Association of obesity and overweight with the prevalence of insulin resistance, pre-diabetes and clinical–biochemical characteristics among infertile Mexican women with polycystic ovary syndrome: a cross-sectional study

Enrique Reyes-Muñoz,1 Carlos Ortega-González,1 Nayeli Martínez-Cruz,1 Lidia Arce-Sánchez,1 Guadalupe Estrada-Gutierrez,2 Carlos Moran,3 Ana Paola Sánchez-Serrano,4 Rodolfo Higareda-Sánchez,4 Julio Francisco de la Jara-Díaz4

ABSTRACT

Objective: To study the association of obesity and overweight with the prevalence of insulin resistance (IR), pre-diabetes and clinical–biochemical characteristics among infertile Mexican women with polycystic ovary syndrome (PCOS).

Design: Retrospective cross-sectional study.

Setting: Level-three medical institution, an infertility clinic in Mexico City.

Participants: We included infertile Mexican women with diagnosis of PCOS according to the Rotterdam criteria: group 1 (n=83), normal weight (body mass index (BMI) 18.5–24.9 kg/m²); group 2 (n=217), overweight (BMI 25–29.9 kg/m²); and group 3 (n=238), obese (BMI≥30 kg/m²).

Primary and secondary outcome measures: IR was determined by homeostatic model assessment (HOMA) >2.5 and pre-diabetes by fasting glucose between 5.6 and 6.9 mmol/L and/or glucose value between 7.8 and 11 mmol/L at 2 hours during an oral glucose tolerance test. We compared clinical–biochemical characteristics among groups.

Results: Prevalence of IR for groups 1, 2 and 3 was 19.3%, 56.2% and 78.2%; overweight and obesity increase the IR OR (CI 95%) to 5.3 (2.9 to 9.8) and 14.9 (8.0 to 28), respectively. Prevalence of pre-diabetes for groups 1, 2 and 3 was 7.2%, 17.5% and 31.5%; overweight and obesity increase the pre-diabetes OR (CI 95%) to 2.7 (1.1 to 6.7) and 5.9 (2.4 to 14), respectively. Acanthosis nigricans was more frequent in group 3 than group 1. Free Androgen Index (FAI) and thyroid-stimulating hormone (TSH) levels were lower in group 1 than in groups 2 and 3. Progesterone and sex hormone-binding globulin (SHBG) levels were higher in group 1 than in groups 2 and 3. Dehydroepiandrosterone sulfate (DHEA-S) was higher in group 1 than group 3.

Conclusions: Obese and overweight infertile Mexican women with PCOS, attending to an infertility clinic, have a higher prevalence of IR and pre-diabetes compared with normal-weight women with PCOS. Therapeutic interventions should include those that improved metabolic functioning prior to attempting pregnancy in these groups of women.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting...
women of reproductive age. The prevalence of PCOS is 4–7% in women of reproductive age using the National Institutes of Health criteria and up to 15–18% using the Rotterdam criteria. PCOS is present in 6.6% of Mexican women. The aetiology of PCOS is not completely understood; however, one condition that correlates closely with the pathogenesis of PCOS is insulin resistance (IR), which is present in 50–75% of women with PCOS. IR is not included in the current diagnostic criteria for PCOS, though some clinicians assume that all women with PCOS exhibit some degree of IR and compensatory hyperinsulinemia.

Another factor frequently identified among women with PCOS is overweight or obesity, with a reported prevalence ranging from 6% to 100% between different populations. Although the mechanisms that link obesity to IR and endocrine abnormalities in women with PCOS are still controversial, the general consensus is that obese women with PCOS are insulin resistant. In contrast, some studies have failed to demonstrate IR in slim women with PCOS.

IR prevalence rates ranging from 44% to 70% have been reported, but most studies did not analyse overweight/obese and normal-weight women separately. A recent systematic review showed that only a few studies compared IR rates between these groups, and only one study compared pre-diabetes among obese, overweight and normal-weight women with PCOS. All of these studies do not provide data from Latin American population.

