A randomized controlled trial of the efficacy of rosiglitazone and clomiphene citrate versus metformin and clomiphene citrate in women with clomiphene citrate–resistant polycystic ovary syndrome

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Objective: To compare the efficacy of rosiglitazone and clomiphene citrate (CC) with metformin and CC in women with CC-resistant polycystic ovary syndrome (PCOS).

Design: Randomized controlled trial (RCT).

Setting: A university teaching hospital in Jeddah, Saudi Arabia.

Patient(s): Twenty-five women with CC-resistant PCOS.

Intervention(s): Twelve women were assigned to the rosiglitazone and CC group, and 13 women were assigned to the metformin and CC group for three treatment cycles. The first cycle was started on the first day of the period with either rosiglitazone (4 mg twice daily) or metformin (500 mg three times daily) and continued for three cycles. Clomiphene citrate (100 mg) from the third day for 5 days was added to each cycle.

Main Outcome Measure(s): Ovulation rate, number of follicles and estradiol (E2) on day 12 of the cycle, pregnancy rate, and changes in fasting glucose, serum insulin, HbA1c, total testosterone (T), free T, luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), 4-androstenedione (Δ4-A), sex hormone-binding globulin (SHBG), insulin-like growth factor (IGF)-1, insulin-like growth factor binding protein (IGFBP)-1, and IGFBP-3.

Result(s): No significant differences were found in the baseline characteristics of both groups. Ovulation rate was significantly higher in the rosiglitazone and CC group (18 out of 28 cycles [64.3%]) than the metformin and CC group (12 out of 33 cycles [36.4%]) (P = 0.035). Similarly, statistically significant differences were found in the number of follicles ≥14 mm in the rosiglitazone and CC group (2.2 ± 1) compared with the metformin and CC group (1.1 ± 0.9) (P = 0.02) and E2 on day 12 of the cycle in the rosiglitazone and CC group (1,991 ± 1,389 pmol/L) compared with the metformin and CC group (548 ± 327) (P < 0.001). The pregnancy rate was also higher in the rosiglitazone and CC group (6 out of 12 [50%] women) than the metformin and CC group (5 out of 13 [38.5%] women), but did not reach statistical significance (P = 0.58). Both groups showed no significant changes in fasting plasma glucose or HbA1c or IGFBP-3 values. However, in both groups, fasting serum insulin, total T, free T, LH, DHEA-S, Δ4A, and IGF-1 levels decreased significantly, and SHBG and IGFBP-1 exhibited significant increases.

Conclusion(s): These findings suggest that short-term use of rosiglitazone and CC is more efficacious than metformin and CC in ovulation induction in women with CC-resistant PCOS. (Fertil Steril 2006;85: 428–35. ©2006 by American Society for Reproductive Medicine.)

Key Words: Rosiglitazone, metformin, PCOS

Polycystic ovary syndrome (PCOS) is a common complex and heterogeneous endocrine disorder affecting up to 10% of women of reproductive age (1). It is frequently associated with insulin resistance (IR) and compensatory hyperinsulinemia. The IR is enhanced by the interaction between obesity and the syndrome (2, 3). The hyperinsulinemia reportedly contributes significantly to the development of ovarian hyperandrogenism and chronic anovulation commonly encountered in women with PCOS. In obese women with PCOS, weight loss usually leads to decrease in insulin and androgen levels with a marked improved fertility outcome (4). Clomiphene citrate (CC) is currently the first-line therapeutic modality for women with infertility and PCOS. Ovulation occurs in 70%– 85% of women, but 33%– 45% achieve pregnancy (5). If CC does result in ovulation, the American College of Obstetricians and Gynecologists recommends the use of the insulin sensitizer metformin and CC regardless of whether there is insulin resistance or not (6). Other insulin sensitizers from the thiazolidinediones family, namely troglitazone, pioglitazone, and rosiglitazone, have been used effectively in women with PCOS (7–10).

