

Prevalence of insulin resistance and determination of risk factors for glucose intolerance in polycystic ovary syndrome: a cross-sectional study of Chinese infertility patients

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Objective: To determine the prevalence of abnormalities in glucose metabolism in patients with polycystic ovary syndrome (PCOS) and control infertility patients in Taiwan, and to determine the predictive risk factors for PCOS.

Design: Cross-sectional study.

Setting: Infertility Center, Taiwan Adventist Hospital.

Patient(s): Three hundred fifty-six patients with PCOS and 974 control infertility patients.

Intervention(s): None.

Main Outcomes Measure(s): Hormone assay and 75-g oral glucose tolerance test.

Result(s): Patients with PCOS were younger (32.7 vs. 35.3 years) with a higher body mass index (BMI) (22.4 vs. 20.6 kg/m²) than controls. Even after BMI adjustment, patients with PCOS still had significantly higher fasting glucose (97.2 vs. 94.4 mg/dL), fasting insulin (5.6 vs. 4.1 μ IU/mL), 2-hour glucose (108.1 vs. 96.0 mg/dL), and 2-hour insulin levels (38.0 vs. 27.0 μ IU/mL), and higher homeostasis model assessment of insulin resistance (HOMA-IR) values (1.3 vs. 1.0) than control patients. The prevalence of impaired glucose tolerance and diabetes mellitus in patients with PCOS was 7.6% and 3.1%, respectively, compared with 2.9% and 0.2% in the control group, respectively. Only fasting glucose and insulin, 2-hour insulin, HOMA-IR, age, androstenedione, and status (PCOS vs. control) had a significant impact on 2-hour glucose level. However, BMI and waist/hip ratio did not show a significant impact on 2-hour glucose level.

Conclusion(s): Chinese women with PCOS are at increased risk for insulin resistance and glucose intolerance compared with controls. Body mass index failed to show significant impact on 2-hour glucose levels in our infertility patients. (Fertil Steril® 2009;91:1864–8. ©2009 by American Society for Reproductive Medicine.)

Key Words: Chinese infertility patients, insulin resistance, glucose intolerance, risk factors, OGTT

Polycystic ovary syndrome (PCOS) is probably the most prevalent endocrine disorder in women and the most common cause of anovulatory infertility today. Hyperinsulinemia in conjunction with hyperandrogenism was reported in 1980, and subsequently the presence of insulin resistance in women with PCOS has been well documented in multiple studies (1–5).

According to the “thrifty gene” hypothesis, some ethnic groups may be more predisposed to insulin resistance (6–8). The extent to which racial background modulates this risk in PCOS has not been determined. The Chinese population comprises more than one fifth of the total world population (World Health Organization [WHO] report,

2004); however, few studies of the metabolic status of Chinese women with PCOS have been performed (9, 10).

Polycystic ovary syndrome has varied onset and clinical presentation. Asian women display stigmata of insulin resistance at a lower body mass index (BMI) than other populations (6–10). Hence, we designed a cross-sectional study to provide an overview of the Chinese population at a single period and to determine the prevalence of glucose intolerance in Chinese patients with PCOS compared with other infertility patients. We also evaluated the risk factors associated with PCOS (11).

MATERIALS AND METHODS

Subjects

From 2004 to 2006, 1330 patients who attended the Infertility Center of Taiwan Adventist Hospital were enrolled in this study. This study was approved by and conducted in accordance with the guidelines of the Taiwan Adventist Hospital Investigational Review Board, and all patients provided written informed consent.

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The age range of the study subjects was 19–44 years. Etiologies of infertility in our patients were ovulation dysfunction (including patients with PCOS) 37.7%, male factor 9.5%, endometriosis 9.0%, tubal factor 1.4%, poor ovarian function 0.6%, multiple factors 15.0%, and unexplained cause 26.7%.

A total of 356 patients with PCOS served as the study group, and the remaining 974 infertility patients constituted the control group. The diagnosis of PCOS was made according to the presence of chronic anovulation associated with clinical or biochemical hyperandrogenism. Patients with prediagnosed diabetes mellitus (DM), nonclassical adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were all excluded from this study (12–15).

Protocol

A standard medical history form was completed that included menstrual history, BMI, blood pressure, and waist/hip ratio (16–22). An overnight fasting blood sample was obtained between 8 and 10 AM during the first 3 days of the menstrual cycle for hormone assays that included FSH, LH, E₂, PRL, T, and androstenedione (A) (20–22). A 75-g oral glucose tolerance test (OGTT) was also performed with blood samples taken 0 and 2 hours after the glucose load (12–16, 18, 19). Patients were classified as normal glucose tolerance (NGT; 0-hour glucose <110 mg/dL and 2-hour glucose <140 mg/dL), impaired fasting glucose (IFG; 0-hour glucose 110–125 mg/dL), impaired glucose tolerance (IGT; 2-hour glucose 140–199 mg/dL), and type 2 DM (0-hour glucose ≥126 mg/dL, 2-hour glucose ≥200 mg/dL; according to the WHO 2005 guideline) (19, 20).

