Chapter 11

The use of metformin in overweight and lean infertile patients with polycystic ovarian Syndrome: a randomized controlled trial

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Abstract

**Objective:** to investigate the potential value of metformin prior to and concomitant with the use of clomiphene citrate and its impact on improving ovulation rate and regularity of the cycle in Polycystic ovarian syndrome women both overweight and lean types

**Setting:** Kasr El-Aini Hospital

**Design:** open labeled randomized controlled trial. Randomisation was done on alternate number.

**Patients & Methods:** sixty infertile women were divided into two groups: Group I: (n=30) had BMI > 28 and Group II : (n=30) had BMI < 28. Each group was further subdivided into 2 subgroups A& B. Group A: no = 15 patients given metformin 500 mg t.d.s for 6 weeks prior to clomiphene citrate, induction for three cycles and continued throughout induction. The other subgroup B: no =15 patients were given placebo instead of metformin. Both subgroups were compared regarding BMI, biochemical criteria, regularity of the cycles and success of ovulation induction before and after taking metformin or placebo respectively

**Results:** A statistically significant difference both in the individual cycles and in the cumulative response regarding ovulation induction was observed between the two subgroups of each group. However, no conception has occurred in both groups.

**Conclusion:** A significantly higher successful ovulation induction rates can be achieved with the use of metformin (prior to and as an adjuvant to clomid), both in overweight and lean women with polycystic ovarian syndrome.
Introduction

Polycystic ovary syndrome (PCO) is a heterogenous syndrome characterized by persistent anovulation, oligomenorrhea or amenorrhea and hyperandrogenism in the absence of thyroid, pituitary, or adrenal disease and is the most common cause of anovulation in adult women. (1). Insulin and insulin-like growth factors (IGFs) integrate endocrine and metabolic axes relevant to polycystic ovarian syndrome. In addition, intraovarian IGFs and related proteins and peptides most likely have a role in hyperandrogenaemia and the arrest of follicular development observed in this disorder. (2)

The association of hyperinsulinaemia and hyperandrogenaemia in women with insulin resistance and PCOS is striking, underscoring the endocrine aspect of the disorder. The use of insulin-sensitizing agents and their effects on ovulation in insulin resistance is an exciting area of clinical reproductive endocrinology. It is hoped that increased understanding of the roles of insulin and IGFs in normal follicle growth and steroidogenesis and in the setting of PCOS will help in the design of therapies directed at restoring ovulation and decreasing hyperandrogenaemia in women at high risk for long-term hyperandrogenic and anovulatory-related health consequences. (2)

With increasing evidence that insulin resistance constitutes a key metabolic element, it seems logical that improving insulin sensitivity and glucose disposal might wholly, or partially, reverse certain features of polycystic ovarian syndrome, including anovulation. However, there were disagreement between different studies (1,3). In the present study, we investigated the potential value of metformin prior to and concomitant with the use of clomiphene citrate (CC) and its impact on improving ovulation rate and regularity of the cycle in polycystic ovarian syndrome women both overweight and lean types.
Participants & Methods

The present study included sixty patients presented to the Outpatient Clinic of Gynecology of Kasr El-Aini Cairo University Hospital, complaining of infertility and diagnosed as having polycystic ovarian syndrome. The study was done in the period from March 2001 to November 2002 after approval of Cairo University research board.

A full history taking and clinical examination was done. Body Mass Index BMI was calculated. A complete fertility workup was done including recent semen analysis hysterosalpingography or diagnostic laparoscopy report. Pelvic ultrasound was performed using a 6.5 MHz transvaginal transducer (Model Sonoace 5000, Medison Corporation, Korea, serial number C070302300) to confirm the presence of polycystic ovaries and to exclude organic pelvic pathology.

Patients presenting with anovulatory infertility in the absence of other causes that could explain their problem were selected into our study. Diagnosis of the cases was based on the criteria for PCOS defined by Homburg; polycystic ovaries shown by vaginal ultrasound (> 8 subcapsular follicles of 3-8 mm diameter in one plane in one ovary and increased stroma.) and at least one of the following symptoms: oligomenorrhea, or amenorrhea, hirsutism (Ferriman-Gallwey score > 7), or acne. (4)

Patients having bilateral tubal block, organic uterine or ovarian pathology, patients with infertile semen analysis of their husbands or patients having hyperglycemia were excluded. We excluded patients with hypo/hyper-thyroidism, hyperprolactinemia and Cushing syndrome as detected by history, examination and investigations.