Recently, the American Society for Reproductive Medicine concluded that “based on the clinical evidence to date,
the use of novel insulin sensitizers such as biguanides and thiazolidinediones promise new treatment options for PCOS for both fertility and long-term disease prevention” (11). The largest published experience with insulin sensitizers in PCOS women has been with metformin. It is a second-generation biguanide used clinically in many different parts of the world to treat type 2 diabetes mellitus. The most common complaint with metformin is gastrointestinal symptoms including diarrhea, nausea, vomiting, and abdominal bloating. Lactic acidosis is a rare risk among patients taking this medication. This most commonly occurs in poorly controlled diabetes and impaired renal function (12).

Trotiglatazone has been removed from the market due to hepatotoxicity. The newer thiazolidinediones rosiglitazone and pioglitazone appear to be safer in terms of hepatotoxicity. Rosiglitazone is a more potent member of thiazolidinediones family, with 100-fold greater binding affinity for peroxisome-proliferator-activated receptor gamma, which decreases peripheral insulin resistance, than that of troglita-zone (13). Currently, no published studies are available to determine which insulin sensitizer is better in women with PCOS. The objective of this study was to compare the efficacy of rosiglitazone and CC with metformin and CC in women with CC-resistant PCOS.

MATERIALS AND METHODS

Subject

The women were recruited from the Infertility Clinic at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, from April 2002 to April 2004. The inclusion criteria for the study included women who were 20–40 years of age with primary infertility and PCOS, wanted to become pregnant, had documented patent tubes by hysterosalpingography, had no other infertility factor, and failed to ovulate with a dose of CC of 150 mg/day for 5 days from day 3 of the period.

The diagnosis of PCOS was based on the presence of oligomenorrhea (i.e., interval between periods was ≥35 days) or amenorrhea (i.e., absence of vaginal bleeding for 6 months), hirsutism, enlarged ovaries with multiple follicles (≥10 measuring 2–8mm in diameter) arranged peripherally and scattered throughout the dense core of stroma on transvaginal ultrasonography (which was performed by the same two ultrasonographers), and/or elevated serum testosterone. In addition, the diagnosis of PCOS was also based on the exclusion of other PCOS-like syndromes, including adrenal dysfunction, Cushing’s syndrome, congenital adrenal hyperplasia, androgen-producing tumors, hyperprolactinemia, and thyroid dysfunction.

Women were excluded from the study if they were diabetic, were taking any medication that could influence carbohydrate metabolism, had hypertension, had used gonadotropins, had undergone ovarian drilling, had IVF, or had abnormal renal or liver function tests. No restrictive diet was recommended, and none of the women studied engaged in intensive aerobic activity during the study. All women examined agreed to participate in the present study, and a written informed consent was obtained from each woman. No financial support was provided for this study by either of the drug companies that manufacture the insulin-sensitizing drug, or by any other drug company. The institutional review board approved the study.

Experimental Protocol

All women were examined clinically, and weight, height, body mass index (BMI), waist-to-hip ratio (WHR), and blood pressure readings were recorded. They were evaluated on the first day of spontaneous cycle or withdrawal bleeding after a 5-day course of medroxyprogesterone acetate (MPA) (Pharmacia and Upjohn, Peapack, NJ), at 10 mg/day. Venous blood was collected between 8:00 AM and 11:00 AM after an overnight fast. The following hormones were measured: follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid-stimulating hormone (TSH), free thyroxin (FT4), total testosterone (T), free T, dehydroepiandrosterone sulfate (DHEA-S), 17-OH-progesterone (17-OH-P), and 4-androstenedione (4-A). Serum levels of sex hormone-binding globulin (SHBG) and insulin (insulin-like growth factor [IGF]-1, insulin-like growth factor binding protein [IGFBP]-1, and IGFBP-3), together with plasma glucose, were also measured. Each woman underwent an oral glucose tolerance test (OGTT) by ingesting a 75-g dextrose solution orally and collecting blood samples for the determination of plasma glucose and insulin at intervals for 2 hours according to World Health Organization (WHO) criteria (14). The plasma glucose and serum insulin responses to OGTT were analyzed by calculating the areas under the curves (AUC) by the trapezoidal rule using absolute values.

