Combined Pioglitazone and Clomiphene Citrate Versus Metformin and Clomiphene Citrate in Clomiphene Citrate Resistant Women with PCOS

MARYAM MAHMOOD, M.D.; HODA ABD EL-AAL, M.D. and DOAA SALAH EL-DIN, M.D.

The Department of Obstetrics and Gynaecology, Faculty of Medicine, Cairo University

Abstract

Background: Clomiphene citrate (CC) is the first line therapy for induction of ovulation in PCOS. Since hyperinsulinaemia plays a pivotal pathophysiological role in PCOS, it is rational to implicate the use of insulin sensitizers in CC resistant PCOS women.

Objective: To investigate and compare the efficacy of addition of two insulin sensitizers, pioglitazone and metformin, to CC in patients with PCOS who are resistant to clomiphene citrate.

Setting: The study was conducted at the infertility outpatient clinic in Kasr Al-Aini Teaching Hospital, Cairo University.

Patients and Methods: We conducted a randomized, clinical trial on sixty women with PCOS who were CC resistant. Patients underwent clinical and biochemical evaluation at baseline. Patients were then randomized to either oral treatment with metformin (1000mg twice daily) or pioglitazone 30mg/day. All patients received CC 100mg starting from day 3 of a spontaneous or induced cycle and for 5 days. The combined insulin sensitizer-clomiphene citrate regimen was used for 3 successive cycles. The initial evaluation was repeated at the end of the study period. Primary outcome measures included ovulation rate, mean no. of dominant follicles/ovulatory cycle, serum progesterone and pregnancy rate. Secondary outcome measures included the effect of therapy on other clinical and laboratory parameters.

Results: The study involved sixty CC-resistant PCOS cases; thirty in each group. The patients were comparable at baseline. Subjects in the pioglitazone (+CC) arm had a significant decrease in WHR while the BMI significantly increased. Serum LH, free testosterone, fasting insulin and QUICKI significantly decreased on pioglitazone therapy. Subjects in the metformin (+CC) arm exhibited significant decreases in BMI, WHR, free testosterone, fasting insulin and QUICKI index. No significant difference was found in the ovulation rate between the two groups (p=0.56); 57/82 cycles (69.5%) in the pioglitazone (+CC) group versus 55/84 cycles (65.5%) in the metformin (+CC) group. Similarly there were no significant differences between the two groups regarding the mean number of dominant follicles (p=0.67) and serum progesterone (p=0.8). Conception rate/cycle was not significantly different between the two groups; 17.07% in the pioglitazone (+cc) group versus 15.48% in the metformin (+cc) group (0.78).

Conclusion: Pioglitazone is as effective as and not superior to metformin in terms of successful ovulation induction and pregnancy achievement.

Key Words: Pioglitazone – Metformin – Clomiphene resistant – Polycystic ovary syndrome.

Introduction

PCOS is a heterogenous clinical and biochemical condition presenting with menstrual disturbances, infertility, hirsutism and metabolic derangements [1]. The mechanisms underlying PCOS are not well understood, yet, insulin resistance (IR) and compensatory hyperinsulinaemia which were 1st described by Burghen in 1980; [2] are now recognized as important pathogenetic factors in determining hyperandrogenism in PCOS women especially when obesity is present [3]. Hyperinsulinaemia acts on cytochrome P450c17a thus directly stimulating ovarian and adrenal androgen production. In addition it suppresses SHBG synthesis, thereby increasing the free androgen portion [4]. A vicious circle is set with hyperandrogenism producing mild IR through increasing type II skeletal muscle fibres which are less insulin sensitive and also through inhibiting muscle glycogen synthetase [5]. Moreover, insulin affects follicular development either directly or indirectly through increasing intra-ovarian androgen levels, or increasing LH secretion [4].

