Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome

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ABSTRACT

Objective: To determine the prevalence of glucose intolerance and parameters associated with risk in polycystic ovary syndrome (PCOS) patients.

Design: case control study

Setting: Al-batool Maternity Teaching Hospital, infertility center.

Materials and methods: From October 2001 to October 2002, one hundred women with, aged 18-44 years met conventional clinical criteria for PCOS, and had ovarian sources of androgen excess, were compared with 60 control women of similar weight and age. Anthropometric measurement the weight, height, and waist: hip measurements and body mass index (BMI) were assessed; two groups were identified, over weight BMI 25 kg/m² and obese as BMI 30kg/m². Fasting serum glucose (FSG), Oral glucose tolerance (OGT) and serum fasting testosterone were done. Patients were divided into three groups: (non diabetics, diabetics and impaired glucose tolerance).

Results: the prevalence of glucose intolerance was significantly higher in PCOS than the controlled group, the risk of glucose intolerance and diabetes was increased with the age, obesity, and the first degree relatives.

Conclusions: PCOS women are at significantly increased risk for impaired glucose tolerance and type 2 diabetes mellitus at all weight and at young age.

Key ward: PCOS, Insulin resistance, type 2 diabetes mellitus, impaired glucose tolerance.

Women with polycystic ovary syndrome (PCOS) are insulin resistant, and at high risk for glucose intolerance. Most physicians would agree that PCOS could be diagnosed clinically in a woman, who has hirsutism, irregular menstrual cycles, obesity, and a classic ovarian morphology, by echography. After considerable debate at 1990 National Institutes of Health Conference on PCOS, two minimal criteria were proposed; Menstrual irregularity, and evidence of hyperandrogenism, whether clinical or biochemical (1-5).

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The association between disorders of carbohydrate metabolism and hyperandrogenism was first described in 1921 by Achard and Thiers. PCOS is an exceptionally common disorder of premenopausal women with 5-10% prevalence, 20% of self-selected normal women had polycystic ovary morphology on ovarian ultrasound (1-2), and found in up to 75% of women with secondary amenorrhea (1-3, 6, 7). Since the report by Burghen et al. in 1980 which showed that PCOS was associated with hyperinsulinemia, the syndrome has major metabolic as well as reproductive morbidities (1, 8-12). Most anovulatory patients (approximately 80%) present with serum FSH and estradiol levels within the normal range.
The skin lesion, acanthosis nigricans, was reported in women with hyperandrogenism and diabetes mellitus by Kierland et al in 1947(14-18), and Kahn and colleagues in 1976 when described a distinct disorder affecting adolescent girls, which they designated the type A syndrome, this group identified a second distinct extreme insulin resistance syndrome in postmenopausal women with acanthosis nigricans and features of autoimmune disease, termed the type B syndrome and determined that it was caused by endogenous anti-insulin receptor antibodies (17-19). Brown and Winkelmann noted in 1968 that it was insulin-resistant diabetes mellitus, and genetic basis was suggested for that (15-18). Burghen and colleagues reported that women with PCOS, had basal and glucose-stimulated hyperinsulinemia compared with weight-matched control women, suggesting the presence of insulin resistance (20-22). In the mid-1980s several groups noted that these women had hyperinsulinemia basally and during an oral glucose tolerance test, compared with appropriately age- and weight-matched control women (22-23).

Obesity is common, and most investigators find at least one half of women with PCOS are obese, which is upper body obesity, with waist-to-hip ratio of greater than 0.85(22-25). Obesity leads to an increased insulin resistance and a rise in insulin circulating levels, which leads to an increased ovarian secretion of androgens and decreased sex hormone binding globulin (26, 27).

Defects in insulin action in muscle leads to reduced glucose disposal, and enhance the steroidogenic effects on theca cells and suppress sex hormone - binding globulin production by hepatocytes, leading to a hyperandrogenemic state (29-33).