Assays

Plasma glucose levels were determined by the glucose oxidase technique and were analyzed 30 minutes after blood

was drawn. Serum insulin and A samples were stored at –20°C and –80°C, respectively, and analyzed within 7 days by RIA (Diagnostic Products Corporation, Los Angeles, CA). Samples for FSH, LH, T, prolactin, and E₂ levels were analyzed on the day of blood sampling by RIA (Diagnostic System Laboratories, Webster, TX). The intra- and interassay coefficients of variation were 3.5% and 5.6% for glucose, 2.5% and 7.1% for FSH, 6.5% and 7.4% for LH, 7.5% and 8.5% for T, 3.7% and 5.4% for A, 2.6% and 5.4% for PRL, 1.65% and 2.87% for E₂, and 8.7% and 9.4% for insulin.

Statistical Analysis

The differences in prevalence of glucose intolerance between patients with PCOS and control infertility patients and between infertility patients and the general population (data as provided by the Bureau of Health Promotion 2002 Taiwan health census) were compared using the WHO criteria.

Categorical data were analyzed using χ^2 , odds ratio (OR), and 95% confidence intervals (CI). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [glucose (mg/dL) × 0.05551 × insulin (μ IU/mL)]/22.5. Age, BMI, waist/hip ratio, A level, T level, fasting and 2-hour glucose level, fasting and 2-hour insulin level, and HOMA-IR were compared between the PCOS and control groups by analysis of variance and Student's *t*-test and are reported as the mean ± 1 SD (12). Testosterone level, fasting insulin level, and HOMA-IR were log-transformed before statistical analysis to ensure normality of distribution (21, 22). After adjusting for the effects of BMI, all data were compared again between the PCOS and control groups (Table 1) (23). A *P* value of ≤ .05 was considered statistically significant.

The trend test was used to assess the prevalence of glucose intolerance by BMI and age in all infertility patients (Table 2) (12). Multiple regressions were performed to determine which variables predicted postchallenge 2-hour

TABLE 1

Demographic characteristics of control and PCOS groups.

| Parameter | Control (n = 974) | PCOS (n = 356) | <i>P</i> | <i>P</i> after BMI adjustment |
|---|-------------------|----------------|----------|-------------------------------|
| Age (y) | 35.3 ± 3.7 | 32.7 ± 4.4 | <.001 | <.001 |
| BMI (kg/m ²) | 20.6 ± 2.4 | 22.4 ± 4.2 | <.001 | — |
| Waist/hip ratio (cm) | 0.7 ± 0.04 | 0.8 ± 0.05 | <.001 | <.077 |
| A (ng/mL) | 1.6 ± 0.9 | 2.0 ± 1.5 | <.001 | <.001 |
| Fasting glucose (mg/dL) | 94.4 ± 6.8 | 97.2 ± 14.9 | <.001 | <.011 |
| 2-h glucose (mg/dL) | 96.0 ± 19.7 | 108.1 ± 40.5 | <.001 | <.001 |
| 2-h insulin (μ IU/mL) | 27.0 ± 22.1 | 38.0 ± 32.2 | <.001 | <.001 |
| T (ng/mL) ^a | 0.3 (1.7) | 0.4 (1.8) | <.001 | <.001 |
| Fasting insulin (μ IU/mL) ^a | 4.1 (2.8) | 5.6 (2.9) | <.001 | <.038 |
| HOMA-IR ^a | 1.0 (2.7) | 1.3 (3.0) | <.001 | <.035 |

^a Transformed to log (variable) and tested by *t*-test geometric mean (GSD).

Wei. Glucose tolerance in Chinese PCOS patients. *Fertil Steril* 2009.

glucose value (12). The candidate predictive variables as listed in Table 1 were fasting glucose level, age, fasting and 2-hour insulin level, HOMA-IR, status (PCOS vs. control), BMI, waist/hip ratio, and A and T levels (Table 3). Data analysis was carried out using Statistical Package for the Social Sciences 11.0 (SPSS, Chicago, IL) and Excel (Microsoft, Redmond, WA).

RESULTS

Clinical and Biochemical Characteristics

Patients with PCOS were younger (32.7 vs. 35.4 years) and heavier than the control group, with an increased BMI (22.4 kg/m² vs. 20.6 kg/m²) and waist/hip ratio (0.8 vs. 0.7; $P < .001$) compared with the control group. The T, A, and glucose parameters, including fasting and 2-hour glucose levels, fasting and 2-hour insulin levels, and HOMA-IR, were also higher in the PCOS group than in the control infertility patients. Even after adjustment for BMI, all the glucose parameters still showed significant statistical differences between the two groups (Table 1).

