Glucose tolerance abnormalities in Australian women with polycystic ovary syndrome

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ABSTRACT

Objectives: To determine the prevalence of glucose tolerance abnormalities and to identify associated risk factors in women with polycystic ovary syndrome (PCOS) attending a reproductive endocrinology clinic.

Design: Retrospective chart review.

Participants and setting: 372 women with confirmed PCOS attending a reproductive endocrinology clinic at Adelaide University's Research Centre for Reproductive Health.

Main outcome measures: Prevalence of glucose tolerance abnormalities and association of such abnormalities with potential risk factors.

Results: 4.0% (15 women) had diabetes mellitus, 15.6% (58) had impaired glucose tolerance and 80.4% (299) had normal glucose tolerance. There was a significant trend towards increasing prevalence of diabetes with increasing age (odds ratio [OR], 0.60; $P = 0.0085$). The prevalence of abnormal glucose tolerance (diabetes and impaired glucose tolerance together) was significantly higher with higher waist circumference (OR, 2.9; $P = 0.05$), higher body mass index (OR, 8.02; $P = 0.0253$), a family history of diabetes (OR, 1.56; $P = 0.0192$) and the presence of metabolic syndrome (OR, 5.62; $P < 0.001$).

Conclusion: The prevalence of diabetes and impaired glucose tolerance is high in women with PCOS, especially in older women and those with abdominal obesity and a family history of diabetes.

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Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in women.[1-4] Its clinical presentation is heterogeneous, and commonly includes menstrual irregularities, infertility, hirsutism, and acne. Metabolic syndrome and its components are more common in women with PCOS compared with age-matched controls.[5]

Women with PCOS have peripheral insulin resistance independent of body mass index (BMI), fat-free mass and fat distribution, with up to 60% of lean women with PCOS showing fasting hyperinsulinaemia.[6-9] Most women with PCOS compensate fully for their insulin resistance, but a substantial proportion, especially those with first-degree relatives with type 2 diabetes, have decreased β-cell response to meals, or rising glucose levels.[10,11] Insulin resistance combined with β-cell dysfunction results in an increased prevalence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM) in these women.[12,13]

Previous studies in the United States have shown that women with PCOS have a higher prevalence of diabetes (8%–12%) and impaired glucose tolerance (30%–35%) than normal women of the same age.[12,13] In contrast, the prevalence of diabetes is lower in Mediterranean regions, with an Italian study reporting prevalences of 15.5% for impaired glucose tolerance and 2.5% for diabetes in women with PCOS.[14] In a Dutch follow-up study in a relatively lean population of women with PCOS, the prevalence of diabetes was increased compared with the general female population, especially in women aged 45–54 years.[15]

There is a paucity of published data on the prevalence of glucose intolerance in women with PCOS in Australia. Here, we report a retrospective data analysis on a large cohort of women with PCOS attending a reproductive endocrinology clinic at our centre. Our aims were to determine the prevalence of glucose tolerance abnormalities and to identify associated risk factors.

METHODS

Case records of 660 women presumed to have PCOS because of a history of chronic anovulation or infertility or oligomenorrhoea or features of hyperandrogenism were reviewed. These women were attending reproductive endocrine clinics for treatment of infertility or features of PCOS. PCOS was confirmed in 372 women based on the presence of two of the following three features:

- chronic anovulation, oligomenorrhoea or menstrual irregularities;
- clinical or biochemical evidence of hyperandrogenism; and
- presence of polycystic ovaries on ultrasound in the absence of other disorders such as hypothyroidism, Cushing's syndrome, hyperprolactinaemia or ovarian and adrenal causes of hyperandrogenism.

These features are known as the Rotterdam 2003 criteria.[16] Inclusion criteria were a previously normal result on an oral glucose tolerance test (OGTT), being contactable by phone and willingness to participate. Exclusion criteria were no previous OGTT and unwillingness to participate.