**MATERIALS AND METHODS**

Over a period of one year starting from October 2001 to the end of October 2002, one hundred PCOS women, aged 18-44 yr, attending Mosul Infertility Center in Al-Batool Maternity Teaching Hospital were included in this study. All women were in good health, for at least one month before study, and were not taking any medication known to affect sex hormone or carbohydrate metabolism. The diagnosis of PCOS was made by the presence of chronic anovulation in association with elevated circulating androgen levels (1-2). Non-classical adrenal 21-hydroxylase deficiency, Hyper-prolactinemia and androgen-secreting tumors were excluded by appropriate tests before the diagnosis of PCOS was made. No PCOS patient had diagnosed diabetes mellitus.

The control group consists of sixty healthy women had regular menstrual cycle every 27-32 days and were not hirsute. To control for conditions altering insulin action, controlled women did not engaged in regular aerobic exercise, nor did they have a history of hypertension, a personal history of diabetes, or a first-degree relative with diabetes.

**Anthropometric measurements**

Weight and height were recorded with the subjects wearing light clothing and without shoes. Accurate balance scales were used and weight was recorded to the nearest 0.1 kg. Height was recorded to the nearest centimeter rounding up if midway, using measuring rod. The same person who recorded the height and weight in the same room recorded the waist and hip measurement, one layer of light clothing over underwear was acceptable. The observer kneeled or sat at an appropriate height in front of the subject, who breathed quietly and normally. Dresser makers measuring tape was used, taking care that it was applied horizontally. Waist girth was measured at the mid point between the iliac crest and the lower margin of the ribs. An approximate indicator of this level was ascertained by asking the subject to bend sideways. Hip girth was recorded as the maximum circumference around the buttock posteriorly and indicated anteriorly by the symphysis pubis. The obesity was defined by body mass index BMI calculation as; (weight/height)² (kg/m)². Overweight was defined as a BMI≥25 and obesity as BMI of ≥30.

**Biochemical assessments**

Blood samples were taken on the second visit. An oral glucose tolerance test was performed between 0800-1000h after an overnight fast of 10-14 h. All subjects were administered a 75g oral glucose challenge.
Table 1. Clinical and biochemical characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCOS women (no. =100)</th>
<th>Control women (no. =60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist/hip ratios</td>
<td>0.85±0.06(0.70-1.0)</td>
<td>0.77±0.07(0.6-0.9)</td>
</tr>
<tr>
<td>T (nmol/L)</td>
<td>2.8±1.3(0.9-1.0)</td>
<td>0.9±0.5(0.5-3.2)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>92±18(52-162)</td>
<td>85±6(57-115)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30±6(18-45)</td>
<td>26±9(17-42)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29±6(18-44)</td>
<td>28±5(18-44)</td>
</tr>
<tr>
<td>2-h glucose (mg/dL)</td>
<td>130±30(70-208)</td>
<td>110±28(60-180)</td>
</tr>
</tbody>
</table>

Blood was obtained for glucose determinations at 0 and 2 h. An additional blood sample was obtained at 0 h for testosterone (T). Plasma glucose (PG) levels were determined by the glucose oxidase method using automated analyzer. Levels of T were determined by VIDAS analyzer; using the ELFA technique (Enzyme linked Fluorescent Assay). Glucose tolerance was assessed by 1985 WHO criteria.

Non-diabetics Group; this group included subjects with FPG <110 mg/dl (6.1 mmol/L) or 2hPG < 140 mg/dl (<7.8 mmol/L).

Diabetics (DM) Group; This group included subjects with FPG≥140 mg/dl (≥7.8 mmol/L) or 2hPG ≥200 mg/dl (≥11.1 mmol/L) following OGTT. Impaired Glucose Tolerance (IGT) Group: This group included subjects who had 2hPG values ranged from 140-199 mg/dl (7.8-11.06 mmol/L) following OGTT.

