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Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome

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BACKGROUND: Cross-sectional studies have shown a high frequency of impaired glucose tolerance (IGT) and non-insulin dependent diabetes mellitus (NIDDM) in women with polycystic ovarian syndrome (PCOS). However, little is known about the change in glucose tolerance that occurs over a period of several years in women with PCOS. METHODS: Sixty-seven women with PCOS received a 75 g glucose tolerance test and measurement of lipids at baseline and at follow-up after an average time of 6.2 years. All women followed prospectively had normal glucose tolerance ($n = 54$) or IGT ($n = 13$) at the start of the study. RESULTS: Change in glycaemic control from baseline was frequent, with 5/54 (9%) of normoglycaemic women at baseline developing IGT and a further 4/54 (8%) moving directly from normoglycaemic to NIDDM. For women with IGT at baseline, 7/13 (54%) had NIDDM at follow-up. Body mass index (BMI) at baseline was an independent significant predictor of adverse change in glycaemic control. CONCLUSIONS: Women with PCOS, particularly those with a high BMI, should be reviewed regularly with respect to IGT or NIDDM, as the frequency of impaired glycaemic control is high, and that the rate of conversion from normal glucose tolerance to IGT or NIDDM, or from IGT to NIDDM is substantial.

Key words: glucose tolerance/non-insulin-dependent diabetes mellitus/normoglycaemia/polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is a common clinical condition affecting ~6–10% of women and is characterized by a heterogenous clinical presentation including menstrual dysfunction, high androgen concentrations and ultrasound evidence of cysts within the ovary (Dunaif, 1994; Franks, 1995). Long-term complications include a significantly increased risk of endometrial cancer, hyperlipidemia, obesity and non-insulin dependent diabetes mellitus (NIDDM) (Dahlgren *et al.*, 1992; Norman and Clark, 1998). Gestational diabetes appears to be common, independent of maternal weight (Lesser and Garcia, 1997; Holte *et al.*, 1998; Paradisi *et al.*, 1998).

Cross-sectional studies of PCOS have indicated a relatively high frequency of impaired glucose tolerance (IGT) and NIDDM (Ehrmann *et al.*, 1999; Legro *et al.*, 1999). Ehrmann *et al.* recently documented that insulin secretory dysfunction in women with PCOS contributed significantly to the observed glucose intolerance with up to 40% of women demonstrating either IGT or NIDDM (Ehrmann *et al.*, 1999). Further, the onset of NIDDM in PCOS women occurs at an earlier age than in the general population, particularly when occurring in combination with obesity. Treatment for ovarian dysfunction has also been associated with NIDDM (Dunaif, 1995). Dahlgren *et al.* found a high prevalence of NIDDM in women who had a wedge resection of the ovary performed some years previously (Dahlgren *et al.*, 1992). In terms of final end points, Pierpoint *et al.* showed an increase in NIDDM on death certificates of women who had PCOS (Pierpoint *et al.*, 1998).

Despite these cross-sectional observations, the longitudinal study of change in glucose tolerance in women with PCOS is rare. For example, Ehrmann *et al.* followed 25 PCOS women over 25.7 months (range 6–60) and showed that of the 11 women with normal glucose tolerance, five (45%) remained normal and 6 (55%) converted to NIDDM or to IGT (Ehrmann *et al.*, 1999). It was also observed that those who became glucose intolerant tended to be more obese than those who did not change.

In summary, although the association of impaired glucose metabolism, resulting in IGT, and NIDDM, to obesity in PCOS women is well documented in cross-sectional studies, prospective long-term studies of glucose metabolism in large groups of subjects with PCOS are lacking. Information on the incidence of IGT and NIDDM would assist clinicians in the assessment and management of risk in women with PCOS, particularly where the condition exists in conjunction with obesity.

The aim of the present study was to establish the frequency of change of IGT and NIDDM over an average period of 6.2 years within a group of women with PCOS.

Materials and methods

Participants were women enrolled during 1991 in a study to investigate the metabolic sub-classification of PCOS (Norman *et al.*, 1995b). For the initial study, women were recruited from a clinical population presenting for routine care as part of clinical practice in reproductive endocrinology within the Queen Elizabeth Hospital, South Australia. Patients with PCOS were defined as those who showed an increased concentration of serum testosterone >2.5 nmol/l or elevated androstenedione, together with a low concentration of sex hormone binding globulin (SHBG) (normal range 20–100 nmol/l), in addition to characteristic ovarian morphology on ultrasound (defined as the presence of eight or more peripheral cysts <10 mm in diameter with increased stroma in one or both ovaries) (Adams *et al.*, 1986). PCOS was defined solely by ovarian morphology as described above. Consensus of two physicians was required for a positive diagnosis. Most subjects had abnormal menstrual function with cycling length <20 days or >35 days and none were smokers. All subjects were Caucasian in origin.