For decades, clomiphene citrate has been the 1st line therapy for induction of ovulation in women with PCOS [6]. The cost of the drug, the fewer side effects, and hence the good patient compliance, the need for less meticulous monitoring and
little experience placed CC in that position. However, CC resistance develops in around 20%-25% of the patients [7]. These cases are in turn candidates for 2nd line therapy with gonadotropins or ovarian drilling; both modalities posing serious potential side effects in the form of high order pregnancy, and OHSS necessitating extensive monitoring with the former [8], and the risk of adhesions with the latter. The pathophysiological role of excess insulin in determining excess androgen availability and activity has lead to the implication of therapeutic modalities aiming at ameliorating insulin resistance in these women. This could be achieved by reducing body weight if obesity is present or by the use of insulin sensitizers. The American Society for Reproductive Medicine stated 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 infertility and long term disease prevention” [9].

Metformin, a second generation biguanide, is the oldest and still the most commonly used insulin sensitizer in many parts of the world to treat type 2 DM [10]. In 1994, Valequez et al., published the first report on the use of metformin in women with PCOS [11]. Since then it has become the most popular insulin sensitizer for PCOS [10].

Pioglitazone, belongs to a new class of drugs; the thiazolidinedione family which has attracted great attention in recent years. It is a peroxisome proliferator-activated receptor (PPAR)-γ agonist with insulin sensitizing and antidiabetic properties [12]. Both drugs proved to be effective in PCOS, however it is not known whether one drug is superior to the other. The aim of the present study is to investigate and compare the efficacy of metformin to that of pioglitazone when combined with clomiphene in clomiphene-citrate resistant women with PCOS.

**Patients and Methods**

A randomized clinical trial comprising women with PCOS was performed between November 2009 and January 2011. The subjects were recruited from the infertility clinic of Kasr Al-Aini teaching hospital in Cairo. Cases included in the study were diagnosed as CC resistant after failure to ovulate on a dose of 150mg CC/day started on the third day of the cycle for at least three successive cycles.

The diagnosis of PCOS was based on the Rotterdam criteria [13] i.e. the presence of any two of the following three criteria (1) clinical and/or biochemical hyperandrogenism; (2) ovarian dys-
thighs, and 9) upper arms. Each area was scored from 0 to 4. Hirsutism was diagnosed when a score ≥7 was evaluated. PCO morphology on ultrasound was diagnosed if at least one ovary with at least 12 follicles of a diameter of 2-9mm or a volume > 10ml was documented.

Serum and plasma samples were obtained during the early follicular phase of a spontaneous menstrual bleeding or withdrawal bleeding induced with norethisterone acetate. After fasting overnight for 10h, blood samples were collected for the following assays: Follicle-stimulating hormone (FSH), luteinizing hormone (LH), free testosterone (T), 17-hydroxyprogesterone (17OHP), dehydroepiandrosterone sulfate (DHEAS), prolactin, TSH, fasting blood glucose and fasting insulin. Complete blood count, hepatic and renal chemistry were performed at baseline and monthly thereafter as a monitor of general drug safety. Insulin sensitivity was measured using the QUICKI index [18].

After baseline clinical and laboratory evaluation, the patients were randomized to receive either pioglitazone or metformin. Randomization was produced from a computer-generated random list. The patients accordingly received Actos, The Arab Pharmaceuticals Manufacturing Co. Ltd, Sult-Jordan, [licensed by Takeda Pharmaceuticals, Osaka-Japan] (pioglitazone 30mg; once daily) or Cidophage, CID, Egypt (metformin 500mg; two tablets bid). In addition to the insulin sensitizer, all patients received Clomid, Global, Napi (clomiphene citrate 50mg bid [CC]) for 5 days from cycle day 3 to day 7. The combined CC-insulin sensitizer regimen was used for three treatment cycles. To minimize side effects, metformin therapy was initiated at a low dose taken with meals, and the dose was then doubled. Patients started with 500mg of metformin twice daily for 1 week; then the dose was increased to 1000mg twice daily.