Information about: age; menarche; menstrual cycles; presence or absence of hirsutism; acne; family history of diabetes and PCOS; anthropometric measurements of weight, height, waist circumference and blood pressure; blood levels of various hormones; and OGTT results with insulin and lipid profile were collected from case notes. Normal glucose tolerance (NGT), DM and IGT were defined according to the criteria proposed by the World Health Organization.[17] Impaired fasting glycaemia (IFG) was defined by the recommendations of the expert committee of the American Diabetes Association.[18] The presence of metabolic syndrome was defined according to guidelines of the Third Report of the National Cholesterol Education Program Expert Panel.[19] A family history of diabetes was considered positive if any first-degree relative (parent or sibling) had a history of DM. Body mass index (BMI) was calculated by the formula: weight in kilograms/(height in metres)^2. A BMI of 18–25 was considered normal, 25.01–30 overweight and > 30.01 obese. Measures of insulin resistance were derived through homeostatic model assessment for insulin resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index 1 (QUICKI1).[20]

Glucose was measured by the glucose oxidase method, and other hormone levels were measured by previously described methods.[21] Testosterone was measured by radioimmunoassay (RIA) kits (Farmos Diagnostica, Turku, Finland). Insulin was meas-

1 Clinical and biochemical parameters of 372 women with polycystic ovary syndrome

Parameter	Diabetes mellitus	Impaired glucose tolerance	Normal glucose tolerance	P*
No. of women	15	58	299	
Age (years)†	35.7 ±6.5	30.7 ±4.8	29.9 ±5.5	0.003
Family history of diabetes	62% (8/13)	28% (16/47)		0.014
Weight (kg)†	103.1 ±23.7	101.8 ±21.6	92.0 ±20.6	0.051
BMI (kg/m^2)†	38.3 ±8.2	37.9 ±7.5	35.14 ±7.60	0.047
Waist (cm)†	122.8 ±10.5	109.1 ±16.5	98.9 ±15.3	0.001
Testosterone (nmol/L)†	3.0 ±1.7	3.6 ±2.5	3.2 ±2.8	ns
Sex hormone binding globulin (nmol/L)†	16.1 ±15.2	19.7 ±18.7	27.6 ±28.9	ns
Fasting insulin (mIU/L)†	33.2 ±15.8	22.3 ±11.4	15.8 ±12.2	0.001
2-hour postload insulin (mIU/L)†	132.2 ±89.5	171.9 ±85.7	80.1 ±60.7	0.001
Fasting glucose to insulin ratio†	0.36 ±0.26	0.37 ±0.29	0.44 ±.26	0.001
HOMA-IR†‡ (ratio)	12.3 ±4.1	5.2 ±2.9	3.4 ±2.9	0.001
QUICKI1†‡ (ratio)	0.41 ±0.02	0.52 ±0.17	0.58 ±0.10	0.001

* One-way analysis of variance. † Values are mean ±SD. ‡ Measure of insulin resistance.
BMI = body mass index. ns = not significant. HOMA-IR = homeostatic model assessment for insulin resistance. QUICKI1 = Quantitative Insulin Sensitivity Check Index 1. ◆

ured by RIA kits from Pharmacia (Sydney, NSW, Australia), and had a cross-reactivity with proinsulin of about 20%. Intra-assay and inter-assay coefficients of variation were 7% and 10%, respectively, for both testosterone and insulin.

Ethical approval was received from the Human Research Ethics Committee of the Women's and Children's Hospital, Adelaide.

Statistical analysis

All data are expressed as mean ±SD and frequencies (%). Categorical data were analysed with the χ^2 test, while analysis of variance or Student's *t* test were used to analyse the difference between groups in continuous variables. A two-tailed *P* value of <0.05 was considered statistically significant. SPSS software, version 13 (SPSS Inc, Chicago, Ill, USA) was used for statistical analysis.

RESULTS

The mean age of the 372 women with PCOS was 30.3 ±5.6 years (median, 30.4 years; range; 15–62 years), and their mean BMI was 35.1 ±8.0 kg/m^2. With the exception of one woman, all of the 73 women with either diabetes or IGT were overweight or obese compared with 84% of the 299 women with NGT. Forty-four per cent of all 372 women had a family history of diabetes. The prevalences of oligomenorrhoea, hirsutism and acne were 75%, 65% and 40%, respectively.

