Prevalence of Impaired Glucose Tolerance and Diabetes in Women With Polycystic Ovary Syndrome

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OBJECTIVE — NIDDM occurs commonly among women with polycystic ovary syndrome (PCOS). The prevalence and natural history of its precursor, impaired glucose tolerance (IGT), is less well known. The objective of this study was to characterize the prevalence and incidence of glucose intolerance in a large cohort of women with well-characterized PCOS.

RESEARCH DESIGN AND METHODS — A total of 122 women with clinical and hormonal evidence of PCOS were recruited from the Medicine, Endocrinology, Gynecology, and Pediatrics Clinics at the University of Chicago. All women had a standard oral glucose tolerance test (OGTT) with measurement of glucose and insulin levels. A subset of 25 women were subsequently restudied with the aim of characterizing the natural history of glucose tolerance in PCOS.

RESULTS — Glucose tolerance was abnormal in 55 (45%) of the 122 women: 43 (35%) had IGT and 12 (10%) had NIDDM at the time of initial study. The women with NIDDM differed from those with normal glucose tolerance in that they had a 2.6-fold higher prevalence of first-degree relatives with NIDDM (83 vs. 31%, $P < 0.01$ by χ^2) and were significantly more obese (BMI 41.0 ± 2.4 vs. 33.4 ± 1.1 kg/m^2, $P < 0.01$). For the entire cohort of 122 women, there was a significant correlation between fasting and 2-h glucose concentrations ($r = 0.76$, $P < 0.0001$); among the subset with IGT, the fasting glucose concentration was poorly predictive of the 2-h level ($r = 0.25$, NS). After a mean follow-up of 2.4 ± 0.3 years (range 0.5–6.3), 25 women had a second OGTT. The glucose concentration at 2 h during the second glucose tolerance test was significantly higher than the 2-h concentration during the first study (161 ± 9 vs. 139 ± 6 mg/dl, $P < 0.02$).

CONCLUSIONS — The prevalence of IGT and NIDDM in women with PCOS is substantially higher than expected when compared with age- and weight-matched populations of women without PCOS. The conversion from IGT to NIDDM is accelerated in PCOS. The fasting glucose concentration does not reliably predict the glucose concentration at 2 h after an oral glucose challenge, particularly among those with IGT, the subgroup at highest risk for subsequent development of NIDDM. We conclude that women with PCOS should periodically have an OGTT and must be closely monitored for deterioration in glucose tolerance.

Diabetes Care 22:141–146, 1999

Impaired glucose tolerance (IGT), a state characterized by mild elevations in blood glucose levels, typically antedates the onset of NIDDM (1). However, IGT is underdiagnosed, even in populations at high risk (2,3), because it is usually asymptomatic and its detection requires an oral glucose tolerance test (OGTT). With appropriate lifestyle or pharmacological intervention, it may be feasible to delay, or possibly prevent, the deterioration from IGT to NIDDM (4,5). Thus, great emphasis has been placed recently on earlier detection of IGT (6).

Women with polycystic ovary syndrome (PCOS) are an ideal population in which to identify individuals with IGT for several reasons. In conjunction with the reproductive dysfunction that characterizes the syndrome, PCOS carries an increased risk of development of NIDDM (7–10). In addition, PCOS is estimated to affect up to 10% of women of reproductive age, making it one of the most common endocrine disorders in this population. Finally, the manifestations of androgen excess typically bring patients with PCOS to clinical attention early in life, when NIDDM is rarely evident, but when strategies for its prevention may be optimally implemented.

While the association between androgen excess and diabetes was first noted some 75 years ago (11), the precise mechanisms that underlie the pathogenesis of abnormal glucose tolerance in PCOS have yet to be established, and our understanding of the natural history of glucose tolerance among those with the disorder remains incomplete. The present study was thus undertaken with the following objectives: to determine the prevalence of glucose intolerance in a large prospectively studied cohort of women with PCOS, to examine the role of both genetic and environmental factors in the development of glucose intolerance in this population, and to characterize the natural history of glucose tolerance in PCOS.

