 subjects after 3-month treatment (66). Limitations of this study include small sample size and lack of a control group; nonetheless, metformin may be a promising treatment for PCOS adolescents with IGT.

Conclusion and Recommendations

Although the strengths of the studies reviewed vary considerably, the expert panel concludes that there is sufficient evidence to recommend support for the following recommendations (Table 5). Because of the high prevalence of glucose intolerance among patients with PCOS, screening is a necessary part of the care of these patients who are at a markedly increased risk for the development of type 2 DM. Because an increased prevalence of both glucose intolerance and type 2 DM has been found in various ethnic populations, screening should be done regardless of ethnicity. Although numerous risk factors such as obesity and age increase the risk of glucose intolerance, women with PCOS of all ages and weights appear to be at greater risk for glucose intolerance than normal controls. Consequently, the panel recommends that all women with PCOS be screened, even in the absence of additional risk factors and regardless of BMI.

Multiple studies have shown that fasting glucose concentrations are not sufficiently sensitive to detect all patients with PCOS who have IGT. Therefore, an OGTT is recommended as the standard screening tool for IGT in these patients and should initially be performed at diagnosis. Although prior studies have suggested women with PCOS and NGT at baseline should be periodically rescreened for the development of IGT, the ideal interval for screening remains uncertain.

Acknowledging the presence of limited data, studies suggest a high (16–19%) annual conversion rate from NGT to IGT in PCOS, and the panel recommends screening PCOS women with NGT at baseline and at least once every 2 yr or earlier if additional risk factors are identified. However, given the high risk of progression to overt diabetes, women with PCOS who have IGT should be screened annually using an OGTT.

Intensive lifestyle modification should be considered the mainstay of treatment in all women with PCOS who have

TABLE 5. Androgen Excess Society screening and treatment recommendations for IGT in PCOS

- All patients with PCOS, regardless of BMI, should be screened for IGT using a 2-h OGTT.[a]
- Patients with NGT should be rescreened at least once every 2 yr or earlier if additional risk factors are identified.
- Patients with IGT should be screened annually for the development of DM.
- The mainstay of treatment for all patients with PCOS and IGT should be intensive lifestyle modification as well as weight loss in obese patients.
- Insulin-sensitizing agents, such as metformin and thiazolidinediones, should be considered in patients with PCOS and IGT.
- Adolescents with PCOS should be screened for IGT using a 2-h OGTT repeated once every 2 yr. If IGT develops, they should be treated with intensive lifestyle modification, and treatment with metformin should be considered.

[a] See *Minority Report*.

IGT to prevent progression to DM. Despite insufficient data in lean women, it is reasonable to recommend that, in all women with PCOS, a lifestyle modification program should consist of at least 30-min moderate activity 5 d/wk. Furthermore, in overweight and obese women with PCOS, a hypocaloric diet is recommended to achieve a minimum of 5–7% weight loss. However, many overweight and obese women with PCOS find significant weight loss difficult to achieve and maintain, and weight loss is not an option for lean women with PCOS. Consequently, the addition of insulin-sensitizing agents such as metformin and thiazolidinediones should be considered in women with PCOS and documented IGT if weight loss attempts fail or are not possible.

Adolescents with PCOS, like their adult counterparts, should be screened for IGT using an OGTT at least once every 2 yr after a normal screen and more frequently after an abnormal screen. Adolescents should also be treated with intensive lifestyle modification, including diet and moderate exercise as initial therapy. The use of metformin or other insulin-sensitizing agents to treat or prevent progression to IGT may be considered but should not be mandated until there have been well-designed, randomized-controlled trials demonstrating their efficacy.

Minority Report

Notwithstanding the aforementioned recommendation to screen all women with PCOS with a 2-h OGTT, it should be noted that a few members of the Androgen Excess Society Board did not agree with this recommendation. Indeed, evidence regarding risk of IGT in lean PCOS women is limited and still emerging (74). Therefore, these Board members recommend screening for IGT and type 2 DM using an OGTT only in obese PCOS patients with a BMI equal to or more than 30 kg/m^2, or alternatively, screening lean patients only if they have at least one additional risk factor for DM, including advanced age, family history of DM, or a personal history of GDM.

Future Directions

The panel also identified that additional research is needed in several key areas. Large studies are needed to determine the ideal frequency for rescreening women with both NGT and IGT at baseline. Investigation into the utility of stratifying women with PCOS to determine who should be screened for IGT should be examined, such as the role of decision tree modeling. It would be ideal to have a registry of patients seen at PCOS clinics that contained information on more patients than a single investigator's cohort that could be a valuable research resource to address some of these questions. In particular, further information is needed regarding the risk of IGT and progression to DM in nonobese women with PCOS. In addition, research is needed to determine the long-term role of insulin-sensitizing medications in preventing the progression to IGT and type 2 DM in both lean and obese women with PCOS. Because the literature in adolescents with PCOS is limited, the panel found several areas that need to be investigated further. Large, multicenter studies are needed to determine a more accurate incidence of adolescents with PCOS and IGT. Randomized-controlled trials are needed to investigate the efficacy of insulin-sensitizing agents *vs.* lifestyle modification *vs.* placebo in the prevention of IGT and type 2 DM in this population, and studies are needed to be done on the effect of oral contraceptives on conversion to IGT and diabetes in adolescents with PCOS.

Acknowledgments

We thank the Androgen Excess Society Board members for their review, comments, and critiques of this manuscript: Drs. Ricardo Azziz, Enrico Carmina, Evanthia Diamanti-Kandarakis, Walter Futterweit, Onno E. Janssen, Jan McAllister, Robert Norman, Ann E. Taylor, and Selma Witchel.

Received July 11, 2007. Accepted September 27, 2007.

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Disclosure Statement: The authors have nothing to disclose.

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