Subjects with PCOS ceased taking all hormone therapy for a month prior to measurements in the original study and were either in the follicular phase of their cycle or anovular, defined as an absence of LH surge. Women with a history of diabetes mellitus were excluded. Family history data of diabetes mellitus was not obtained at the initial interview.

Procedures at baseline

All subjects underwent an oral glucose tolerance test (GTT) using a standard 75 g glucose dose and lipid and other metabolic measurement studies were performed on the fasting specimen as described previously (Norman *et al.*, 1995a,b). NIDDM and IGT were defined according to the World Health Organization criteria (Alberti and Zimmet, 1998), viz. IGT being a glucose value at 2 h after 75 g glucose ingestion of between 7.8 and 11.0 mmol/l and NIDDM as ⩾11.1 mmol/l.

Follow-up study

All women from the original study with normal glucose tolerance or IGT in the initial study were contacted in 1997 (n = 148). Sixty-seven of the women with PCOS (54.9% of initial group) agreed to be re-examined and returned for a second glucose tolerance test using the same protocol, assays, and laboratory as the initial study. These methods have been described previously (Norman *et al.*, 1995b). Interassay variation within years during the period of follow up has always been <7%. The length of follow-up from the initial examination was normally distributed with an average follow up of 6.2 years (SD 1.2 years, range 4.0–8.6 years).

Hormone and lipid measurements

These have been fully described previously (Norman *et al.*, 1995b). In brief, glucose was measured by a glucose oxidase method. Cholesterol was measured by a cholesterol esterase-cholesterol oxidase method while triglyceride was measured by an enzymatic glycerokinase method. The apolipoproteins (A1 and B) were assayed nephelometrically. Testosterone and androstenedione were both measured using radioimmunoassay techniques while insulin was measured with an immunoradiometric assay.

Table I. Patient age, BMI and fasting glucose and insulin concentrations (mean ± SEM) in the initial study (before) and in the follow-up study (follow-up)

	Before	Follow-up
Age (years)	32.5 ± 0.8	38.9 ± 0.8
BMI (kg/m^2)	28.7 ± 0.9	30.6 ± 1.0
Fasting glucose (mmol/l)	4.45 ± 0.09	5.17 ± 0.16
Fasting insulin (mIU/l)	11.58 ± 0.65	8.07 ± 0.57

Table II. Change in glucose tolerance status over the follow-up period. Figures in parentheses are percentages

Original classification	Present classification		
	Normoglycaemic	IGT	NIDDM
Normal (n = 54)	45 (83)	5 (9)	4 (8)
IGT (n = 13)	2 (15)	4 (31)	7 (54)

Statistical analysis

Chi-square (χ^2) or Fisher's exact test was used to test the difference in proportions of IGT or NIDDM between examinations. Student's t-tests were used to assess the change in body mass index (BMI), weight and waist measurements over the follow-up period.

Results

The 67 women studied here were aged 38.9 ± 6.4 years (mean ± SD) after an average follow-up period of 6.2 ± 1.2 years (range 4.0–8.6), by which time a total of 13.4% (9/67) of subjects had IGT, and 16.4% (11/67) had NIDDM. The basic group characteristics at the previous and present study are shown in Table I.

We assessed the potential for bias by comparing baseline characteristics of participants and non-participants. There were no significant differences between participants and non-participants with regard to initial BMI (29.4 versus 28.5 kg/m^2, $P > 0.05$), fasting glucose (4.6 versus 4.5 mmol/l), 2 h glucose (6.0 mmol/l both), fasting insulin (12.3 versus 13.2 mIU/l) and 2 h insulin (73.4 versus 76.6 mIU/l) concentrations, though differences in the extent of the possible symptoms associated with PCOS/PCO could not be assessed.

Table II shows the frequency of change in glycaemic status of women from a baseline. Of women who were normoglycaemic at baseline, 9% had developed IGT (n = 5) and 8% developed NIDDM (n = 4), at an annualized incidence rate of 2.2%. Of those with IGT at baseline, 54% converted to NIDDM at follow-up. This represents an annualized incidence rate of 8.7%. Some 15% of those with IGT at baseline obtained a normal GT measurement at follow-up, and 31% remained in the same category as baseline.

Table III shows mean BMI, weight and waist measurement at baseline and follow-up for those with stable normoglycaemia compared with those who had an adverse change in status from normal to IGT or NIDDM, or from IGT to NIDDM.