For all patients folliculometry was performed (via transvaginal US) starting from day 10 of the cycle and every other day or daily thereafter (according to the ovarian response) until a dominant follicle ≥18mm in mean diameter was reached and intercourse was then advised. Ovulation was further confirmed by serum progesterone on day 22-24 of the cycle.

Cases with evidence of ovulation and absence of menstruation, had a blood pregnancy test, and if positive were asked to discontinue the insulin sensitizer. A pelvic ultrasound was done at six weeks of gestation to document the pregnancy. As for cases without evidence of ovulation (and negative pregnancy test), the insulin sensitizer was continued and another withdrawal menses was initiated to start the next treatment cycle. Also, those subjects with evidence of ovulation but with negative pregnancy test continued their insulin sensitizer. For all cases with negative pregnancy test, CC was added from day 3 of the cycle and for 5 days. The same procedure was repeated for the remaining treatment cycle. At the end of the follow-up period the baseline evaluation was repeated.

The primary outcome measures included number of responders, ovulation rate per cycle, mean no. of dominant follicles per ovulatory cycle, progesterone levels, and conception rates per patient and per cycle. Secondary outcome measures included drug effects on LH, serum androgens and parameters of insulin sensitivity (fasting blood sugar, fasting insulin, and QUICKI).

Regarding laboratory assays, hormones were measured by chemiluminescent immunoassay on Immulite (Abott). Fasting blood sugar was measured using enzymatic hexokinase in vitro method on Hitachi (Rosche) Liver and kidney functions were measured on Cobas Integra autoanalyzer (Rosche) and CBC on Gen s coulter (Beckman-Coulter).

Data were statistically described in terms of mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison between the study groups was done using Student t-test for independent samples. Within group comparison of numerical variables was done using paired t-test. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. p-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Sixty four women with PCOS who were proved resistant to CC were recruited and randomized to receiving either pioglitazone or metformin. Two patients were lost to follow-up from the pioglitazone arm while two other cases dropped from the metformin arm due to intolerance to side effects (nausea and diarrhea). Sixty patients completed the study: 30 in each arm. The baseline clinical and endocrinical characters of the two groups were comparable as shown in Table (1).
The effect of medical therapy on the clinical parameters is shown in Table (2). The mean BMI and WHR were significantly decreased in the metformin group \((p<0.001\) and 0.01 respectively) Pioglitazone therapy resulted in a significant increase in BMI \((p<0.001)\) but with a favourable significant improvement in WHR \((p<0.001)\).

The hormonal profile of the studied cases is shown in Table (3). Serum LH was significantly decreased in both pioglitazone \((p<0.001)\) and metformin \((p<0.001)\) groups. DHEAS levels were not affected by either therapy.

Insulin levels were significantly reduced and insulin sensitivity significantly improved on either therapy \((p<0.001)\).

The reproductive outcome of the studied groups is shown in Table (3). There was no statistically significant difference in the number of subjects responding to therapy; 80% of the cases in the pioglitazone arm ovulated versus 76.6% of the cases in the metformin arm \((p=0.75)\). The ovulatory rate in the pioglitazone group \((57\) out of \(82\) cycles=69.5\%) was not significantly different from that in the metformin group \((55\) out of \(84\) cycles=65.5\%) \((p=0.56)\).

The mean number of dominant follicles/ovulatory cycle was not significantly different between the two groups \((1.37\pm0.39\) versus \(1.33\pm0.39\) \(p=0.67)\). Similarly midluteal serum progesterone did not differ significantly between the two treatment arms \((p=0.8)\).

In the pioglitazone group fourteen out of thirty women \((46.7\%)\) got pregnant while thirteen out of thirty women \((43.3\%)\) became pregnant in the metformin group \((p=0.8)\). The conception rate/cycle in the pioglitazone arm was 17.07\% versus 15.8\% in the metformin arm \((p=0.78)\). Pregnancies in both treatment arms were singleton pregnancies.

Regarding the occurrence of side effects in the subjects completing the study; 7 cases \((21\%)\) experienced nausea and diarrhea in the metformin group while one case \((3\%)\) had mild lower limb oedema in the pioglitazone group. Complete blood counts, liver and renal functions remained within normal ranges during and after treatment.