After the OGTT the women were randomized by a research nurse into two groups: rosiglitazone (Avandia; Smith-Kline Beecham Pharmaceuticals, Philadelphia, PA) (4 mg twice daily) and CC (Clomid; Hoechst Marion Roussel, Paris, France) (100 mg daily from the third day of the period for five days), or metformin (Glucophage, Liphia Sante, Lyon, France) (500 mg three times daily) and CC (100 mg daily) from the third day of the period for five days. The randomization was completed by opening sealed envelopes containing numbers from a computer-generated random table.

Women of both groups had transvaginal ultrasonography and E2 on cycle day 12. Ovulation was determined by measuring P levels on cycle days 21, 24, and 28. When ovulation was evident (a serum progesterone level >5.0 ng/mL [15.9 nmol/L] and a blood pregnancy test was positive, the woman was asked to discontinue rosiglitazone or metformin, and a pelvic ultrasound was arranged to document the pregnancy. Women without evidence of ovulation and with negative pregnancy test were asked to continue
Rosiglitazone or metformin, and were given another course of MPA to initiate another treatment cycle. Similarly, women who ovulated but did not get pregnant continued rosiglitazone or metformin. Starting on day 3 of the period or withdrawal bleeding, CC (100 mg/day for 5 days) was added. The same process was repeated for the third treatment cycle. No other co-interventions, such as hCG or IUI, were performed.

Safety measures included clinical assessment for adverse events and monitoring of complete blood count and renal and liver function tests at the end of each treatment cycle. Tests performed at the baseline were repeated again on the first day of menses in women who did not become pregnant after three cycles of rosiglitazone and CC or metformin and CC. The primary outcome of the present study was ovulation rate, and the secondary outcomes included the number of follicles and E2 on day 12 of the cycle, pregnancy rate, and changes in the fasting levels of plasma glucose and other endocrine indices, including serum insulin, total T, free T, LH, FSH, DHEAS, 4-A (intra- and interassay CVs: 4.5% and 4.5%); TSH (4.3% and 5.1%); FT4 (2.1% and 4.3%); T (2.2% and 3.5%); free T (2.7% and 4.1%); E2 (2.2% and 3.5%); insulin (3.0% and 4.5%); and DHEA-S (4.2% and 5.1%), respectively. 84-A (intra- and interassay CVs: 6.5% and 7.1%, respectively) was measured by EIA Kits (Diagnostic Systems Laboratories, Inc., Webster, Texas). 17-OH-P was measured with an Immunochem Dou-

Assays
All hormones were measured by methods based on electro-chemiluminescence immunoassay (ECLIA) using Elecsys 2010 Autoanalyzer System (Boehringer Mannheim, Germany) with dedicated reagents obtained from Boehringer Mannheim. The intra- and interassay coefficients of variation (CVs) for the hormones measured were as follows: FSH (1.6% and 4.5%); LH (1.1% and 2.9%); PROL (2.7% and 4.0%); TSH (4.3% and 5.1%); FT4 (2.1% and 4.3%); T (2.2% and 3.5%); free T (2.7% and 4.1%); E2 (2.2% and 3.5%); insulin (3.0% and 4.5%); and DHEA-S (4.2% and 5.1%), respectively; 84-A (intra- and interassay CVs: 6.5% and 7.1%, respectively) was measured by EIA Kits (Diagnostic Systems Laboratories, Inc., Webster, Texas). 17-OH-P was measured with an Immunochem Double Antibody [1125] RIA Kit (intra- and interassay CVs: 5.1% and 7.6%, respectively); (ICN Pharmaceuticals, Inc., Costa Mesa, CA); and SHBG with an immunoradiometric assay (IRMA) kit (intra- and interassay CVs: 4.5% and 5.6%, respectively); (Orion Diagnostica, Espoo, Finland).