While many women with PCOS are overweight or obese, findings on the effects of excess weight on the clinical and biochemical characteristics of PCOS have been inconsistent. Some studies have reported that obese patients with PCOS have a higher prevalence of clinical manifestations such as hirsutism and menstrual disorders than non-obese women with PCOS; other studies, however, have not found these differences. Moreover, a few studies have explored IR and pre-diabetes in infertile women with PCOS categorised by body mass index (BMI).

The aim of this study was to analyse the association of obesity and overweight with the prevalence of IR, pre-diabetes and clinical–biochemical characteristics among infertile Mexican women with PCOS.

METHODS

Participants

This retrospective cross-sectional study was approved by the Internal Review Board of the Instituto Nacional de Perinatología (register number 212250-42131). All women diagnosed with PCOS according to the Rotterdam criteria without other additional causes of infertility, treated at the Infertility Clinic of the Instituto Nacional de Perinatología in Mexico City from 2009 to 2013, were enrolled. All women were presented sequentially during the study period and were recruited at the first visit; they were not exposed to metformin or lifestyle modification intervention 3 months prior to this study. Clinical hyperandrogenism was defined by the presence of hirsutism (Ferriman-Gallway Score ≥8) or acne, and biochemical hyperandrogenism was defined by a Free Androgen Index (FAI) ≥4.5% or by androstenedione ≥3.6 mg/L. FAI was calculated by dividing total serum testosterone (nmol/L) by sex hormone-binding globulin (SHBG, nmol/L) ×100. Oligo-ovulation and anovulation were defined by a menstrual cycle length ≥35 days and serum progesterone <4 ng/dL as measured on days 21–23 after progesterone-induced bleeding. Polycystic ovary was defined by the presence on ultrasound of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 mL); ultrasound was performed intravaginally using a General Electric (GE) RIC5-9-D endovaginal ultrasound probe 4–9 MHz (GE Voluson E8 machine).

Studies have been reported to define PCOS according to the BMI (BMI=weight/(kg)/height (m2)): group 1, normal weight (BMI 18.5–24.9 kg/m2); group 2, overweight (BMI 25.0–29.9 kg/m2); and group 3, obese (BMI≥30 kg/m2).

Procedure

All women seen at the infertility clinic with diagnosis of PCOS were evaluated for endocrine ovarian function. The following variables at the first clinical visit were systematically recorded: weight, height, BMI, irregular cycle, Ferriman-Gallway Score, acne, anacinesis, characteristics of ovaries and uterus measured by vaginal ultrasound. Fasting glucose was measured in the Vitros DT60 II Chemistry System (Ortho-Clinical Diagnostics, Tilburg, the Netherlands), sensitivity (S): 1.11 nmol/L and coefficient of variation (CV): 1.4–1.8%, and hormonal profile was measured by chemiluminescence (IMMULITE 2000 Immunoassay System) on days 3–5 of the menstrual cycle including insulin, S: 2 μIU/mL, and CV: 4.1–7.3%, luteinising hormone (LH) (S: 0.005 mIU/mL, CV: 6.1–26.3%), follicle-stimulating hormone (FSH) (S: 0.1 mIU/mL, CV: 4.1–7.9%), oestradiol (S: 15 pg/mL, CV: 6.7–16.0%), total testosterone (S: 0.5 nmol/L, CV: 7.2–24.3%), and SHBG (S: 0.02 nmol/L, CV: 4.2–6.6%), androstenedione (S: 0.3 ng/mL, CV: 8.5–17.8%), dehydroepiandrosterone sulfate (DHEAS) (S: 3 μg/mL, CV: 9.3–13.0%), TSH (S: 0.004 μIU/mL, CV: 5.1–12.5%), total triiodothyronine (total T3) (S: 19 ng/mL, CV: 5.5–15.0%), free thyroxine (free T4) (S: 0.11 ng/dL, CV: 3.6–10.2%) and PRL (S: 0.5 ng/mL, CV: 4.0–5.3%). Progesterone was determined by chemiluminescence (IMMULITE 2000 Immunoassay System) on days...
21–23 of the natural or induced menstrual cycle, S: 0.1 ng/mL and CV: 9.5–21.7%. 17-Hydroxyprogesterone (17-OHP4) was determined by radioimmunoassay (Cobra II Gamma Counter), S: 0.08 ng/mL and CV: 7.4–14.2%. An oral glucose tolerance test with 75 g (75 g OGTT) was performed in all women with fasting glucose >5.2 nmol/L. Diagnosis of type 2 diabetes mellitus was made with fasting glucose ≥7 nmol/L or glucose ≥11.1 mmol/L at 2 hours during the OGTT. Clinical and ultrasound data were obtained from clinical records, and biochemical data were obtained from the database of the Endocrinology Department. A written informed consent from participants is not required by the Internal Review Board at our Institution for retrospective studies.