According to WHO criteria based on a 2-hour postload glucose measurement during an OGTT,[17] of the 372 women with PCOS, 4.0% (15) had DM, 15.6% (58) had IGT, and 80.4% (299) had NGT. When fasting glucose levels were analysed according to the recommendations of the American Diabetes Association,[18] 2.7% (10) had DM, 3.0% (11) had IFG and 94.6% (352) had normal fasting glucose levels. The clinical and biochemical features of the women grouped according to their OGTT results are summarised in Box 1.

Women who had diabetes were significantly older (*P* = 0.003) than those who had IGT or normal glucose tolerance (Box 1). There was no difference between the three groups in weight and BMI, but women with diabetes or IGT had predominantly abdominal obesity and a significantly higher waist circumference (*P* = 0.001) than those in the NGT group. There was no difference between groups with respect to age of menarche, frequency of menstrual irregularities, acne and hirsutism.

As expected, the DM and IGT groups had significantly higher fasting insulin levels than the NGT group (*P* < 0.0001). Women with diabetes and IGT had marked insulin resistance as shown by the higher HOMA-IR (*P* < 0.0001) and lower QUICKI1 (*P* < 0.0001) values compared with the NGT group (Box 1). In the NGT group, obese patients had significantly higher fasting and 2-hour glucose levels (*P* < 0.001), and they were insulin resistant compared with normal-weight patients. Lipid profiles were comparable in the three groups.

Box 2 shows the prevalence of glucose tolerance abnormalities by age range for the three groups. There was a significant trend of an increasing prevalence of DM with increasing age (*P* = 0.0085).

Box 3 examines the prevalence of abnormal glucose tolerance in relation to age, BMI, waist circumference, family history of diabetes and metabolic syndrome. The prevalence of abnormal glucose tolerance (DM and IGT together) was higher with higher waist circumference (*P* = 0.05) and increased BMI (*P* = 0.0253). A higher prevalence of DM was seen in women with a family history of diabetes (*P* = 0.0192) and in those with metabolic syndrome (*P* < 0.001). When multiple logistic regression was applied using all these factors, only the presence of metabolic syndrome was independently

2 Prevalence of glucose intolerance by age of women with polycystic ovary syndrome

Age (years)	Total number	Diabetes mellitus	Impaired glucose tolerance	Normal glucose tolerance
14–20	16	0	6.3% (1)	93.8% (15)
> 20–25	45	2.2% (1)	11.1% (5)	86.7% (39)
> 25–30	118	1.7% (2)	15.3% (18)	83.1% (98)
> 30–35	127	3.9% (5)	19.7% (25)	76.4% (97)
> 35–40	48	4.2% (2)	16.7% (8)	79.2% (38)
> 40–45	12	25.0% (3)	8.3% (1)	66.7% (8)
> 45–50	2	50.0% (1)	0	50.0% (1)
> 50	1	0	0	100% (1)

3 Prevalence of abnormal oral glucose tolerance test outcome by potential demographic risk factors in women with polycystic ovary syndrome

Variables	Total number	Abnormal glucose tolerance*	Normal glucose tolerance	OR (95% CI)
Age (years)				
< 30	181	28	153	0.60 (0.35–1.03)
⩾ 30	188	44	144	
Waist (cm)				
> 88	195	40	155	2.90 (0.99–8.56)
⩽ 88	49	4	45	
BMI (kg/m^2)				
< 25	36	2	34	8.02 (1.87–34.38)
⩾ 25	219	67	142	
Family history of diabetes				
Yes	91	24	67	1.56 (0.86–2.80)
No	192	36	156	
Metabolic syndrome				
Yes	100	36	64	5.62 (2.73–11.56)
No	132	12	120	

*Diabetes mellitus and impaired glucose tolerance groups.
OR = odds ratio. BMI = body mass index. ◆

associated with an increase in glucose tolerance abnormality (odds ratio, 2.213; 95% CI, 1.061–4.617).