The PCOS women were studied for diabetes diagnostic categories based on postchallenge glucose levels, using WHO criteria compared to those determined according to the 1997 ADA (American Diet Association) criteria based on fasting glucose values, normal fasting glucose, <110 mg/dl (< 6.1 mmol/L); impaired fasting glucose 110-125 mg/dl (6.1-6.9 mmol/L); diabetes ≥126 mg/dL (7.0 mmol/L). A multiple regression analysis was preformed to determine which variables predicted postchallenge glucose values. To control for the potential confounding effects of a family history of diabetes, we included only control and PCOS women without a first degree relative with diabetes in this analysis. The candidate predictive variables were status (PCOS vs. control), age; body mass index (BMI), waist/hip ratio, and fasting glucose values. Androgen values were not considered as candidate predictive variables, because they were used to make the diagnosis of PCOS. The criterion for a predictive variable to remain in the model was P≤0.15. All analyses were performed using the SPSS (statistical package for social sciences).

Table 2. Prevalence of glucose intolerance by BMI in PCOS, and in control group

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>PCO</th>
<th>NGT</th>
<th>%</th>
<th>No.</th>
<th>IGT</th>
<th>%</th>
<th>No.</th>
<th>DM</th>
<th>%</th>
<th>No.</th>
<th>Control</th>
<th>%</th>
<th>No.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>4</td>
<td>100</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>100</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>17</td>
<td>88</td>
<td>15</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>94</td>
<td>17</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>23</td>
<td>65</td>
<td>15</td>
<td>31</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>26</td>
<td>96</td>
<td>25</td>
<td>4</td>
<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>28</td>
<td>50</td>
<td>14</td>
<td>43</td>
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<td>7</td>
<td>2</td>
<td>8</td>
<td>87</td>
<td>7</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>35-39</td>
<td>22</td>
<td>64</td>
<td>14</td>
<td>27</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>67</td>
<td>2</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-44</td>
<td>5</td>
<td>60</td>
<td>3</td>
<td>20</td>
<td>1</td>
<td>20</td>
<td>1</td>
<td>1</td>
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<td>0</td>
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<td>1</td>
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<td>45-49</td>
<td>1</td>
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<td>0</td>
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<td>0</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>100</td>
<td>65</td>
<td>65</td>
<td>28</td>
<td>28</td>
<td>7</td>
<td>7</td>
<td>60</td>
<td>92</td>
<td>55</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NGT, normal glucose tolerance; IGT, impaired glucose tolerance.
Table 3. Prevalence of glucose intolerance by age in PCOS women, and in control group

<table>
<thead>
<tr>
<th>AGE</th>
<th>PCOS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>%</td>
</tr>
<tr>
<td>15-19</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>20-24</td>
<td>17</td>
<td>88</td>
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<td>25-29</td>
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<td>30-39</td>
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<tr>
<td>35-39</td>
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<td>62</td>
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<tr>
<td>40-44</td>
<td>6</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>65</td>
</tr>
</tbody>
</table>

RESULTS

Clinical and biochemical characteristics of the subjects are summarized in Table 1. Their age ranged between 18-44 years with a mean of 29.5 years.

Prevalence of glucose intolerance by BMI (Table 2): In PCOS, and in control group, this showed that; In PCOS 21% of women were none obese (BMI<25 kg/m²), 23% were overweight (BMI>25 kg/m²), and 56% were obese (BM> 30 kg/ m²). Overall 35% of the PCOS women had either IGT (28%) or diabetes (7%) by WHO criteria. The non-obese and overweight PCOS women, 9% had IGT, and 1% had diabetes. In control group eight percent of the women had IGT, and none had diabetes. Although IGT and diabetes were detected in non-obese and/or young PCOS women, the prevalence of both significantly increased with BMI (by Pearson correlation test, P <0.0001; Table 2) and with age (by Pearson correlation test, P 0.001)

The prevalence of glucose intolerance studied in PCOS women without a first degree relative with diabetes (n = 68) compared to that in control women (n = 60), to adjust for confounding effects of family history of diabetes. These PCOS women were significantly more obese than control women (30 ± 4 vs. 26 ±9 kg/m2) respectively, with P value of 0.001, with no significant difference in age (29± 6 vs. 28 ± 5 kg/m2) respectively. They had a significantly higher prevalence of glucose intolerance (23.6% IGT; 4.4% diabetes) compared to control women (8% IGT; 0% diabetes; x²=8; P= 0.005; OR = 4; 95% CI =1.5-10.5).