Study variables
The first aim was to compare IR across the three study groups. IR was calculated using the homeostasis model assessment (HOMA)-IR equation: HOMA-IR=insulin (µU/mL)×glucose (mg/dL)/405.19 Women with a HOMA-IR value ≥2.5 were considered insulin resistant; this cut-off point represents the 90th centile of the normal-weight Mexican population as previously reported.20 The second aim was to compare the prevalence of pre-diabetes as defined by the American Diabetes Association:21 fasting glucose ≥5.6 mmol/L or glucose level between 7.8 and 11 mmol/L at 2 hours during a 75-g OGTT. The final aim was to compare the phenotypic, clinical and hormonal characteristics among the three groups.

Sample size
The sample size was calculated to observe a minimum difference of 20% in the prevalence of IR between obese and normal-weight women with PCOS, with an α of 0.05 and β of 0.20. Although the number required was 82 women per group, we decided to include all women with PCOS during the period of study.

Statistical analysis
Statistical analysis was performed using the Statistical Package for Social Sciences Software (SPSS V.15, Chicago, Illinois, USA). Continuous variables were expressed as mean±SD and categorical variables as frequency and proportions, according to data distribution; one-way analysis of variance (ANOVA) with Bonferroni correction or the Kruskal-Wallis test was used to compare continuous variables and the χ² test or Fisher’s exact test to evaluate differences in proportions. Statistical significance was set to p≤0.05.

RESULTS
During the study period, 613 women with PCOS were sequentially identified; 75 of them were excluded because they did not fulfil the inclusion criteria (35 due to TSH<5 µIU/mL, 21 due to PRL>25 ng/mL, 2 due to 17-OHP>10 ng/mL and 17 due to incomplete records). The remaining 538 women with PCOS were included in the study: group 1, normal weight (n=83; 15.4%); group 2, overweight (n=217; 40.3%); and group 3, obese (n=238; 44.3%). The diagnostic criteria for PCOS and phenotype at the moment of PCOS diagnosis of women enrolled in this study are shown in tables 1 and 2, respectively. Hyperandrogenism was present in 85.5%, oligoanovulation in 94.4% and polycystic ovary in 60.2%. The most common phenotype was hyperandrogenism+oligo-ovulation or anovulation+polycystic ovary, and the least frequent was hyperandrogenism+polycystic ovary. With respect to clinical characteristics (table 3), there were no differences in age, hirsutism and acne among the study groups. Weight and BMI showed a significant increase from group 1 to group 3. Oligomenorrhea was present in 69.5% of all women and showed a trend to be higher but not significant in obese women, and it was significantly higher in overweight women compared with normal-weight women. Frequency of acanthosis nigricans was higher in obese women than in normal and overweight women.