<p>| Table (1): Clinical and laboratory parameters of PCOS subjects before treatment. |
|---------------------------------|-----------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pioglitazone Group (n=30)</th>
<th>Metformin Group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.07±3.89</td>
<td>26.47±4.03</td>
</tr>
<tr>
<td>WHR</td>
<td>28.26±2.61</td>
<td>27.93±2.54</td>
</tr>
<tr>
<td>LH (µU/ml)</td>
<td>0.885±0.02</td>
<td>0.88±0.04</td>
</tr>
<tr>
<td>Free Testosterone (pg/ml)</td>
<td>9.09±1.91</td>
<td>9.89±1.79</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>11.03±2.93</td>
<td>10.72±2.45</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>260.74±81.42</td>
<td>251.12±79.71</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml)</td>
<td>94.37±8.84</td>
<td>94.37±8.84</td>
</tr>
<tr>
<td>QUICKI</td>
<td>19.94±4.89</td>
<td>20.34±4.78</td>
</tr>
<tr>
<td></td>
<td>0.309±0.01</td>
<td>0.306±0.01</td>
</tr>
</tbody>
</table>

| Table (2): Clinical and laboratory parameters of PCOS subjects before and after treatment. |
|---------------------------------|-----------------|-------------------|
| | Pioglitazone Group | Metformin Group | Post ttt p-value between groups |
|---------------------------------|-----------------|-------------------|
| | Baseline | Post ttt | p-value | Baseline | Post ttt | p-value | |
| BMI (kg/m²) | 28.26±2.61 | 29.08±2.76 | <0.001 | 27.93±2.54 | 26.99±2.16 | <0.001 | 0.002 |
| WHR | 0.885±0.04 | 0.868±0.04 | <0.001 | 0.88±0.04 | 0.872±0.04 | 0.01 | 0.63 |
| LH (µU/ml) | 9.09±1.91 | 7.5±1.36 | <0.001 | 9.89±1.92 | 9.43±1.97 | 0.1 | 0.001 |
| Free Testosterone (pg/ml) | 11.03±2.93 | 8.8±2.49 | <0.001 | 10.72±2.45 | 8.4±1.97 | <0.001 | 0.47 |
| DHEAS (µg/dl) | 260.74±81.42 | 257.65±83.18 | 0.08 | 251.12±79.71 | 250.83±79.46 | 0.71 | 0.75 |
| FBG (mg/dl) | 94.37±8.84 | 93.5±8.35 | 0.2 | 94.37±8.84 | 93.5±8.35 | 0.2 | 0.43 |
| Fasting Insulin (µU/ml) | 19.94±4.89 | 12.2±3.93 | <0.001 | 20.34±4.78 | 12.97±3.45 | <0.001 | 0.42 |
| QUICKI | 0.309±0.01 | 0.332±0.018 | <0.001 | 0.306±0.01 | 0.328±0.016 | <0.001 | 0.34 |
Discussion

This is a randomized clinical trial to evaluate and compare the efficacy of two insulin sensitizers in clomiphene citrate resistant PCOS cases. Although pioglitazone possesses different biological mechanisms from those exhibited by metformin, both drugs proved effective in inducing ovulation in >75% and achieving pregnancy in >40% of the study population. The ovulation rate/cycle was 69.5% and 65.5% in the pioglitazone and metformin arms respectively. The conception rates/cycle were 17.07% and 15.48% in the pioglitazone and metformin arms respectively.