DISCUSSION

To our knowledge, this is the first study to describe the range of glucose abnormalities in an Australian population of women with PCOS defined by the Rotterdam criteria. The prevalence of DM in our study was 4.0% and that of IGT was 15.6%, both of which are higher than the prevalences of these conditions in the general population of Australian women of similar age.[22] We have previously reported a high rate of conversion to glucose intolerance or DM in a similar cohort.[23] The high prevalences of IGT and DM in this population are probably the consequence of insulin resistance coupled with obesity. These prevalences are comparable to those reported in Italian women with PCOS, but are lower than those reported in women with PCOS in the US and Asia.[12-14,24] This discrepancy could be the result of differences in the study populations or in the diagnostic criteria used to define PCOS; another possible reason for the discrepancy with the US study is the prevalence of obesity, which is much higher in the American population. It has been shown that women with PCOS from South Asia have higher fasting insulin concentrations and lower insulin sensitivity than white women.[25] Much harder to define and probably equally influential are the effects of genetic, environmental and lifestyle factors on the manifestation of the clinical features, including insulin levels, in women with PCOS.[14]

The above findings were based on 2-hour postload OGTT results. If we base them on fasting glucose levels, as recommended by the American Diabetes Association, five women diagnosed to have diabetes by OGTT would have been missed. Similarly, in an Australian study based on fasting glucose levels, diabetes was diagnosed in 1.8% of participants.[26] This is substantially lower than the rate of 2.9% based on 2-hour postload glucose criteria alone, and than the rate of 3.7% based on both the values, as recommended by the WHO.[26] Thus, 2-hour postload OGTT may be required in populations at higher risk of diabetes, like women with PCOS or certain ethnic groups.

Women with PCOS with obesity and glucose intolerance are characteristically more insulin resistant and have more hyperandrogenism. It has been reported that there is a higher frequency of oligomenorrhoea or hirsutism in women with IGT.[14] However, we found that frequencies of oligomenorrhoea, hirsutism and acne and mean androgen levels were comparable in all groups irrespective of OGTT results, and were higher than those reported from Italy. This probably reflects a high proportion of infertile patients in our study group.

We also identified demographic risk factors for developing DM or IGT in our cohort. Women with DM were significantly older than those with IGT and NGT, similar to earlier reports.[12,14] The significant trend of increasing prevalence of DM with increasing age concurs with the findings of previous studies.[27] Obesity, particularly abdominal obesity, increases the risk of DM. Women with DM and IGT had a significantly higher waist circumference than women in the NGT group. The prevalence of abnormal glucose tolerance (DM and IGT together) was significantly higher among women with a waist circumference over 88 cm. A family history of diabetes is an important risk factor for glucose tolerance abnormalities, and the prevalence of DM was significantly higher in such women in our cohort. It has previously been reported that women with PCOS and DM had a 2.6-fold higher prevalence of a family history of DM.[12] Insulin resistance and hyperinsulinaemia not only increase the risk of DM, but are also correlated with an increased risk of cardiovascular disease and are a main pathogenic mechanism of metabolic syndrome. The prevalence of DM was significantly higher in women who had features of metabolic syndrome.

The strengths of our study include its having the largest cohort of women with PCOS reported worldwide, that the diagnosis of PCOS was based on the newly established Rotterdam 2003 criteria,[16] and that OGTT was prospectively carried out. Its major limitations are its retrospective data collection (resulting in some missing measurements), and that patients were recruited from an infertility clinic, so there could be a selective bias to a particular type of PCOS.

To conclude, our study shows that the prevalence of glucose intolerance abnormalities is high in women with PCOS, especially in older women and those with abdominal obesity and a family history of diabetes. It is recommended that all women with PCOS have a 2-hour postload OGTT and lipid profile testing at diagnosis. Regular follow-up can be useful in both long-term clinical management and encouraging patient lifestyle modification.

COMPETING INTERESTS

None identified.

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