Regarding the impact of family history of diabetes; the prevalence of glucose intolerance in PCOS women were compared, and found that it was significantly higher in PCOS women with a first degree relative with diabetes (50%) vs. 30% no first degree relative with diabetes; X²= 4.65; P <0.03; OR = 2.57; 95 % CI = 1.09-6).

Comparison of diabetes diagnostic criteria

The majority of PCOS women with glucose intolerance had normal fasting glucose levels by ADA criteria. Using the ADA criteria, 4% of PCOS women would be classified as having diabetes; whereas 7% would be classified as having diabetes by WHO criteria, a difference of 3%. Thus, 3 of 7 (43%) PCOS women with diabetes diagnosed by WHO criteria would have been missed using ADA criteria. No PCOS women considered diabetes by fasting glucose values,and did not have it by postchallenge glucose. According to the ADA criteria, 9% of PCOS women had impaired fasting glucose, whereas 28% had IGT by postchallenge glucose values.

DISCUSSION

Women's health is about the prevention, screening, diagnoses, and treatment of disorder that are unique to women. PCOS is extremely prevalent and probably constitutes the most frequently encountered endocrinopathy in women of reproductive age. Having the disorder may significantly impact the quality of life of women
during the reproductive years, and it contributes to morbidity and mortality by the time of menopause. PCOS women had a later menopause, and they had experienced a higher hysterectomy rate. Most importantly, there was a high prevalence of diabetes (16%) and hypertension (40%) (33, 34).

This is the first controlled study of glucose tolerance in PCOS in Mosul city in Iraq, and we document that these women are at significantly increased risk for IGT and type 2 diabetes mellitus compared to concurrently studied age, weight, comparable reproductively normal women. The prevalence rates of glucose intolerance in PCOS was 28% IGT, and 7% undiagnosed diabetes, and are substantially higher than those found in the general population of similar age, but somewhat lower than that reported in previous studies performed in the U.S. and Asia Although all PCOS women with GI investigated in this study were obese, it is noteworthy that nearly 80% of obese PCOS subjects had NGT.

Despite the fact that hyperinsulinemia, reflecting some degree of peripheral insulin resistance, was well recognized in PCOS by the mid-1980s, glucose tolerance was not systematically investigated until Dunaif study in 1987(40), he found that obese PCOS women had significantly increased glucose levels during an oral glucose tolerance test compared with age- and weight-matched ovulatory hyperandrogenic and control women. The effects of insulin on glucose metabolism are usually examined in studies of insulin resistance (41). This can be studied quantitatively in humans with the euglycemic glucose clamp technique: a desired dose of insulin is administered and euglycemic is maintained by a simultaneous variable glucose infusion (41, 42). At steady state, the amount of glucose that is infused equals the amount of glucose taken up by the peripheral tissues and can be used as a measure of peripheral sensitivity to insulin, known as insulin-mediated glucose disposal. Making a diagnosis of insulin resistance in an individual is problematic; First, there is a wide range of insulin sensitivities in normal individuals as 25% of normal subjects have insulin action values that overlap with those presenting with glucose intolerance (GI) states. PCOS women with normal glucose tolerance (81.8%) were subdivided into two groups: those who were overweight or obese and those of normal weight, they found that 2.5% of PCOS women had type 2 diabetes and 15.7% had IGT. This prevalence rate was significantly higher than that described in the general population of similar age, but somewhat lower than that reported in previous studies performed in the U.S. and Asia Although all PCOS women with GI investigated in this study were obese, it is noteworthy that nearly 80% of obese PCOS subjects had NGT.