Metformin, a biguanide approved as an oral hypoglycaemic in T2DM, has been proved to be effective in CC-resistant PCOS women by many authors. In 1998, Nestler et al., [16] conducted a multicenter placebo-controlled study involving CC-resistant obese PCOS women and found that 90% of the women in the combined metformin +CC arm ovulated. In another multicenter placebo-controlled trial, Vandermolen and associates [17] demonstrated that ovulation occurred in 75% of the subjects receiving combined metformin and CC while 55% of them became pregnant and the reported pregnancy rate per cycle was 21%. The dose of metformin used in these two trials was 500mg tds. Later on, Kocak et al., [18] reported the occurrence of ovulation in 77.7% and pregnancy in 14% of the CC resistant subjects in their study population who were assigned to metformin +CC. Also, Malkawi and Kublan [19] reported an ovulatory rate of 68.6% and a pregnancy rate of 56.3% in a group of CC-resistant PCOS women receiving metformin+CC. The dose of metformin used by Kocak et al. [18] and Malkawy & Kublan [19] was 850mg bid. Rouzi and Ardawy [20] noted that 77% of the women in the metformin +CC group ovulated and reported an ovulatory rate of 36.4% and a pregnancy rate of 15.2%. In a randomized placebo controlled study Kazerooni et al. [21] reported the occurrence of ovulation in 88.9% and pregnancy in 16.6% of the cases assigned to metformin +CC. Recently, in a large study, Abu Hashim et al. [22] reported an ovulatory rate of 62% (65% of their cases) and a pregnancy rate of 11.2% (24% of their cases) and in another study, Abu Hashim and colleagues [23] reported an ovulatory rate of 67% and a pregnancy rate of 15.4% in patients receiving combined metformin and clomiphene citrate. The dose of metformin used in the last four trials was 500mg tds. Indeed, the review by Moll et al. [24] reported that combined metformin and CC led to a significantly higher clinical pregnancy rate and live birth rate than CC alone. On the other hand, Sturrock et al. [25] conducted a randomized placebo-controlled trial for 6m and found no benefit from the addition of metformin (500mg tds) to cc in CC-resistant PCOS women in terms of ovulation induction and pregnancy (p=0.63 and p=0.59 respectively).

It has been suggested that the increased response to CC on addition of metformin may be due to amelioration of insulin resistance or direct inhibition of androgen production in human theca cells [26]. In this study, therapy with the insulin sensitizer was initiated in the same treatment cycle as CC and proved successful. With the exception of the study conducted by Rouzi and Ardawy [20], all the previously mentioned trials [16-19,21-23] used a metformin pretreatment (i.e. before addition of CC) for 4-8 weeks. However, the efficacy of starting the insulin sensitizer in the same treatment cycle as CC has been previously demonstrated [20,27]. It is not clear whether our results are attributable to the larger dose of metformin we used (2000mg/day) or to whether pretreatment with the insulin sensitizer is actually unnecessary. This issue may require further studies [20].

Metformin seems to display vast metabolic actions, as vast as the metabolic derangements displayed by the addressed syndrome. Regarding anthropometric measures metformin therapy resulted in significant decrease in BMI and WHR. The reduction of BMI with metformin has been successively reported in initial data of use in women with PCOS [11], in non obese subjects [28], in obese and morbidly obese women [29,30], and in CC resistant PCOS [18,21]. A significant reduction in WHR on metformin therapy has also been reported by some authors [16,29]. On the other hand, others [31-33] found no significant variations in BMI or WHR during metformin therapy. On hormonal basis, metformin significantly improved hyperandrogenaemia. In accordance with our findings, this has been reported by many [16,18,21,32] but not all [29,31].
authors. As expected, metformin therapy significantly reduced fasting insulin, and improved insulin sensitivity. This agent improves insulin sensitivity by reducing hepatic glucose production, increasing peripheral glucose uptake by the liver, skeletal muscle and adipose tissue, stimulating glycolysis in the liver, reducing lipolysis in the adipose tissue [therefore, decreasing free fatty acid (FFA) concentrations] and inhibiting intestinal glucose absorption [34]. Significant decrease in fasting insulin concentrations was noted by many authors [29,33,35]. Significant improvement in insulin sensitivity during metformin treatment has also been reported [31,35]. It is therefore not surprising that recent consensus on treatment of infertile women with PCOS who were resistant to clomiphene and dexamethasone. Ota et al. studied the efficacy of pioglitazone monotherapy on fecundity in nine infertile patients with PCOS who were resistant to clomiphene and dexamethasone. The dose of pioglitazone ranged from 15-30mg/day and the treatment continued for up to 32 weeks. Seven of nine women became pregnant at an average of 11.3 weeks of initiation of therapy. The reported pregnancy rate was impressively high (77.78%), however the study sample was too small to withdraw such a conclusion. Kim et al. studied the efficacy of pioglitazone monotherapy on fecundity in nine infertile patients with PCOS who were resistant to clomiphene and dexamethasone. The dose of pioglitazone ranged from 15-30mg/day and the treatment continued for up to 32 weeks. Seven of nine women became pregnant at an average of 11.3 weeks of initiation of therapy. The reported pregnancy rate was impressively high (77.78%), however the study sample was too small to withdraw such a conclusion.