RESEARCH DESIGN AND METHODS

Selection and definition of study subjects

Beginning in June 1990, women ≥2 years postmenarche who presented to the Medicine, Endocrinology, Gynecology, and Pediatrics Clinics at the University of Chicago with oligo/amenorrhea plus hirsutism, acne, or infertility and hyperandrogenemia (plasma free testosterone ≥10 pg/ml [34.6 pmol/l]) (12) were eligible for study. All subjects had further documentation of an

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Received for publication 20 July 1998 and accepted in revised form 29 September 1998.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics of study subjects*

	Normal	IGT	NIDDM
Number of subjects	67 (55)	43 (35)	12 (10)
Positive family history NIDDM	21 (31)	24 (56)	10 (83)*
Age (years)	24.9 ± 0.8	25.5 ± 1.2	29.0 ± 2.0
BMI (kg/m^2)	33.4 ± 1.1	36.9 ± 1.2	41.0 ± 2.4†
Ethnicity			
Caucasian	37 (55)	23 (54)	3 (25)
African-American	22 (33)	15 (36)	7 (57)
Hispanic	3 (4)	1 (2)	1 (8)
Asian	5 (8)	4 (8)	1 (8)
OGTT			
Fasting glucose (mg/dl)	85.6 ± 1.5	94.8 ± 1.6‡	124.2 ± 9.5†§
2-h glucose (mg/dl)	113.7 ± 1.9	159.2 ± 2.6‡	245.3 ± 16.7†§
AUC glucose (mg · dl^{-1} · min)	20,936 ± 390	26,869 ± 392	39,776 ± 2,785
Fasting insulin (pmol/l)	166 ± 15	224 ± 34	299 ± 74
2-h insulin (pmol/l)	887 ± 94	2312 ± 373‡	1327 ± 523
AUC insulin (pmol · l^{-1} · min)	157,418 ± 17,335	298,872 ± 47,466‡	228,921 ± 80,822
Androgen levels			
Total testosterone (ng/dl)	79 ± 4	107 ± 9‡	115 ± 32†
Free testosterone (pg/ml)	24 ± 1	35 ± 3‡	41 ± 10†

Data are *n* (%) or means ± SEM. *NIDDM vs. normal by χ^2 test. ANOVA with Scheffé post hoc correction: †NIDDM vs. normal, ‡IGT vs. normal, and §NIDDM vs. IGT. AUC, area under the curve.

ovarian source of androgen excess by either lack of suppression of plasma free testosterone after administration of dexamethasone (0.5 mg four times daily for 4 days) or a supranormal plasma 17-hydroxyprogesterone response to a test dose of a gonadotropin-releasing hormone (GnRH) agonist (nafarelin or leuprolide), as previously reported (12,13). Women with hyperprolactinemia, Cushing syndrome, and nonclassic congenital adrenal hyperplasia were excluded from study, as were those women taking medication known to affect carbohydrate metabolism. Gonadotropin levels and transvaginal ultrasound imaging were obtained in most individuals, but were not used to assign a diagnosis of ovarian androgen excess, given their low sensitivity and specificity (12). Thus, all women met both the conventional clinical criteria for PCOS (14) as well as the more stringent criterion that requires demonstration of an ovarian source of androgen excess (12,13). After a diagnosis of ovarian androgen excess was established, an OGTT was requested of all subjects, without regard to their personal or family history of glucose intolerance.

Beginning in June 1996, a recall program was initiated to retest all women who had been given an OGTT at least 6 months before and whose glucose tolerance was either normal or impaired at the time of the first test; those with an initial diagnosis of NIDDM were not retested, since all were on treatment for the disorder.

The racial/ethnic composition of the study subjects was representative of that of women attending our clinics: 63 (52%) Caucasian, 44 (36%) African-American, 10 (8%) Asian, and 5 (4%) Hispanic subjects. All protocols were approved by the Institutional Review Board of The University of Chicago. Written informed consent was obtained from each subject; parental consent was obtained for subjects <18 years of age. A family history of NIDDM was considered positive if at least one first-degree relative (parent or sibling) had NIDDM either by documentation or upon direct testing.