Prevalence of Glucose Intolerance

Of 356 patients with PCOS, 38 had glucose intolerance (IGT 7.6%; DM 3.1%) compared with 28 of 974 control patients (IGT 2.9%; DM 0.2%; $\chi^2 = 29.41$; OR = 4.04 [95% CI 2.4–6.7]). The prevalence rate of IFG was also higher in the infertility patients than in the general population (2.3% vs. 1.1%; $\chi^2 = 12.25$; $P < .05$; data not shown).

Of 356 patients with PCOS, 98 (27.5%) were overweight (BMI ≥ 24) and 12.6% were obese (BMI > 27), whereas 8.9% of control infertility patients were overweight and 2.6% were obese. Of 43 patients with PCOS with abnormal

glucose tolerance (including IFG cases), 24 (55.8%) were overweight. In contrast to the PCOS group, only 30.4% of the control infertility patients (14 of 46) with abnormal glucose tolerance were overweight. Although our patient population was relatively lean, the prevalence of glucose intolerance still increased significantly with an increase in BMI (by the stratified trend test, $P < .0001$; Table 2). But the prevalence of glucose intolerance did not show an increase with increasing age (by the stratified trend test, $P = .564$; Table 2). The youngest infertility patient diagnosed with DM using the OGTT was only 24 years of age, and the youngest patient with IGT was 26 years old; both had PCOS.

Comparison of Glucose Intolerance Diagnostic Criteria

There were 13 newly diagnosed patients with type 2 DM (using the OGTT) in our total patients based on WHO criteria (23, 24). Using the fasting glucose screening test alone, 5 patients would have been undiagnosed ($\chi^2 = 3.47$; $P > .05$). There were 53 patients with IGT, but only 7 had concomitant IFG, and 46 patients would have been undiagnosed using only the fasting glucose screening test. There were 30 patients with IFG, and 7 had combined IGT. Comparing the oral glucose challenge test and fasting glucose screening, the 75-g OGTT detected more patients with glucose intolerance than the routine fasting glucose screening test ($\chi^2 = 14.04$; $P < .05$).

Impact Factors for Glucose Intolerance

All 1330 patients were analyzed with multiple regression models using the variables in Table 1. Fasting glucose and insulin levels, 2-hour insulin level, A level, HOMA-IR, age, and status (PCOS vs. control) had significant impact on 2-hour glucose level ($P < .001$ for fasting glucose level, fasting insulin level, 2-hour insulin level, and HOMA-IR; $P = .003$ for age and A level; $P = .007$ for PCOS status; Table 3). But BMI, waist/hip ratio, and T level failed to show statistical significance ($P = .403$ for BMI; $P = .056$ for waist/hip ratio; $P = .457$ for T level; Table 3). The model (r^2) accounts for 53.9% of the total variation.

DISCUSSION

The prevalence of glucose intolerance in patients with PCOS was higher than in the control infertility patients. The prevalence of IFG was also higher in the infertility patients than in the general population (data derived from the Bureau of Health Promotion 2002 Taiwan health census; 2.3% vs. 1.1%; $\chi^2 = 12.25$; $P < .05$; Table 2). However, the prevalence of glucose intolerance in our patients was much lower when compared with their white counterparts (12, 25, 26). It was also much lower compared with other Asian countries (e.g., in South Asia, China, and Korea), but their studies were comparatively few in number, with small numbers of subjects (10, 31), or immigrants in Western countries were involved in the studies (12, 29, 32).

Average BMI in our patients with PCOS was within the normal range (22.42 kg/m²), and only 12.6% were obese. Most studies show that average patients with PCOS have a BMI > 30 kg/m² (12, 24–30). Most studies also failed to

TABLE 2

Prevalence of glucose intolerance as a function of BMI and age in infertility patients.

| Parameter | n | NGT | IGT | Type 2 DM |
|-------------------------------|-----|------------|-----------|-----------|
| BMI (kg/m²) | | | | |
| <18.5 | 202 | 96.0 (194) | 3.5 (7) | 0.5 (1) |
| 18.5 to <24 | 944 | 95.4 (901) | 4.3 (41) | 0.2 (2) |
| 24 to <27 | 114 | 86.0 (98) | 11.4 (13) | 2.6 (3) |
| ≥ 27 | 70 | 68.6 (48) | 21.4 (15) | 10.0 (7) |
| Age (y) | | | | |
| <25 | 12 | 91.7 (11) | 0 | 8.3 (1) |
| 25–29 | 115 | 91.3 (105) | 7.8 (9) | 0.9 (1) |
| 30–34 | 526 | 93.2 (490) | 6.1 (32) | 0.8 (4) |
| 35–39 | 529 | 94.1 (498) | 4.7 (25) | 1.1 (6) |
| 40–44 | 148 | 92.6 (137) | 6.8 (10) | 0.7 (1) |

Note: Values in the columns are in percentages (number of patients).