We next assessed the prevalence of IR, pre-diabetes and type 2 diabetes (table 4), finding that fasting glucose and insulin levels were significantly higher in overweight and obese women than in normal-weight women. Prevalence of IR (CI 95%) was 19.3% (12.2% to

| Table 1 Criteria for the diagnosis of PCOS among infertile Mexican women |
|-----------------------------|----------|----------|----------|----------|
| **Criterion**               | **Total n=538** | **Normal weight n=83** | **Overweight n=217** | **Normal vs overweight p** | **Obese n=238** | **Normal vs obese p** |
| Hyperandrogenism             | 480 (89.2) | 71 (85.5) | 195 (89.9) | 0.45 | 214 (89.2) | 0.37 |
| Only clinical                | 190 (35.3) | 29 (34.9) | 72 (33.2) | 0.91 | 89 (37.4) | 0.78 |
| Only biochemical             | 414 (77) | 60 (72.2) | 172 (79.3) | 0.25 | 182 (76.5) | 0.54 |
| Clinical and biochemical     | 120 (21.6) | 18 (21.6) | 48 (21.2) | 0.94 | 54 (21.8) | 0.97 |
| Oligo-ovulation or anovulation | 508 (94.4) | 78 (94) | 203 (93.5) | 0.89 | 227 (95.4) | 0.83 |
| Polycystic ovary             | 409 (76) | 65 (78.3) | 162 (74.6) | 0.67 | 182 (76.4) | 0.94 |

Values expressed as frequency and (proportion).

χ² test.

PCOS, polycystic ovary syndrome.
29%), 56.7% (49.5% to 62.6%) and 78.2% (72.4% to 82.9%) for normal-weight, overweight and obese women, respectively. Prevalence significantly increased from normal-weight to obese women, with a total prevalence of 60.2% (CI 95% 55.9% to 64.3%). Prevalence of pre-diabetes (CI 95%) was 7.2% (2.9% to 15.6%), 17.5% (12.8% to 23.3%) and 31.5% (25.7% to 37.8%) for normal-weight, overweight and obese women, respectively. Pre-diabetes was significantly higher in overweight and obese than in normal-weight women. There were no differences in the prevalence of type 2 diabetes mellitus among the three groups.

There were positive correlations between BMI and (1) IR, (2) pre-diabetes and (3) type 2 diabetes mellitus (r=0.38, p=0.0001; r=0.24, p=0.0001; and r=0.08, p=0.03, respectively). No significant correlations for age and hyperandrogenism (clinical and/or biochemical hyperandrogenism) with IR, pre-diabetes and diabetes were observed. However, positive correlations among androstenedione, FAI and biochemical hyperandrogenism with HOMA-IR (r=0.15, p=0.001; r=0.19, p=0.0001; and r=0.09, p=0.02, respectively) were found.

We assessed fasting insulin, fasting glucose, HOMA-IR and the prevalence of IR, pre-diabetes and type 2 diabetes according to the phenotype (table 5). There were higher fasting insulin and HOMA-IR among women with phenotypes that included hyperandrogenism+oligoanovulation with or without polycystic ovary than women with hyperandrogenism and polycystic ovary phenotype. Although a higher prevalence of IR and pre-diabetes among groups with hyperandrogenism+oligoanovulation than with hyperandrogenism+polycystic ovary phenotype was observed, they were not statistically different.

Regarding biochemical characteristics, there were no differences in levels of LH, FSH, LH/FSH, oestradiol, PRL, 17-OHP4, total testosterone and androstenedione among the three groups (table 6). Progesterone levels were significantly lower in overweight and obese women than in normal-weight women. The frequency of progesterone levels <4 ng/dL was 84.3% in normal-weight women, 91.2% in overweight women and 94.1% in obese women. This frequency was significantly higher in obese than in normal-weight women (p=0.01). TSH concentration was significantly higher among obese and overweight women than among normal-weight women, though all women had TSH<5 µIU/mL. SHBG was significantly lower among overweight and obese women than among normal-weight women. A similar relationship occurred with DHEA-S; however, this marker was significantly lower in obese women only. The FAI was higher in overweight and obese women than in normal-weight women. There was a negative correlation between SHBG and HOMA-IR (r=−0.13, p=0.01).