In the group converting to IGT or NIDDM, there was

Table III. Changes in body size over the observation period (mean ± SEM)

	BMI (kg/m^2)		Weight (kg)		Waist (cm)	
	Before	Follow-up	Before	Follow-up	Before	Follow-up
Normoglycaemic throughout (n = 45)	27.0 ± 1.1	28.3 ± 1.2	72.2 ± 3.2	75.2 ± 3.4	82.0 ± 3.1	86.5 ± 2.5
Significance	NS		NS		NS	
Normoglycaemic to IGT or NIDDM (n = 9)	35.9 ± 1.1	41.0 ± 1.1	94.2 ± 4.0	107.4 ± 4.0	102.6 ± 2.3	114.5 ± 1.7
Significance	$P < 0.01$		$P < 0.05$		$P < 0.001$	

Table IV. The relative risk (RR) of converting to IGT/NIDDM by BMI over the follow-up period

BMI (kg/m^2)	RR and 95% CI
<25 (reference group)	1
25–30	7.1 (3.3–11.0)
>30	10.2 (3.9–16.5)

significantly greater BMI, weight, waist circumference and waist:hip ratio gain (data not shown) compared with those who remained normoglycaemic.

Table IV shows the relative risks of change from normoglycaemic to IGT or NIDDM by BMI category. Obese PCOS women (BMI > 30 kg/m^2) had a tenfold increase in their risk of developing IGT or NIDDM compared with women with BMI < 25 kg/m^2 ($P < 0.01$). For women with BMI of 25–30 kg/m^2, the 7-fold relative risk was still very substantial ($P < 0.01$).

Discussion

This study reports a high frequency IGT and NIDDM among women with PCOS and a high rate of adverse change in glucose metabolism over an average period of 6.2 years, which was reflected in an overall conversion rate to NIDDM of 2.6% per annum. The conversion rate to NIDDM was particularly high for those women with IGT at baseline (8.7% per annum). As a consequence, a total of 54% of women with IGT at baseline had developed NIDDM at follow-up. The overall rate of conversion to NIDDM observed in this study was lower than that reported by Ehrmann *et al.* (Ehrmann *et al.*, 1999), but their study suffered high loss to follow-up, included heavier women, and included a relatively high proportion of women with IGT at the start of the study (56%) which is consistent with a higher subsequent conversion rate from IGT to clinical diabetes. A small percentage of women in our study had a reversal from IGT to normal glucose tolerance, which may have been due to either improved glucose disposal due to a factor such as exercise or weight loss, minor measurement variation around the cut-off for IGT, or misclassification.

It would be valuable to compare the rates obtained in this study with population estimates for women in a comparable age group, but as yet there are no reliable published population estimates of prevalence or incidence of IGT or NIDDM for the Australian population, although estimates for women aged 35–44 years from a representative national survey are likely to yield prevalence estimates of 6% for IGT and 2% for clinical diabetes (P.Zimmet, personal communication). A further indication of the relative magnitude of the IGT and NIDDM reported here can be made by comparing our results with those of a large screening survey of patients aged >40 years and identified at elevated risk of NIDDM by general practitioners in Western Australia on the basis of a questionnaire (Welborn *et al.*, 1997). Patients with elevated risk were given an oral glucose tolerance test. Among the 50 859 high risk patients completing the study, 2.0% were newly diagnosed with diabetes, 3.4% had IGT, and 10.8% had previously diagnosed diabetes. These estimates emphasize the high rates of IGT (13.4%) and NIDDM (16.4%) observed in the present study, particularly as the present study precluded from follow-up, patients with NIDDM at baseline, and the observed changes in the present study were achieved over a relatively short period of 6.2 years.

This study also confirmed that obesity is a strong predictor of deteriorating glucose metabolism. Obese PCOS women had a 10-fold increase in their risk of suffering from IGT or NIDDM compared with normal weight (BMI <25 kg/m^2) PCOS women. Even those moderately obese PCOS women (BMI 25–30 kg/m^2) still had an approximately 7-fold increase.

The capacity to generalize the results of the present study was limited by the number of women studied, and the use of a sample drawn from a patient population. Nevertheless, the rate of change in glucose tolerance observed here is important for presenting a clear image of the population of patients presenting routinely and repeatedly for care in an infertility clinic. Despite non-significant differences in baseline characteristics between participants and non-participants, it is possible that the rates of change observed in this study are elevated to some extent by participation bias, as those women with an emergent disorder of glucose metabolism may have been more willing to participate in the follow-up study.

It is concluded that women with PCOS presenting for infertility care have a high frequency of hyperinsulinaemia and NIDDM, which is associated with a high concomitant incidence of deterioration in glycaemic control over 6 years. Routine assessment of glucose tolerance should occur in women with PCOS, particularly those with a high BMI.

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