For all patients hormonal profile was done on the third day of normal cycle or progestin withdrawal bleeding after fasting for 8 hours. FSH, LH, PRL, DHEAS, free Testosterone, and fasting Insulin in serum were measured by ELISA chemiluminescence on immulite analyzer using immulite® Rapid FSH, LH, PRL, DHEAS, Testosterone, Insulin kits supplied by DPC (diagnostic product corporation Los Angeles, CA).

Blood sugar was done collecting samples in polypropylene tubes containing sodium fluoride. Samples were analyzed using autoanalyzer Hitachi 704, Hitachi Inc.; Japan. BMI was calculated according to which they were classified into two groups viz. those with BMI more than or equal to 28 and those with BMI less than 28. Patients were instructed not to change their eating habits.
The patients were divided into two groups: Group I: (n=30) had BMI> 28 and Group II: (n=30) had BMI< 28. Each group was further subdivided to subgroup A: no = 15 patients given metformin 500 mg tds (Metformin HCl; Chemical Industries Development (CID), Giza, Egypt) for 6 weeks prior to CC induction for three cycles and continued throughout induction. The other subgroup B: no = 15 patients were given placebo instead (vit. B-complex; The Alexandria Co. For Pharmaceuticals. Alexandria- Egypt.). Both subgroups were compared regarding BMI, biochemical criteria, regularity of the cycles and success of ovulation induction before and after taking metformin or placebo respectively.

After 6 wks of taking either drug, hormonal profile and BMI were re-assessed and regularity of the menstrual cycles was rechecked. We performed transvaginal ultrasonographic serial folliculometry to check ovulation on metformin monotherapy during the 6 wks. of therapy. In addition to either drug induction of ovulation was then started using CC 50 mg tab. (Clomid ; Global Napi Pharmaceuticals under license of Hoechst Marion Roussel France.) using a dose of 100 to 250 mg daily according to BMI and previous response, starting second day of the cycle (normal cycle or progestin withdrawal bleeding) for 5 days.

Success of ovulation induction was monitored by transvaginal ultrasound done on eighth day of the cycle and every two days. Human chorionic gonadotropin 10,000 IU (HCG; Pregnyl, NV Organon International, The Netherlands.) was administered via intramuscular single injection when the leading follicle reached 20 mm in diameter. Ovulation induction was repeated for all patients for three cycles in addition to Metformin or placebo using the same dose or increasing it according to the response.

Data were statistically represented in terms of range, mean, frequency tables, & standard deviation (S.D.) where appropriate. For statistical analysis, the Fisher exact test or the chi² test was used where appropriate. Continuous data were analyzed with the unpaired (two sample) student's t test where appropriate. All statistical calculations were done using the computer programs Arcus Quickstat Biomedical version 1.0 & Microsoft Excel version 2000.
Results

Comparing the change in biochemical features of each subgroup after the administration of metformin or placebo we found that there was statistically significant lowering in LH level in subgroup 1-A (overweight-metformin) after the intake of metformin however this was observed also in subgroup 1-B (overweight-placebo) after the intake of placebo.

Highly significant lowering in LH level was also observed in subgroup 2-A (lean-metformin) after the intake of metformin, which was not the case in subgroup 2-B (lean-placebo) after the intake of placebo. There was also statistically significant lowering in FSH level in subgroup 2-A (lean-metformin) after the intake of metformin. This was not observed in the other subgroups. No significant change in the other hormones levels in any of the subgroups (tables I). Also no significant change in BMI occurred in either subgroup after the intake of the corresponding drug (table II).

Comparing the clinical data of the two corresponding subgroups of each group after the intake of either drug (metformin vs. placebo) we found that there was no significant change in the regularity of cycles in each subgroup, where none of the patients who had irregular cycles before metformin nor placebo had regular cycles after.