### Table 2 Phenotype at the moment of PCOS diagnosis among infertile Mexican women

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Normal weight n=83</th>
<th>Overweight n=217</th>
<th>Normal vs overweight p*</th>
<th>Obese n=238</th>
<th>Normal vs obese p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenism+oligo-ovulation or anovulation</td>
<td>36 (43.3)</td>
<td>110 (50.6)</td>
<td>0.31</td>
<td>120 (50.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hyperandrogenism+oligo-ovulation or anovulation</td>
<td>30 (36.1)</td>
<td>71 (32.7)</td>
<td>0.67</td>
<td>83 (34.9)</td>
<td>0.94</td>
</tr>
<tr>
<td>Hyperandrogenism+polycystic ovary</td>
<td>5 (6)</td>
<td>14 (6.5)</td>
<td>0.89</td>
<td>11 (4.6)</td>
<td>0.83</td>
</tr>
<tr>
<td>Oligo-ovulation or anovulation +polycystic ovary</td>
<td>12 (14.4)</td>
<td>22 (10.1)</td>
<td>0.39</td>
<td>24 (10.1)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Values expressed as frequency and (proportion). *χ² test.

PCOS, polycystic ovary syndrome.

### Table 3 Clinical characteristics among infertile Mexican women with polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal weight n=83</th>
<th>Overweight n=217</th>
<th>Normal vs overweight p*</th>
<th>Obese n=238</th>
<th>Normal vs obese p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.6±4.2</td>
<td>28.7±4.5</td>
<td>0.19</td>
<td>28.5±3.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.5±4.9</td>
<td>66.8±5.6</td>
<td>0.0001</td>
<td>83.4±10.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8±1.6</td>
<td>27.6±1.3</td>
<td>0.0001</td>
<td>34.0±3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oligomenorrhoea</td>
<td>48 (57.8)</td>
<td>161 (74.2)</td>
<td>0.009</td>
<td>165 (69.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>21 (25.3)</td>
<td>67 (30.9)</td>
<td>0.42</td>
<td>81 (34)</td>
<td>0.18</td>
</tr>
<tr>
<td>Acne</td>
<td>11 (13.3)</td>
<td>17 (7.8)</td>
<td>0.22</td>
<td>21 (8.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>13 (15.7)</td>
<td>38 (17.5)</td>
<td>0.83</td>
<td>95 (39.9)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD and/or frequency and (proportion).

*Analysis of variance (ANOVA) or χ² test.

BMI, body mass index.
### Table 4  Insulin resistance, pre-diabetes and type 2 diabetes among infertile Mexican women with polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total women n=538</th>
<th>Normal weight n=83</th>
<th>Overweight n=217</th>
<th>Normal vs overweight p</th>
<th>Obese n=238</th>
<th>Normal vs obese p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>16.5±11.6</td>
<td>9.3±8.2</td>
<td>14.7±9.1</td>
<td>0.0001</td>
<td>20.6±12.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.26±0.82</td>
<td>4.82±0.44</td>
<td>5.22±0.82</td>
<td>0.0001</td>
<td>5.45±0.87</td>
<td>0.0001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.0±3.1</td>
<td>2.06±2.0</td>
<td>3.5±2.4</td>
<td>0.001</td>
<td>5.1±3.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>HOMA-IR ≥ 2.5</td>
<td>324 (60.2)</td>
<td>16 (19.3)</td>
<td>122 (56.2)</td>
<td>0.0001</td>
<td>186 (78.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>119 (22.1)</td>
<td>6 (7.2)</td>
<td>38 (17.5)</td>
<td>0.03</td>
<td>75 (31.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>24 (4.5)</td>
<td>1 (1.2)</td>
<td>11 (5.1)</td>
<td>0.23</td>
<td>12 (5)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Values expressed as mean±SD and/or frequency and (proportion). OR (95% CI). HOMA-IR, homeostatic model assessment of insulin resistance.