The IGF-1, IGFBP-1, and IGFBP-3 serum levels were measured by ELISA kits (intra- and interassay CV%: 3.8% and 3.7% for IGF-1; 4.7% and 3.7% for IGFBP-1; and 5.5% and 4.8% for IGFBP-3, respectively) (Diagnostic Systems Laboratories, Inc.,). Glucose levels and renal (creatinine, urea) and liver (aspartate and alanine aminotransferases, bilirubin, albumin, alkaline phosphatase, and gama-glytamyltransferase) function tests were measured by methods using an Autoanalyzer (Hitachi 912; Boehringer Mannheim) with dedicated reagents obtained from Boehringer Mannheim. Insulin resistance in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated with the follow-

RESULTS
During the study period, 360 women were evaluated for infertility. Twenty-six women were eligible, but 25 entered and completed the study. One woman refused to participate in the study before randomization. Three women were excluded because of diabetes mellitus. Twelve women were assigned to the rosiglitazone and CC group, and 13 were assigned to the metformin and CC group. All women received and continued the assigned treatments, were available to follow up, and were included in the analysis. The results were analyzed according to intention-to-treat principle. No significant differences were found in the baseline characteristics of both groups (Table 1). The women studied were young (28.58 ± 3.73, 23–36 years [mean ± SD, range] in the rosiglitazone and CC group and 27.38 ± 4.29, 23–35 years in the metformin and CC group) but obese, and all had abdominal obesity with a WHR greater than 0.8. Before treatment, 18 women were oligomenorrheic (8 in rosiglitazone group vs. 10 in metformin group) and 7 were amenorrheic. All studied women were insulin-resistant as indicated by their fasting insulin levels, GIR, and HOMA values, which were >95th percentile of healthy, normo-

In the rosiglitazone and CC group, 11 of 12 (91.7%) women ovulated (18 out of 28 cycles [64.3%]) compared with 10 of 13 (76.9%) women (12 out of 33 cycles [36.4%]) in the metformin and CC group. This was a statistically significant difference (P = .035). Similarly, statistically significant differences were found in the number of follicles ≥14
mm in the rosiglitazone and CC group (2.2 ± 1) (mean ± SD) compared with the metformin and CC group (1.1 ± 0.9) (P=.02) and E₂ on day 12 of the cycle in the rosiglitazone and CC group (1,991 ± 1,389 pmol/L) compared with the metformin and CC group (548 ± 327) (P<.001). In contrast, no statistically significant difference was found in the pregnancy rate. Six of 12 (50%) women in the rosiglitazone and CC group became pregnant, whereas 5 of 13 (38.5%) women became pregnant in the metformin and CC group (P=.58). These findings have a power of 0.17 for ovulation, 0.79 for the number of the follicles, 0.94 for E₂ level, and 0.08 for pregnancy with an α of 0.05 and two-tailed tests. The pregnancy rate per cycle was 21.4% for rosiglitazone and CC and 15.2% for metformin and CC. The cumulative conception curve for both groups is depicted in Figure 1. One twin pregnancy occurred in the rosiglitazone and CC group. One first trimester abortion occurred in each group, and the rest of the pregnant women completed their pregnancies with successful live births.

Both the rosiglitazone and CC and metformin and CC groups showed no significant changes in either fasting plasma glucose or HbA₁c (Table 2). However, fasting serum insulin levels decreased significantly in both groups: by 50.4% in the rosiglitazone and CC group (P=.004) and by 49.9% in the metformin and CC group (P<.001). The latter was accompanied by a significant increase in the GIR values in both groups (93.4% vs. 123.1%, respectively) and a significant decrease in the HOMA values in both groups (50.9% vs. 50.6%), respectively, which confirm improvements in insulin sensitivity.