Experimental protocols

All studies were performed after an overnight fast. Intravenous catheters were placed into antecubital veins. Where appropriate, one catheter was used for administration of secretagogues, while the catheter in the contralateral forearm was used for blood sampling; the blood sampling arm was heated to obtain arterialized venous samples.

OGTT

Blood samples were obtained at baseline and at 30-min intervals for 3 h for measurement of glucose and insulin after ingestion of a 75-g glucose load. Glucose tolerance was evaluated using both the criteria of the World Health Organization (15) and the recently revised criteria for the diagnosis and classification of diabetes from the American Diabetes Association (16).

Assay methods

Plasma glucose was measured immediately using a glucose analyzer (YSI Model 2300 STAT; Yellow Springs Instruments, Yellow Springs, OH). The coefficient of variation of this method is <2%. Serum insulin was assayed by a double antibody technique (17) with a lower-limit sensitivity of 20 pmol/l and an average intra-assay coefficient of variation of 6%. The cross reactivity of proinsulin in the radioimmunoassay for insulin is ~40%.

Plasma testosterone was measured using a kit from Diagnostic Products (Los Angeles, CA). The free fraction of plasma testosterone and the concentration of sex-hormone binding globulin were measured by a competitive protein binding assay as previously described (18). The intra- and interassay coefficients of variation were 3.8 and 8.7%, respectively. Plasma levels of 17-hydroxyprogesterone (17-PROG) were determined by radioimmunoassay after chromatographic purification as previously reported (13). The precision of this assay averaged 7% (intra-assay coefficient of variation) and 12% (interassay coefficient).

Statistical methods

The significance of differences between groups was determined using the unpaired *t* test, analysis of variance (ANOVA), or analysis of covariance (ANCOVA) with Scheffé's allowance for multiple comparisons, as appropriate. Between-group differences were assessed by χ^2 testing. For all analyses, a two-tailed *P* value of <0.05 was considered to indicate statistical significance. Unless otherwise noted, all results are expressed as means ± SEM. Data analysis was performed using StatView and SuperANOVA for the Macintosh (Abacus Concepts, Berkeley, CA).

RESULTS

Clinical characteristics of study subjects

During the defined period, 122 women were diagnosed with PCOS and consented to an OGTT. Using the 2-h glucose level during the OGTT, glucose tolerance was normal in 67 (55%) of the 122 women, 43

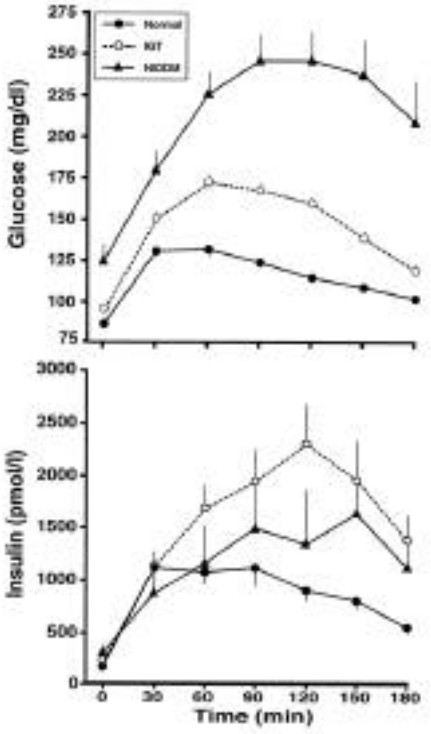

Figure 1—*Glucose (upper panel) and insulin (lower panel) responses to a 75-g oral glucose challenge in women with PCOS (n = 122). The area under the insulin response curve was significantly higher ($P < 0.05$) in those with IGT compared with that in those whose glucose tolerance was normal. Data are means ± SEM.*