A comparison of the results of the successful ovulation induction between the two subgroups of each group showed statistically significant difference both in the individual cycles and in the cumulative response (table III). However there was no statistically significant difference between successful ovulation inductions in the first cycle in the two subgroups of group 2. In addition, no conception has occurred in both groups.
Table I: Comparison between different subgroups regarding biochemical analysis

<table>
<thead>
<tr>
<th></th>
<th>Group I (A)</th>
<th></th>
<th>Group II (A)</th>
<th></th>
<th>Group I (B)</th>
<th></th>
<th>Group II (B)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Metformin</td>
<td>After Metformin</td>
<td>Before Metformin</td>
<td>After Metformin</td>
<td>Before Placebo</td>
<td>After Placebo</td>
<td>Before Placebo</td>
<td>After Placebo</td>
</tr>
<tr>
<td>FSH</td>
<td>4.71 ± 1.52</td>
<td>4.13 ± 0.93</td>
<td>5.34 ± 1.66</td>
<td>4.6 ± 1*</td>
<td>4.72 ± 1.49</td>
<td>5.1 ± 1.79</td>
<td>5.67 ± 1.39</td>
<td>5.71 ± 1.7</td>
</tr>
<tr>
<td>LH</td>
<td>8.89 ± 4.7</td>
<td>5.93 ± 2.27*</td>
<td>9.15 ± 2.88</td>
<td>6.37 ± 0.82**</td>
<td>8.72 ± 4.59</td>
<td>5.95 ± 2.04*</td>
<td>8.55 ± 3.54</td>
<td>9.73 ± 4.16</td>
</tr>
<tr>
<td>Testost.</td>
<td>1.42 ± 0.71</td>
<td>1.17 ± 0.73</td>
<td>1.25 ± 0.47</td>
<td>1.7 ± 0.39</td>
<td>1.27 ± 0.64</td>
<td>1.29 ± 0.63</td>
<td>1.13 ± 0.41</td>
<td>1.13 ± 0.42</td>
</tr>
<tr>
<td>DHEAS</td>
<td>176.93 ± 51.25</td>
<td>168.87 ± 44.03</td>
<td>156.8 ± 65.13</td>
<td>148.4 ± 50.56</td>
<td>172.33 ± 45.42</td>
<td>164 ± 40.51</td>
<td>158.2 ± 57.3</td>
<td>159.13 ± 55.88</td>
</tr>
</tbody>
</table>

*statistically significant difference
Data are presented as Mean ± S.D

Table (II): Comparison between BMI of women in the 4 subgroups before and after either drug.

<table>
<thead>
<tr>
<th>BMI</th>
<th>1-A</th>
<th></th>
<th>1-B</th>
<th></th>
<th>2-A</th>
<th></th>
<th>2-B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max</td>
<td>min</td>
<td>mean</td>
<td>SD</td>
<td>max</td>
<td>min</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>39.84</td>
<td>28.96</td>
<td>32.12</td>
<td>3.34</td>
<td>38.28</td>
<td>28.96</td>
<td>32.09</td>
<td>2.89</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td>38</td>
<td>29</td>
<td>31.71</td>
<td>2.81</td>
<td>37.4</td>
<td>28</td>
<td>32.06</td>
</tr>
<tr>
<td>P value</td>
<td>0.359</td>
<td>0.489</td>
<td>0.439</td>
<td>0.410</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table (III): Comparison of ovulation induction success between the 2 subgroups of group 1 (overweight)

<table>
<thead>
<tr>
<th>Ovulation rate</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; cycle</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; cycle</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; cycle</th>
<th>Cumulative Ovulation rate</th>
<th>Response</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; cycle</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; cycle</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; cycle</th>
<th>Cumulative Ovulation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-A (overweight-metformin)</td>
<td>40%</td>
<td>66.6%</td>
<td>73.3%</td>
<td>73.3%</td>
<td>2-A (lean-metformin)</td>
<td>53.3%</td>
<td>80%</td>
<td>86.6%</td>
<td>86.6%</td>
</tr>
<tr>
<td>1-B (overweight-placebo)</td>
<td>0%</td>
<td>0%</td>
<td>13.3%</td>
<td>13.3%</td>
<td>2-B (lean-placebo)</td>
<td>20%</td>
<td>26.6%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>P value</td>
<td>0.022</td>
<td>0.001</td>
<td>0.003</td>
<td>0.003</td>
<td>P value</td>
<td>0.130</td>
<td>0.010</td>
<td>0.023</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Discussion