The serum levels of IGF-1 before treatment were similar in women of both groups, but a significant decrease was observed after treatment (by 27.8% in the rosiglitazone and CC group vs. 25.3% in the metformin and CC group), although values remained within the reference ranges of healthy age-matched non-PCOS women. Both groups exhibited significant increases in the serum levels of IGFBP-1 (by 86.9% in the rosiglitazone and CC group vs. 73.9% in the
metformin and CC group, respectively). In addition, both groups induced a significant decrease in the IGF-1:IGFBP-3 ratio (the mean percentage decrease was 28.4% in the rosiglitazone and CC group vs. 26.3% in the metformin and CC group). No significant changes were observed in the serum levels of IGFBP-3 in both groups.

Although both the rosiglitazone and CC and metformin and CC groups exhibited a significant decline in the levels of LH (by 22.6% vs. 25.6%), no significant differences were observed in the FSH values. However, there were significant decreases in the levels of total T (50.5% vs. 39.9%), free T (62.8% vs. 54.9%), δ4A (26.3% vs. 19.8%) and DHEAS (23.9% vs. 22.2%) in the rosiglitazone and CC and metformin and CC groups, respectively. Both groups showed significant increases in the levels of SHBG in response to treatment (102.3% vs. 118.4%).

The BMI remained unchanged, and no significant changes were observed in the liver or renal function tests or the complete blood counts after treatment. One woman developed bilateral lower limb edema in early pregnancy after the use of rosiglitazone and CC. Her investigations were normal. She was managed conservatively, and the edema subsided within 1 week. Four (31%) women in the metformin and CC complained of diarrhea, nausea, and abdominal bloating. These were mild, tolerated, and did not cause discontinuation of the medications.

DISCUSSION
In 1994, Velazquez et al. published the first report on the use of metformin in women with PCOS (17). In this case series, 26 women were given PCOS treatment with metformin for 8 weeks and showed improved insulin sensitivity, lowered serum testosterone concentration (by 50%), and increased SHBG. Furthermore, three pregnancies occurred. Subsequently, several studies were published on the effects of metformin in women with PCOS. In a meta-analysis of randomized clinical trials between metformin vs. placebo or no treatment, significantly increased ovulation rates (odds ratio 3.8 [95% CI 2.25 to 6.69]) and significant reduction in fasting insulin (odds ratio −5.37 [95% CI −8.11 to −2.63]) were observed (18). In contrast, some studies did not report benefits from metformin therapy. Morbidly obese women (BMI as high as 50 in one study and >37 in another study) with PCOS did not respond to metformin in the usual doses (19, 20). With respect to metformin and CC in women with CC-resistant PCOS, Nestler et al., showed that 19 out of 21 (90%) obese women with CC-resistant PCOS ovulated in response to metformin and CC therapy via decreasing insulin secretion compared with 2 out of 25 (8%) women in the corresponding placebo and CC control group (21). Vandermolen et al., in a multi-center RCT of 25 women with CC-resistant PCOS reported that metformin and CC treatment increased ovulation rates as compared with the placebo and CC (75% vs. 27%) and pregnancy rates (55% vs. 7%), respectively (22). Moreover, Kocak et al., in a larger study involving 56 CC-resistant women with PCOS, demonstrated significantly higher ovulation rates in women treated with metformin and CC as compared with the placebo and CC group (77.7% vs. 14.2%) as well as greater pregnancy rates (14% vs. 0%) (23).
Rosiglitazone and CC were also used to treat women with PCOS resistant to metformin. Ghazeeri et al. treated 25 such women with rosiglitazone and CC (13 women) or rosiglitazone and placebo (12 women) for 2 months only (8). The primary outcome was ovulation rate; changes in insulin sensitivity and androgens were some secondary outcomes. The ovulation rate in women treated with rosiglitazone and CC was 77% compared with 33% in women treated with metformin only. Belli et al. demonstrated that treatment with rosiglitazone decreased LH levels, improved IR parameters, and normalized the menstrual cycles in women with IR and PCOS (24). More recently, Sepilian and Nagamani studied the effect of 6-month rosiglitazone therapy in 12 obese women with PCOS but with severe IR. Eleven (91%) women reverted to regular ovulatory cycling during the treatment period (25).