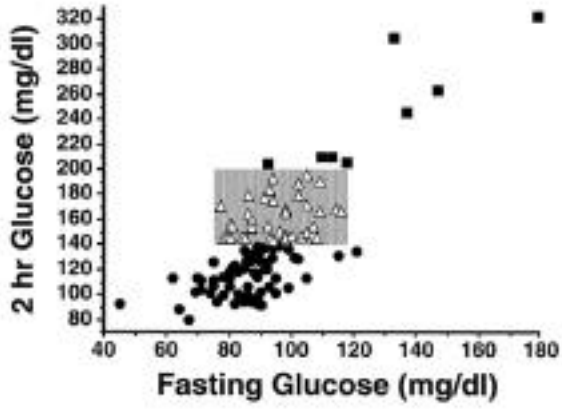

Figure 2—*Relationship between glucose concentrations at fasting and 2-h time points during a 75-g oral glucose challenge in women with PCOS. The relationship between these measures for the entire cohort (n = 122) is significant (r = 0.76, $P < 0.0001$), while subgroup analysis in those with IGT alone is r = 0.25, NS. The shaded area depicts the range of observed fasting glucose concentrations in the IGT group (2-h glucose range 140–200 mg/dl, by definition). ●, Normal glucose tolerance; △, IGT; ■, NIDDM.*

(35%) had IGT, and 12 (10%) had NIDDM at the time of initial study (Table 1). When fasting glucose levels were analyzed according to the recent recommendations of the Expert Committee of the American Diabetes Association (16), we found that 104 (85%) women had a normal fasting glucose (<110 mg/dl), 11 (9%) had impaired fasting glucose (≥110 and <126 mg/dl), and 7 (6%) were diabetic (>126 mg/dl).

For the entire cohort, the mean age at presentation was 25.5 ± 0.7 years (range 13.5–40). Although the women with NIDDM tended to be slightly older (mean age 29.0 ± 2.0 years), this difference in age was not significantly different from those with normal or IGT. The women with NIDDM differed from those with normal glucose tolerance in that they had a 2.6-fold higher prevalence of first-degree relatives with NIDDM (83 vs. 31%, $P < 0.01$ by χ^2) and were significantly more obese (BMI 41.0 ± 2.4 vs. 33.4 ± 1.1 kg/m^2, $P < 0.01$). Although there was a slight preponderance of African-American women in the group with NIDDM, the ethnic composition of the subgroups did not differ significantly.

Glucose and insulin responses to an oral glucose challenge

Glucose and insulin responses to the oral glucose challenge are depicted in Fig. 1. Fasting insulin concentrations were elevated in all three groups, but did not differ significantly between them. There was, however, a significantly higher insulin response to the oral glucose challenge in those with IGT compared with that in those with normal glucose tolerance, as assessed by area under the insulin response curve (298,872 ± 47,466 vs. 157,418 ± 17,335 pmol · l^{-1} · min, $P < 0.05$). This difference remained significant ($P < 0.01$) even when the effects of the higher BMI in the IGT group were accounted for by ANCOVA. In contrast, the insulin response to the oral glucose challenge in subjects with NIDDM did not differ significantly from that in those whose glucose tolerance was normal (228,921 ± 80,822 vs. 157,418 ± 17,335 pmol · l^{-1} · min, NS) or impaired (228,921 ± 80,822 vs. 298,872 ± 47,466 pmol · l^{-1} · min, NS). This finding may be interpreted to indicate an inappropriately low insulin response in those with NIDDM when considered in relation to the prevailing glucose levels and is typical of what has been observed in other populations with IGT (1).

For the entire cohort of 122 women, there was a significant correlation between the fasting glucose concentration and the glucose concentration 2-h post-glucose challenge ($r = 0.76$, $P < 0.0001$) (Fig. 2). However, in the subgroup of those with IGT, the fasting glucose concentration was not predictive of the glucose level at 2-h post-glucose challenge ($r = 0.25$, NS) (Fig. 2).