Pioglitazone, a thiazolidinedione approved for treatment of type 2 DM, has been less investigated. A couple of reports studied the efficacy of this drug in CC resistant PCOS women. Ota et al. [37] studied the efficacy of pioglitazone monotherapy on fecundity in nine infertile patients with PCOS who were resistant to clomiphene and dexamethasone. The dose of pioglitazone ranged from 15-30mg/day and the treatment continued for up to 32 weeks. Seven of nine women became pregnant at an average of 11.3 weeks of initiation of therapy. The reported pregnancy rate was impressively high (77.78%), however the study sample was too small to withdraw such a conclusion. Kim et al. [38] studied the role of pioglitazone on ovarian stimulation and IVF outcome in CC resistant PCOS patients who were scheduled to an IVF protocol involving the use of a GnRH antagonist and oral contraceptive (OC) pretreatment. Pioglitazone therapy was started with the OC. The achieved clinical pregnancy rate was 36% (11/30). However, our results are not comparable due to the difference in the adopted study design.

Regarding comparing pioglitazone to metformin in PCOS, a couple of studies were reported in the literature. Ortega-González [39] conducted a study on 52 obese women with PCOS. Their results suggested that pioglitazone (30mg/day) was as effective as metformin (850mg/lds) in improving insulin sensitivity and hyperandrogenism, despite an increase in BMI and WHR associated with pioglitazone. Also, treatment with pioglitazone or metformin was associated with the occurrence of pregnancy (n=5 and n=3, respectively). Naka et al. [35] compared the effect of metformin (850mg bid) and pioglitazone (30mg/day), on endothelial function in women with PCOS. Both insulin sensitizers induced favorable changes in insulin resistance and hyperandrogenism indices. Again, our results are not comparable; for, to our knowledge, this is the first study to compare these two drugs in CC-resistant PCOS women. However, it is noteworthy, that the efficacy of the combined use of pioglitazone (45mg/day) and metformin has been reported by Glueck et al. [40] who noted improvement in menstrual irregularity in a group of 13 obese PCOS women previously non responsive to metformin. Thus, according to the authors, pioglitazone maybe considered effective in obese patients with metformin-resistant PCOS but further research is required to confirm this.

Pioglitazone may exert its reproductive hormonal effects in PCOS either directly on the ovary or indirectly by reducing circulating insulin levels. It has been suggested that PPAR-represent a novel regulatory system in the human ovary. TZD were found to enhance progesterone production, and completely abolish insulin-induced stimulation of testosterone production. Thiazolidinediones have been shown to inhibit the steroidogenic enzymes p450c17 and 3β-hydroxysteroid dehydrogenase and their encoding genes [41,42].

In this study, pioglitazone improved PCOS related hormonal abnormalities. We observed significant lowering of serum LH consistent with that reported by Brettenhaler et al. [43] and Koo et al. [44] and reemphasized in the metaanalysis by Li et al. [45]. Pioglitazone therapy also resulted in a decrease in serum androgens. Amelioration of hyperandrogenaemia on pioglitazone use in PCOS has been reported by several authors [35,39,43,45]. On the other hand, Koo et al. [44] and Aroda et al. [46] failed to elicit any changes in total and free testosterone levels.