In contrast, the previous studies of metformin and CC or rosiglitazone and CC vs. placebo and CC, the present study intended to compare metformin and CC to rosiglitazone and CC. Furthermore, rosiglitazone or metformin were started in the same treatment cycle with CC. Recent studies documented the effectiveness of this approach (8, 9). Currently, no clear recommendations exist on how long the insulin sensitizer need to be given before starting CC to achieve maximal success. It has been suggested that pretreatment with metformin for 5 weeks should be given before starting CC (12). This remains an area of further research.

In the present study, insulin-sensitizing therapy with rosiglitazone and CC or metformin and CC resulted in increased rates of ovulation (64.3% vs. 36.4%) and pregnancy (58.3% vs. 38.5%), respectively, in CC-resistant women with PCOS. In addition, hyperinsulinaemia and hyperandrogenism were also decreased. These findings were in agreement with previous studies. Higher ovulation rates, number of follicles and E2 on day 12 of the cycle, and the pregnancy rates that were observed in the present study (in the rosiglitazone and CC group as compared with that of the metformin and CC group) suggest that rosiglitazone and CC may be the favorable therapeutic modality for obese women with PCOS who desire fertility.

Both therapy groups showed an improvement in IR, as indicated by the changes in the calculated values of GIR and HOMA, which were associated with a decrease in the levels of serum insulin. The latter is consistent with the mechanism of rosiglitazone therapy, which was not accompanied by changes in fasting plasma glucose levels (13). The studied women were not diabetic, and the duration of the therapeutic intervention was relatively short to demonstrate any signif-

### TABLE 2

Endocrine and metabolic parameters of women with PCOS before and after treatment with rosiglitazone or metformin.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rosiglitazone group (n = 6)</th>
<th>Metformin group (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>FSH (mIU/L)</td>
<td>6.09 ± 1.67</td>
<td>6.14 ± 1.49</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>11.13 ± 5.50</td>
<td>8.62 ± 4.42</td>
</tr>
<tr>
<td>T (nmol/L)</td>
<td>1.86 ± 0.90</td>
<td>0.92 ± 0.43</td>
</tr>
<tr>
<td>Free T (pmol/L)</td>
<td>35.34 ± 15.20</td>
<td>17.15 ± 6.35</td>
</tr>
<tr>
<td>Δ4-A (nmol/L)</td>
<td>4.71 ± 0.47</td>
<td>3.47 ± 0.41</td>
</tr>
<tr>
<td>DHEAS (nmol/L)</td>
<td>3.93 ± 0.63</td>
<td>2.99 ± 0.44</td>
</tr>
<tr>
<td>SHBG</td>
<td>34.17 ± 2.39</td>
<td>69.11 ± 15.09</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.83 ± 0.68</td>
<td>4.81 ± 0.62</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>144.9 ± 17.36</td>
<td>71.9 ± 18.69</td>
</tr>
<tr>
<td>GIR × 100</td>
<td>3.33 ± 0.31</td>
<td>6.44 ± 1.37</td>
</tr>
<tr>
<td>HOMA</td>
<td>5.14 ± 0.92</td>
<td>2.54 ± 1.07</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.91 ± 0.65</td>
<td>5.83 ± 0.72</td>
</tr>
<tr>
<td>IGFBP-1 (ng/mL)</td>
<td>439.4 ± 116.2</td>
<td>317.2 ± 75.9</td>
</tr>
<tr>
<td>IGFBP-1 (ng/mL)</td>
<td>4.50 ± 1.86</td>
<td>8.41 ± 1.83</td>
</tr>
<tr>
<td>IGFBP-3 (ng/mL)</td>
<td>5474 ± 1172</td>
<td>4885 ± 2123</td>
</tr>
<tr>
<td>IGFBP-3 (ng/mL)</td>
<td>8.66 ± 5.05</td>
<td>6.91 ± 1.97</td>
</tr>
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</table>

Note: Data are presented as mean ± SD. NS = not significant (P>.05); FSH = follicle-stimulating hormone; LH = luteinizing hormone; T = testosterone; Δ4-A = Δ4-androstenedione; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin; GIR = glucose-to-insulin ratio; HOMA = homeostasis model assessment; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein.