Glucose tolerance at follow-up

As noted, 12 of the 122 women were diagnosed with NIDDM and did not undergo a subsequent OGTT. A small subset of the remaining 110 women ($n = 25$, 23%) have

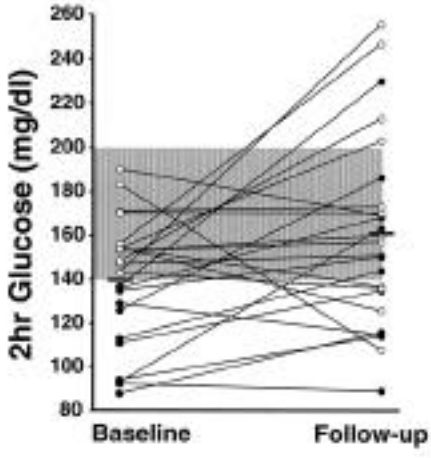

Figure 3—*Glucose concentration at 2 h after a 75-g oral glucose challenge in nondiabetic women with PCOS (n = 25) at baseline (initial OGTT) and at follow-up (second OGTT). The shaded area depicts the defined range for IGT. The mean glucose concentration is significantly higher at follow-up than at baseline (161 ± 9 vs. 139 ± 6 mg/dl, $P < 0.02$), as depicted by the solid horizontal bars. The symbols indicate level of glucose tolerance at baseline: ●, normal glucose tolerance; ○, IGT.*

had a subsequent OGTT. The glucose levels at 2-h post-glucose challenge, both at baseline and in a follow-up study, are depicted in Fig. 3. The glucose concentration at 2 h during the second OGTT was significantly higher than the 2-h concentration at baseline (161 ± 9 vs. 139 ± 6 mg/dl, $P < 0.02$). Of this subset, 10 women (40%) had a deterioration in glucose tolerance over a mean follow up of 34.2 ± 6.6 months (range 12–75); 15 (60%) maintained or improved their glucose tolerance after a mean follow-up of 25.7 ± 4.3 months (range 6–60). There was no significant difference in the length of time for follow-up between the two subgroups when expressed in either months or in person-years (2.9 ± 0.5 person-years in the group who progressed vs. 2.2 ± 0.4 person-years in the group without progression). Of note, the ethnic composition of the follow-up group of 25 women was similar to the original cohort: 15 (60%) were Caucasian, 8 (32%) were African-American, and 2 (8%) were Asian; none, however, were of Hispanic origin.

Follow-up of group with normal glucose tolerance at baseline. Of the 25 women in the follow-up group, 11 (44%) had normal glucose tolerance at their initial study. Of these 11, 5 (45%) maintained normal glucose tolerance at follow-up. Six (55%) women experienced a deterioration in glucose tolerance: five converted to IGT and one to NIDDM. Thus, the incidence rate for conversion to IGT or NIDDM from normal was 6 cases in 17.75 person-years of follow-up (i.e., 338 cases per 1,000 person-years of observation). Those whose glucose tolerance deteriorated were slightly more obese (BMI 44.6 ± 3.5 vs. 40.4 ± 4.4 kg/m^2), but were of similar age (27.0 ± 2.6 vs. 26.1 ± 4.1 years) to those with stable glucose tolerance. The presence of a family history of NIDDM was not more prevalent among those whose glucose tolerance deteriorated from normal.

Follow-up of group with IGT at baseline. The 14 women with IGT at baseline demonstrated the following at the time of their second OGTT: 3 (21%) reverted to normal glucose tolerance, 7 (50%) had persistent IGT, and 4 (29%) progressed to NIDDM. Thus, the incidence rate for conversion from IGT to NIDDM was 4 cases in 10.75 person-years of follow-up (i.e., 372 cases per 1,000 person-years of observation). Those who converted to NIDDM from IGT were significantly more obese at the time of the second OGTT when compared with those who did not progress (BMI 44.9 ± 2.3 vs. 36.2 ± 1.3 kg/m^2, $P = 0.005$). There was no significant age difference between those who did and those who did not progress (27.1 ± 1.8 vs. 26.9 ± 1.8 years). A family history of NIDDM was present in all 4 women who developed NIDDM compared with the 6 of 10 who maintained or improved their level of glucose tolerance, although this difference did not reach statistical significance.

Androgen levels

Women with glucose intolerance (IGT or NIDDM) had significantly higher levels of both total and free testosterone (Table 1). In addition, there was a statistically significant correlation between the area under the insulin curve during the baseline OGTT and the levels of total testosterone ($r = 0.36$, $P = 0.0002$) and free testosterone ($r = 0.35$, $P = 0.0006$).