Although we found that pioglitazone therapy led to a favourable significant reduction in WHR, this was accompanied by a significant increase in BMI. The increase in body weight has been attributed to expansion of the subcutaneous fat depot, and in some patients to oedema, whereas the mass of visceral fat remained unchanged or decreased [47]. Available data in the literature regarding the effect of pioglitazone on anthropometric measures has been conflicting. Significant increase in BMI [35,46], an increase in both BMI and WHR [39], a decrease in WC [35] and a decrease in BMI [44] were reported on pioglitazone use. On the other hand, no effect on WHR [46] and on both BMI and WHR [43] were observed by others.
TZD bind to PPARγ, promoting synthesis of glucose transporters and up-regulating the expression of multiple genes mediating insulin function [12]. Treatment with PPAR-γ agonist is followed by decreased peripheral adipocyte lipolysis, decreased free fatty acid (FFA) levels, and visceral fat redistribution [48]. Thiazolidinediones exert their insulin-sensitizing actions through two mechanisms: Directly, by the so-called ‘fatty acid steal’ hypothesis, and indirectly, by increasing the expression of 11β-hydroxysteroid dehydrogenase type 1. The fatty acid steal hypothesis entails promotion of fatty acid uptake and storage in peripheral adipose tissue thereby increasing adipose tissue mass while protecting insulin sensitive tissues namely skeletal muscle, liver and pancreas from adverse effects of high FFA concentrations. TZD are therefore claimed to keep fat where it belongs [47]. As expected, pioglitazone resulted in significant reduction in serum insulin levels with subsequent improvement in insulin sensitivity. Our results are in line with those reported by others [35,39,43,46]. On the other hand, Koo et al. [44] found no effect of pioglitazone on parameters of insulin resistance in non obese PCOS women. Pioglitazone is now the only “freely” surviving thiazolidinedione. In January 1997, the first thiazolidinedione, troglitazone was approved as a glucose-lowering therapy for patients in the US with type 2 DM [47]. Troglitazone was subsequently withdrawn from the market, in March 2000 because of hepatotoxicity [48]. The other two PPAR-γ agonists, rosiglitazone and pioglitazone, were approved in the US in 1999 [47]. In September 2010, the FDA required that GSK develop a restricted access program for Avandia (rosiglitazone) under a risk evaluation and mitigation strategy, or REMS. “Under the REMS, Avandia will be available to new patients only if they are unable to achieve glucose control on other medications and are unable to take Actos (pioglitazone), the only other drug in this class” stated the FDA. These new restrictions were in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with Avandia [50]. In Egypt rosiglitazone was banned and is currently unavailable in the Egyptian drug market. Whether or not pioglitazone will continue to survive remains a question to be answered. Recently, Glintborg, and Andersen [51] concluded that glitazones do not seem to possess significant metabolic or clinical advantages compared to metformin treatment and also necessitate safe birth control, facts which limit their use in the daily practice. Katsiki et al. [52] may thus be justified to recommend the use of TZDs only in substitution of or in addition to metformin in insulin-resistant or obese PCOS women who either do not tolerate [53] or do not respond to metformin therapy [54]. In this study, pioglitazone did not prove superior to metformin in terms of successful ovulation induction nor pregnancy achievement. Besides, metformin has the advantage of decreasing BMI. Furthermore, the discrepancy in treatment cost cannot be overlooked. We, therefore, agree with Abu Hashim, et al. [22] in that, combined metformin-CC therapy seems to be both economic and safe. In developing countries where economic aspects of therapy are to be taken into consideration, it is rational to start with this therapy in CC-resistant PCOS patients before moving on to more expensive or invasive modalities [22].

References
10- NESTLER J.E., STOVALL D., AKHTER N., IJOURNO M.J. and JAKUBOWIZ D.J.: Strategies for use of insulin