icant changes in the levels of HbA1C. The rosiglitazone and CC group showed significant decreases in the serum levels of LH, total T, free T, DHEAS, and δ4-A, which were accompanied by increase in the levels of SHBG. Similar results were obtained in the metformin and CC group. Ehrmann et al. reported significant decreases in androgen levels accompanied by improved glucose tolerance, together with decreased plasminogen activator inhibitor-1 activity, in women with PCOS who were treated with troglitazone (26). Ghazeeeri et al. demonstrated significant decreases in the serum levels of LH, total T, and DHEAS with increase in SHBG in CC-resistant women with PCOS (8). The changes in LH levels were different from that described in previous studies in women with PCOS treated with troglitazone, which showed decreases in circulating androgen levels but without any changes in LH values (27, 28). This was attributed to the fact that the obese women with PCOS and severe IR did not exhibit increased LH levels at baseline (28). Furthermore, More et al. demonstrated low LH levels in obese women with PCOS but with severe IR (29). Others have suggested two possible distinct phenotypes of women with PCOS: a low-LH high insulin group and a high-LH low insulin group (29, 30). It is not clear whether the decrease in DHEAS levels observed in the present study was related to the correlation of hyperinsulinemia per se or was due to the direct effects of rosiglitazone on the steroidogenic enzymes in the adrenal gland. Azziz et al. observed similar effect on DHEAS levels with troglitazone therapy for 20 weeks (31).

Serum levels of IGF-1 were decreased in both treatment groups with concurrent significant increase in the serum levels of IGFBP-1 and decrease in the IGF-I: IGFBP-III and IGF-I: IGFBP-I ratios in both therapy groups. This was consistent with the study of Belli et al., inwomen with PCOS, in response to rosiglitazone therapy (24). In contrast, other studies did not observe any changes in IGF-1 levels in response to metformin (32, 33) or rosiglitazone therapy (9). However, a significant increase in the serum levels of IGFBP-1 was evident in both groups after therapy. The latter is consistent with the diminished IR in response to both metformin and rosiglitazone therapy and may contribute to a decrease in the bioavailability of IGF-I to the ovaries. Similar findings were obtained by De Leo et al. during treatment with metformin (34). However, others did not observe any changes in the levels of IGFBP-1 in response to metformin therapy (32).

The mechanisms of IR in women with PCOS, and the ways that both rosiglitazone and metformin therapy may produce their effects at the level of insulin action and/or metabolism, are still largely under investigation. Such drugs appear to act at different levels of glucose metabolism. Accordingly, interindividual variations in the efficacy of such drugs might be observed according to the specific defects producing the impaired insulin action related to the specific drug effects. However, the normalization of insulin levels in response to therapy with different insulin-sensitizing drugs, including rosiglitazone, metformin, and others, in women with PCOS suggest that the metabolic and reproductive abnormalities might be related to the hyperinsulinaemia per se and not to any specific mechanism of IR.

Unlike metformin, rosiglitazone decreases hepatic fat content and increases insulin sensitivity in muscles. These effects make the drug more useful in patients with insulin resistance. Adverse effects were reported with rosiglitazone therapy, including peripheral edema and slight decreases in hemoglobin and hematocrit. The idiosyncratic liver toxicity with troglitazone does not appear to be a class effect (35). Alanine aminotransferase levels more than 10 times the upper limit of normal were observed in 0.68% of patients taking troglitazone, compared with none in the patients taking rosiglitazone or pioglitazone. In the present study, one woman developed lower limb edema, which resolved spontaneously. In contrast, 31% of the women receiving metformin therapy complained of gastrointestinal symptoms commonly reported in the literature, which may influence the degree of compliance with using the drug.

In conclusion, it appears that in women with CC-resistant PCOS, treatment with insulin sensitizers rosiglitazone or metformin is promising, although preference is given to the use of rosiglitazone as indicated by better therapy outcomes.

REFERENCES