CONCLUSIONS — NIDDM affects between 3 and 4% of the adult U.S. population, and ~625,000 new cases are diagnosed annually (2,3,19). Because NIDDM imposes extraordinary health and economic costs, strategies designed to prevent, or at least delay, its onset have recently received great attention (6,20). One approach has been to identify populations highly predisposed to NIDDM to allow intervention at a point prior to its development. Individuals with IGT are typically targeted for such interventions, since if left untreated, NIDDM will develop at an average rate of ~6% per year, with rates as high as almost 9%, particularly among ethnic minorities (20).

Prevalence and incidence data for glucose intolerance in PCOS derived from prior studies have had several limitations, including small sample size, the cross-sectional nature of their study design, and the possible introduction of selection bias, given that they were undertaken primarily to assess the nature of insulin resistance in PCOS. Finally, although one retrospective study (21) documents the risk of NIDDM over time, the natural history of glucose tolerance in PCOS has not been examined.

In this study, we have prospectively characterized oral glucose tolerance in the largest cohort of women with PCOS reported to date. Our objectives were to determine the prevalence of and contributing factors to the development of glucose intolerance in this disorder. Our findings confirm that obese women with PCOS seem to be at highest risk for development of glucose intolerance (7). However, our analysis indicates that additional factors, some of which may have a genetic basis, contribute to the pathogenesis of glucose intolerance in this disorder and hold the potential to stratify and predict NIDDM risk among an already predisposed population.

We have found that 35% of women with PCOS have IGT, while 10% are diabetic before reaching their 4th decade. This prevalence is substantially higher than expected when compared with age- and weight-matched populations of women without PCOS (2,3,20,22). Indeed, the prevalence of IGT in our cohort approximates that found in similarly aged Pima Indian women, who originate from a population with one of the highest prevalences of NIDDM in the world (20,22). Extrapolation of the present findings to the ~49 million reproductive-age women in the U.S. has significant public health implications. Assuming a prevalence of PCOS of 10% and a combined 45% prevalence for IGT and NIDDM, the number of women in this age-group with IGT or NIDDM associated with PCOS may exceed 2 million.

The prevalence of IGT and NIDDM is not affected by whether the criteria of the World Health Organization or American Diabetes Association were applied, since both rely on the 2-h glucose level during the OGTT (15,16). It is of interest to note, however, that a diagnosis of diabetes could be made in 6% and a diagnosis of impaired fasting glucose in 9% of the women with PCOS when the newly revised criteria of the American Diabetes Association, which use fasting glucose, are applied (16). In addition, use of the American Diabetes Association criteria would allow assignment of a diagnosis of diabetes to two additional women (compared with use of World Health Organization criteria) by virtue of a fasting plasma glucose >126 mg/dl.

What factors could account for this high prevalence of glucose intolerance in PCOS? Obesity, particularly upper-body obesity (23), is common among women with PCOS, and it is well-known that obesity increases the risk of NIDDM. The extent to which obesity impacts the risk of NIDDM in PCOS, however, has not been specifically examined. We have found that diabetic women with PCOS are significantly more obese than those with normal glucose tolerance (BMI 41.0 ± 2.4 vs. 33.4 ± 1.1 kg/m^2, $P < 0.01$). In addition, among the cohort of 25 women followed to the point of a second glucose tolerance test, the BMI of those

whose glucose tolerance deteriorated was significantly higher than that of the group whose glucose tolerance improved or remained stable (44.7 ± 2.1 vs. 37.7 ± 1.8 kg/m^2, $P < 0.02$). It is thus likely that obesity acts in concert with the intrinsic and apparently distinctive defects in insulin action in PCOS (24) to enhance the risk of NIDDM.