### Table 5  Insulin resistance, pre-diabetes and type 2 diabetes among infertile Mexican women with polycystic ovary syndrome (PCOS) according to phenotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HA+polycystic ovary n=30</th>
<th>HA+oligo-ovulation or anovulation+polycystic ovary n=266</th>
<th>p*</th>
<th>HA+oligo-ovulation or anovulation n=184</th>
<th>p*</th>
<th>Oligo-ovulation or anovulation+polycystic ovary n=58</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>11.9±6</td>
<td>17.1±11</td>
<td>0.009</td>
<td>17.4±12</td>
<td>0.01</td>
<td>13.2±8</td>
<td>0.80</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.08±0.72</td>
<td>95.1±17</td>
<td>0.20</td>
<td>5.2±0.66</td>
<td>0.10</td>
<td>5.19±0.55</td>
<td>0.28</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.7±1.7</td>
<td>4.1±3.3</td>
<td>0.01</td>
<td>4.2±3.2</td>
<td>0.02</td>
<td>3.1±2.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>13 (43.3)</td>
<td>166 (62.4)</td>
<td>0.06</td>
<td>114 (62)</td>
<td>0.08</td>
<td>31 (53.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>4 (13.3)</td>
<td>52 (19.5)</td>
<td>0.56</td>
<td>49 (26.6)</td>
<td>0.18</td>
<td>14 (24.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>1 (3.3)</td>
<td>14 (5.3)</td>
<td>0.98</td>
<td>8 (4.3)</td>
<td>0.81</td>
<td>1 (1.7)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test or χ² test.

Values expressed as mean±SD and/or frequency and (proportion).

HA, hyperandrogenism; HOMA-IR, homeostatic model assessment of insulin resistance.
but significantly higher than in Thai women. However, there are few reports about BMI and its relationship to IR. The prevalence of IR in US women with PCOS ranges from 44% to 70%, similar to our results but significantly higher than in Thai women. However, there are few reports about BMI and its relationship to IR. Most studies report a significant difference in the index used to measure IR between normal-weight and obese women with PCOS, but researchers have not defined the cut-off for IR and therefore have not reported IR prevalence among groups. According to our results, the most metabolically affected phenotypes included hyperandrogenism and oligomenorrhea, as has been reported previously.

The prevalence of pre-diabetes/impaired glucose tolerance (IGT) and of type 2 diabetes among US women with PCOS has been reported to be between 23% and 35% and between 4% and 10%, respectively, and the prevalence of pre-diabetes has been reported as higher in obese women than in non-obese women, similar to our findings. However, the prevalence of pre-diabetes/IGT was found to be 17.0% vs 5.9% in obese versus lean Korean women with PCOS—a result that differs significantly from ours and that might be attributable to ethnic group.

The mechanisms regulating DHEA and DHEAS production remain uncertain. In addition to ageing, other factors known or suspected to affect adrenal androgen production include obesity, low-density lipoprotein production, ethnicity, gender, ovarian androgen production, menopausal status, insulin and insulin-like growth factors. Some studies have demonstrated diminished DHEAS production in the presence of hyperinsulinemia in normal women, and one study showed diminished production in Caucasian women with PCOS. In women with PCOS and hyperandrogenism, most studies have shown a stimulatory effect by insulin on adrenal androgen production. However, some researchers have reported the opposite relationship, and others have failed to demonstrate an association between DHEA concentrations and circulating insulin in women with PCOS. In a small study of 27 African-American women with PCOS, no association between DHEA-S and BMI was detected, whereas in a population of Swedish women with PCOS, researchers found a positive association between BMI and DHEA-S. In our study, DHEA-S was higher in overweight and obese women. In contrast, higher levels of TSH and FAI were observed in overweight and obese women. FAI concentration is an indirect measure of free testosterone (fT) that correlates positively with HOMA-IR. Although the use of FAI as an indirect method to measure free testosterone (fT) is controversial, studies performed in normal women and women with PCOS have shown a good correlation of FAI with fT measured by liquid chromatography–tandem mass spectrometry versus immunassay. Bui et al. reported reference intervals and biologic variation for testosterone, fT and FAI in women with accurate methods, showing the discriminative value of these
parameters in a PCOS population. These authors found that the areas under the curve (AUCs) of receiver operator characteristic plots were not different for testosterone, IT or FAI when testosterone was measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS) and by Architect 2nd Generation T Immunoassay. Barth et al. reported an LC–MS/MS method for analysing testosterone and androstenedione to study the reference ranges and diagnostic utility in PCOS. The diagnostic capacity using receiver operator characteristic plots showed AUC for FAI 0.81, testosterone 0.75 and androstenedione 0.66.