The most recent class of pharmacologic agents to gain popularity in treatment of polycystic ovarian syndrome women is the "insulin sensitizers". Most studies or case reports of metformin (5-14), but not all (15-17), have demonstrated that metformin administration at a dose of 500 mg. three times daily increases menstrual regularity, improves spontaneous ovulation, and promote fertility. In this prospective randomized study, we used the same dose of metformin for only 6 week prior to, and in conjunction with, clomiphene citrate induction of ovulation for both overweight and lean polycystic ovarian syndrome women vs. the use of placebo.

In the present study, comparing the biochemical features of the two main groups (overweight and lean), there was statistically significant difference between their fasting insulin levels, hyperinsulinemia was seen only in the overweight group. This does not mean that lean polycystic ovarian syndrome patients are not insulin resistant, given the wide range of normal fasting insulin level. Because the majority of women with polycystic ovarian syndrome are overweight, it seemed initially that their insulin resistance could be accounted for on this basis alone; however the studies of other investigators firmly established that the magnitude of insulin resistance is greater in women with polycystic ovarian syndrome than...
in controls matched either for total or fat-free body mass (18-20). The lean women with polycystic ovarian syndrome appear to have a form of insulin resistance that is intrinsic (and perhaps) unique to the syndrome and is poorly understood. (21) But the overweight woman with polycystic ovarian syndrome possesses not only the form of insulin resistance intrinsic to the syndrome, but also has an added burden of insulin resistance that is related to her excess adiposity.

It has never been tested whether the fasting glucose-to-insulin ratio is predictive of response to insulin-sensitivity therapy. (22). Finally, overweight women with polycystic ovarian syndrome are by definition insulin-resistant on the basis of their obesity alone(23), and studies have demonstrated that insulin sensitivity drugs are efficacious in lean women with polycystic ovarian syndrome (24,25).

Therefore, from a practical point of view, it is reasonable to regard all women with polycystic ovarian syndrome as being insulin-resistant, and many investigators stated that their practice in the clinical setting not to attempt to document or quantify insulin resistance (26).

It is also worth mentioning that the hormonal response to metformin among the 2 groups was different. As in the lean group there was a significant lowering in the levels of both LH and FSH as compared to lowering of the LH only in the overweight group. This may be related to the duration of the treatment being limited to 6 weeks. Different hormone response may need longer duration of treatment. Another explanation may be related to the hypothalamic pituitary response to the insulin sensitizing medications and/or the intrinsic ovarian metabolic changes.

In group 1 (overweight patients with BMI more than or equal to 28) there was no statistically significant difference between the clinical or biochemical data of the two groups (those given metformin vs. those given placebo). Comparing the effect of administration of meformin vs. placebo for 6 weeks on their biochemical features we found that both lead to statistically significant lowering of LH level. This could be attributed to the central effect of taking a placebo. Also evidence suggesting that insulin may enhance LH secretion originated from the studies of rat pituitary cells in vitro, in which hyperinsulinemia potentiated both LH and FSH release to GnRH stimulation of the pituitary gland which was not the case when tested in vivo (27).
Decreases in plasma insulin by the administration of metformin or troglitazone have been associated with a reduction in mean plasma LH in some (19) but not all studies (15). Additionally, overweight women with polycystic ovarian syndrome have higher levels of plasma insulin in spite of comparable high LH levels when compared with the level in lean women with polycystic ovarian syndrome. (28). Thus, the effects of insulin on gonadotrophins secretion remain unclear.

There was no statistically significant reduction in fasting insulin nor testosterone levels after intake of metformin or placebo, this is in agreement with other investigators who stated that both the glucose and insulin responses to an oral glucose challenge and the profound insulin resistance of overweight women with polycystic ovarian syndrome were not improved by metformin (17).

Reviewing the clinical benefits of metformin therapy, there was no statistically significant change in the BMI of patients who were treated with metformin nor in the subgroup taking placebo, i.e. the benefits seen with metformin are independent of weight loss.