Another contributing factor to the glucose intolerance of PCOS relates to elevated androgen concentrations. It is well recognized that a dynamic interaction exists between hyperinsulinemia and hyperandrogenemia. Most evidence favors insulin resistance and the compensatory hyperinsulinemia as the predominant, perhaps primary, defect in PCOS (25,26). The hyperinsulinemia appears to synergize with pituitary gonadotropins to stimulate ovarian theca cell androgen production, which in turn, exacerbates the insulin resistance. Our finding that women with PCOS and either IGT or diabetes have significantly higher levels of both total and free testosterone when compared with those with normal glucose tolerance can be interpreted to indicate that hyperandrogenemia contributes to the development of glucose intolerance. Alternatively, because the androgen levels were highly correlated with the insulin concentrations during the OGTT, this finding may also be interpreted to indicate that hyperandrogenemia is merely a marker of insulin resistance without pathogenetic significance in the development of diabetes. Our data do not permit distinction between these two alternatives.

The high prevalence of glucose intolerance in PCOS cannot be accounted for by insulin resistance alone, however, since glucose intolerance should manifest only in the presence of coexisting defects in insulin secretion and insulin action (1). Indeed, it has been previously shown that alterations in insulin secretion (10,27,28) are demonstrable in PCOS and, further, that these alterations may have a genetic basis, since they are present more often in those women with PCOS who have a first-degree relative with NIDDM (10). The findings from the present study are consistent with a genetic basis for NIDDM in PCOS in that 83% of the diabetic women with PCOS had a first-degree relative with NIDDM, while NIDDM was present in only 31% of the first-degree relatives of the PCOS subjects with normal glucose tolerance ($P < 0.05$). However, whether there are heritable defects in insulin secretion, insulin action, or both, cannot be answered from the results of the present studies.

Our data also indicate that the conversion from IGT to NIDDM is accelerated, perhaps as much as 5- to 10-fold, in PCOS. Risk factors reported to accelerate the rate of conversion include higher levels of fasting or post-challenge glucose, family history of NIDDM, greater levels of obesity, lower stimulated insulin levels, and ethnicity. A recent analysis of six prospective studies examining predictors of progression from IGT to NIDDM found an overall NIDDM incidence rate of 57.2/1,000 person years with a range from 35.8/1,000 person years to 87.3/1,000 person years among Pima Indians (20). Thus, our finding of a conversion rate of 372 cases per 1,000 person-years of follow-up is of note. It must be pointed out, however, that the conversion rates in this cohort are based on relatively small numbers of women observed over modest periods of follow-up. In addition, conclusions drawn from our findings must be tempered by the limitations related to the inherent shortcomings in reproducibility of the OGTT, particularly among those with IGT (29). Nonetheless, these represent the only prospective data to date, and the incidence rates for NIDDM are likely to be substantially elevated in women with PCOS followed over even longer periods of time.

It has been previously reported that among women of Hispanic-Caribbean origin, ethnicity impacts on the risk of developing NIDDM in PCOS (30). However, we have found that the ethnic make-up in the groups with glucose intolerance (IGT and NIDDM combined) was virtually the same as that with normal glucose tolerance. In addition, the ethnic composition of the group of women whose glucose tolerance declined was similar to that of the group with stable or improved oral glucose tolerance.

It is important to emphasize that among those with IGT, i.e., the subgroup at highest risk for subsequent development of NIDDM, the fasting glucose concentration did not reliably predict the glucose concentration at 2 h, the time point used to assign the diagnosis. Thus, it would appear that to adequately define the at-risk population, oral glucose tolerance testing may be advisable in all PCOS women at the time of diagnosis and yearly thereafter.

Taken together, it appears that women with PCOS are an ideal population in which to develop and implement strategies for the prevention of NIDDM. These women are identifiable at an early age and those at highest risk for development of IGT and NIDDM can be targeted for intervention programs with the ultimate goal of reducing the enormous impact of NIDDM on quality and length of life. In addition, further characterization of genetic and environmental factors that contribute to the expression of glucose intolerance in PCOS may provide insights into the pathogenesis of NIDDM in this as well as other high-risk populations.

Acknowledgments — These studies were supported in part by grants DK-02315, DK-31842, DK-20595, HD-06308, and DK-07011-17, and by General Clinical Research Center grant MO1-RR00055.

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