\[ \text{Table 4. Prevalence of glucose intolerance by W/H ratio in PCOS women and control group (Without family history of DM)} \]

<table>
<thead>
<tr>
<th>W/H ratio</th>
<th>PCOS</th>
<th></th>
<th></th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>Total</td>
</tr>
<tr>
<td>&lt;0.85</td>
<td>25</td>
<td>76</td>
<td>19</td>
<td>24</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>0.85-0.89</td>
<td>18</td>
<td>78</td>
<td>14</td>
<td>22</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>18</td>
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<tr>
<td>0.90-0.94</td>
<td>16</td>
<td>69</td>
<td>11</td>
<td>25</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>0.95-0.99</td>
<td>8</td>
<td>63</td>
<td>5</td>
<td>25</td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1.0-1.04</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>68</td>
<td>72</td>
<td>49</td>
<td>24</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>
from insulin-resistant individuals. Second, clinically available measures of insulin action, such as fasting or glucose-stimulated insulin, do not correlate well with more detailed measurements of insulin sensitivity in research settings. In view of these constraints, it is prudent to consider all PCOS women at risk for insulin resistance and they should have fasting and 2-h post-75g glucose load glucose levels as a screen for glucose intolerance (43-45).

The age in women studied ranged from 18-44 years with a mean age of 29 years. Although IGT and diabetes were detected in young women, the prevalence of both were significantly increased with age (p<0.001) Table (3).

In the current study, the non obese PCOS women also have glucose intolerance (9% IGT, 1% diabetes), but the prevalence rates of glucose intolerance was significantly increased with BMI (P<0.0001), and an increased W/H ratio was significantly affecting the rate of IGT (Table 4).

Euglycemic glucose clamp studies have demonstrated significant and substantial decreases in insulin-mediated glucose disposal in PCOS (41). This decrease (35-40%) is of a similar magnitude to that seen in NIDDM. Obesity (fat mass per se), body fat location (upper vs. lower body, e.g., waist to hip girth ratio), and muscle mass all have important independent effects on insulin sensitivity. Since muscle is the major site of insulin-mediated glucose use, androgens can increase muscle mass, potential androgen-mediated changes in lean body (primarily muscle) mass must also be controlled for in PCOS (41, 48-50). These detects are much more pronounced in PCOS women who have a first-degree relative with NIDDM, suggesting that such women may be at particularly high risk to develop glucose intolerance. Consistent with this hypothesis, we showed that a first degree relative with diabetes was associated with an increased risk of glucose intolerance in PCOS women figure (7). However, the prevalence of glucose intolerance in PCOS, even in those women without a first degree relative with diabetes, was still significantly higher than that in control women Figure 2. However, to our knowledge, no studies have been performed on subjects from the Mediterranean region before this. Studies in American and Asian subjects have shown that women with PCOS compared with the general population have an increased risk for impaired glucose tolerance (IGT) and type 2 diabetes, with a tendency toward early development of glucose intolerance (GI) states. The strong connection between PCOS and GI states is further emphasized by the high prevalence of polycystic ovarian morphology found on ultrasound scans in premenopausal women with type 2 diabetes and those with previous gestational diabetes (12).

CONCLUSIONS

PCOS women have significantly increased prevalence rates of IGT and undiagnosed diabetes. Although obesity and age substantially increase the risk, IGT and diabetes can occur in young, non-obese PCO women.

Fasting glucose levels are poor predictors of diabetes in PCOS women. It is advisable to perform an OGTT at the time of diagnosis of PCOS, and periodically thereafter. Women, who are diagnosed with polycystic ovarian disease and subsequently get pregnant, should have routine glucose testing performed in pregnancy, perhaps more than once. Women who have gestational diabetes in pregnancy should be tested after pregnancy for polycystic ovaries.

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Received on January 12, 2005; revised and accepted on June 21, 2005