As for regularity of menstrual cycles and spontaneous ovulation none was observed with either drug, this could be attributed to the small size of the sample (15 patients) or to the short course of monotherapy with metformin (6 weeks).

Recently two randomized, prospective, placebo controlled trials found striking and sustained improvements in menstrual abnormalities and resumption of ovulation but after relatively long-term metformin treatment in overweight women with polycystic ovarian syndrome viz Moghetti et al, 2000 who used metformin for 6 months and Fleming et al, 2002 who used metformin for 16 weeks. The authors also identified higher plasma insulin, lower serum androstendione and less severe menstrual abnormalities as baseline predictors of clinical response to metformin (10,29).

On the other hand, in this work a statistically significant difference in successful ovulation induction was observed in overweight patients taking metformin and CC vs. those who took placebo (73.3% vs.13.3%). This is consistent with the results of Nestler et al, who found an ovulatory response of 90 % compared with an 8% response rate in women who took placebo in concert with CC. Their results also agreed with ours in the lack of reduction in free testosterone levels in the metformin treated group. They inferred from their results that metformin could act to enhance ovulation without changing the steroid milieu (8).
In our study the subgroup that took metformin has shown highly significant lowering of LH levels and a significant fall in FSH level too than the subgroup that took placebo. This is consistent with the findings of other investigators (25). This is in contrast to the lowering of LH level in both the metformin and placebo subgroups in the overweight group, i.e. there was more substantial biochemical benefit in the lean metformin subgroup than in the overweight patients who took metformin. Such results agree with Morales et al, who concluded that the effects of insulin on gonadotrophins secretion remain unclear. They observed that there is a discrepancy between the higher plasma insulin levels in overweight polycystic ovarian syndrome and comparable high LH levels between overweight and lean polycystic ovarian syndrome women (28).

On the other hand lean patients too did not show any significant change in their fasting insulin or testosterone levels after the intake of metformin as in overweight patients. This may mean that hyperandrogenism and insulin-resistance do not completely solve the endocrinologic mystery of the patient with polycystic ovarian syndrome. For example how does the partial destruction of the ovary (e.g. Wedge resection or ovarian drilling by laser or cautery), which does not affect insulin resistance result in ovulatory cycles? Why does the administration of excessive exogenous insulin in the case of the insulin-dependent diabetic fail to cause hyperandrogenism? (30)

Similarly as in the overweight group, the clinical effects of metformin in our study did not cause any significant change in BMI or regularity of cycles in lean women, however there was a significant difference in ovulation induction success on adding CC, compared to women who took placebo. This success was more in the lean (86.6%) than in the overweight (73.3%) subgroup taking metformin without a statistically significant difference. Moreover, there was no conception in both groups. The lower ovulation rate and failure to achieve pregnancy could be explained by the small sample size of our study.

Therefore, the question arises: is the administration of metformin in combination with clomiphene more efficacious than treatment with either drug alone? From our data there was no improvement in regularity of cycles nor spontaneous ovulation on metformin alone, this could be explained by the short duration of metformin monotherapy. However we observed that there was a significant benefit for ovulation induction in the overweight, and even more so in the lean subgroups who took metformin in conjunction with CC.
Moreover, can those women who are clomiphene resistant be rendered clomiphene responsive by addition of metformin to clomiphene treatment? Only three studies to date have addressed this issue — two with metformin and one with troglitazone. The results were promising. (26). Our results should be taken with caution as the sample size of each study group does not satisfy significant power for most of the outcomes except ovulation rates. A large-scale, head-to-head, randomized, prospective study of metformin vs. clomiphene for initial ovulation induction in women with polycystic ovarian syndrome is warranted to definitively address this important clinical issue.

In conclusion, the present study showed a significant clinical benefit not accompanied by biochemical changes (as regards fasting insulin, androgen levels) for metformin intake prior and as an adjuvant to CC induction of ovulation, both in overweight and lean women with polycystic ovarian syndrome manifested by significantly higher successful ovulation induction rates. However, for an infertility patient it is inconvenient to let her wait for the long periods needed by the metformin monotherapy to accomplish clinical benefit, and it is our recommendation to use combination protocol i.e. metformin 500 mg tds for 6 wks prior and as an adjuvant to clomiphene citrate induction of ovulation.
References