It is generally accepted that obesity is associated with chronic low-grade inflammation, which may contribute to IR. PCOS is also associated with low-grade systemic inflammation, as evidenced by elevation of multiple markers of inflammation such as C reactive protein, tumour necrosis factor α, cytokines such as interleukin 6 (IL-6) and IL-18, and white cell count. Obese women with PCOS have a different metabolic profile than normal-weight women with PCOS. This finding is supported by evidence that obesity and PCOS per se show low-grade systemic inflammation and higher prevalence of IR and pre-diabetes, as confirmed by our findings. Therefore, the presence of obesity or excess weight in infertile women with PCOS implies different therapeutic interventions emphasizing improvements in metabolic function prior to attempting pregnancy.

The present study has some limitations, including the use of HOMA for IR diagnosis, a technique which is not the most appropriate for clinical practice in the evaluation of IR. Although the hyperinsulinemic–euglycemic clamp technique is the gold standard for measuring insulin sensitivity, it is too expensive, time-consuming and labour-intensive to be of practical use in an office setting. In a recent meta-analysis, Quantitative Insulin Sensitivity Check Index (QUICKI) showed a better correlation than HOMA (r=0.61, CI 0.55 to 0.65 vs r=-0.53, CI -0.60 to -0.46, respectively); however, we decided to use HOMA because we have a cut-off to define IR for Mexican population and we do not have a cut-off to define IR by QUICKI. Another limitation was that the 75 g OGTT for diagnosis of pre-diabetes was employed only when fasting glucose was >5.22 mmol/L at the first medical visit, a factor that could affect the real prevalence of pre-diabetes. Finally, the severity of hirsutism is not comparable among groups, because in our institution, the total Ferriman-Gallwey Score is not documented; only a Ferriman-Gallwey Score >8 is considered as hirsutism.

Our results should be interpreted with caution, as we included only Mexican women with PCOS and infertility; therefore, the outcomes are not generalisable to patients with PCOS without infertility. Future research in Mexican women with PCOS is needed to clarify whether the high prevalence of IR and pre-diabetes is due to PCOS or BMI per se, as well as to establish androgen normal ranges and QUICKI values in this population.

CONCLUSIONS
Infertile Mexican women with PCOS who are obese or overweight show a higher prevalence of IR and pre-diabetes compared with normal-weight women with PCOS. IR and pre-diabetes should be considered when tailoring approaches to PCOS, with an emphasis on therapeutic interventions to improve metabolic function prior to attempting pregnancy, particularly in these groups of women.

Author affiliations
1Department of Endocrinology, Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, Mexico City, Mexico
2Biomedical Research Branch, Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, Mexico City, Mexico
3Research Unit of Reproductive Medicine, Health Research Council, Mexican Institute of Social Security, IMSS, Mexico City, Mexico
4Division of Reproductive Medicine, Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, Mexico City, Mexico

Twitter Follow Rodolfo Higareda-Sánchez at @DrHigareda

Contributors ER-M and CO-G conceived and designed the study, analysed the data and wrote the paper. NM-C, LA-S, GE-G and CM analysed the data and wrote the paper. APS-S, RH-S and JFdlJ-D acquired the data, interpreted the results and reviewed the paper.

Funding This work was supported by the Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, grant number 212250-42131.

Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval Internal Review Board of the Instituto Nacional de Perinatología.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES


Association of obesity and overweight with the prevalence of insulin resistance, pre-diabetes and clinical–biochemical characteristics among infertile Mexican women with polycystic ovary syndrome: a cross-sectional study

Enrique Reyes-Muñoz, Carlos Ortega-González, Nayeli Martínez-Cruz, Lidia Arce-Sánchez, Guadalupe Estrada-Gutiérrez, Carlos Moran, Ana Paola Sánchez-Serrano, Rodolfo Higareda-Sánchez and Julio Francisco de la Jara-Díaz

*BMJ Open* 2016 6:
doi: 10.1136/bmjopen-2016-012107