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TABLE 3

Impact of variables associated with the 2-h postchallenge glucose value from a multiple linear regression model in infertility patients.

| Factor | Unit change | Effect on 2-h postchallenge glucose (mg/dL) | 95% CI | P |
|---------------------------|---------------------|---|--------------|-------|
| Fasting glucose | 1 mg/dL | 1.02 | 0.87, 1.17 | <.001 |
| Fasting insulin | 1 μ U/mL | -2.75 | -3.56, -1.94 | <.001 |
| 2-h insulin | 1 μ U/mL | 0.4 | 0.35, 0.45 | <.001 |
| HOMA-IR | | 11.38 | 8.17, 14.6 | <.001 |
| Age | 1 y | 0.46 | 0.16, 0.76 | .003 |
| A | 1 ng/mL | 1.82 | 0.62, 3.02 | .003 |
| Status (PCOS vs. control) | PCOS | 3.94 | 1.06, 6.82 | .007 |
| Waist/hip ratio | 0.1 U | 26.74 | -0.71, 54.81 | .056 |
| BMI | 1 kg/m ² | 0.21 | -0.28, 0.69 | .403 |
| T | 1 ng/mL | -1.39 | -5.06, 2.28 | .457 |

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show a significant difference in glucose parameters between PCOS and control patients with or without BMI adjustment (12, 22, 23). However, our data showed higher glucose parameters before and even after BMI adjustment. This may be more significant, considering that our study involved a racially homogenous Chinese population, and different ethnic groups have different presentations (6–8, 10, 12, 26, 31).

From multiple regression, the impacting factors shown positively affecting the 2-hour glucose level in our infertility patients were fasting glucose and insulin levels, age, 2-hour insulin level, HOMA-IR, status (PCOS vs. control) and A level ($P < .001$ for fasting glucose level, fasting insulin level, 2-hour insulin level, and HOMA-IR; $P = .003$ for age and A level; $P = .007$ for PCOS status; Table 3). However, BMI, waist/hip ratio, and T level did not show statistical significance ($P = .403$ for BMI; $P = .056$ for waist/hip ratio; $P = .457$ for T level; Table 3). These data were very different from those from other Western studies (12, 13). This is also one of only few reports involving a Chinese PCOS population (10).

It is widely recognized that management strategies are directed toward weight reduction and exercise to improve glucose resistance (33, 34); but our study involving lean Chinese patients with PCOS suggests that treatment for insulin resistance should not focus only on body weight reduction. In Taiwan, protein consumption has switched from mainly plant-based to animal-based, and fat consumption has increased steadily since 1960 (35, 36). In our patients overeating may be not the cause of insulin resistance. Most patients are lean when compared with whites (12, 13, 32). We are inclined to think that nutrition imbalance, not total caloric intake, is the cause of the problem (22, 37).

In this study, patients with PCOS constituted 56% of patients with ovulation dysfunction. They were younger and heavier than the control patients. Even after adjustment for BMI, patients with PCOS still had elevated glucose parameters, a higher HOMA-IR index, and higher T and A levels.

Glucose intolerance was associated with increasing BMI and age in most studies (12, 13). However, in our studies, there was no association found with glucose abnormality and increasing age. This may suggest that glucose intolerance is also a problem in our young Chinese generation. Measures must be initiated earlier in our young generation to prevent metabolic syndrome in the future.

Using only fasting glucose as a screening test, some infertility patients with DM were missed, although this finding failed to reach statistical significance ($\chi^2 = 3.47$; $P > .05$) when compared with the 75-g OGTT. Only 8 patients had both IFG and IGT, and 47 patients with IGT alone would have been undiagnosed if only fasting glucose was tested ($\chi^2 = 12.22$; $P < .05$). Our Chinese infertility patients, like their white counterparts, exhibited a higher prevalence of IGT even with normal fasting glucose levels, and the 75-g OGTT may be a better diagnostic tool for detecting glucose intolerance (12, 13).

A weakness of this study is that it involved only infertility patients, which may or may not represent the entire PCOS population; but our study involved more Chinese patients with PCOS than other similar studies (10).

In conclusion, the present management of PCOS is mostly directed toward weight reduction and improving glucose metabolism. But in our patients, who were generally lean and who exhibited no association between BMI and 2-hour blood glucose level, new modes of treatment should be explored. From our data, glucose intolerance also occurs in our young patients, and early prevention should be emphasized (24, 38).

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