Subject Area: Obstetrics and Gynecology

**Effect of Empagliflozin Metformin with Clomiphene Citrate versus Metformin with Clomiphene Citrate on cases of Polycystic Ovary Syndrome**

Diaa Shams Eldin El Gohary  
*Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.*,  
elgohary.diaa@yahoo.com

Mohammed Mohammed Ismail  
*Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.*

Ahmed Mahmoud El khayat  
*Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.*

Sherin Barakat Elbohoty  
*Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.*

Follow this and additional works at: [https://jmisr.researchcommons.org/home](https://jmisr.researchcommons.org/home)  
☑️ Part of the [Medical Sciences Commons](https://jmisr.researchcommons.org/home), and the [Medical Specialties Commons](https://jmisr.researchcommons.org/home)

**Recommended Citation**

El Gohary, Diaa Shams Eldin; Ismail, Mohammed Mohammed; El khayat, Ahmed Mahmoud; and Elbohoty, Sherin Barakat (2023) "Effect of Empagliflozin Metformin with Clomiphene Citrate versus Metformin with Clomiphene Citrate on cases of Polycystic Ovary Syndrome," *Journal of Medicine in Scientific Research*: Vol. 6: Iss. 2, Article 3.  
DOI: [https://doi.org/10.59299/2537-0928.1025](https://doi.org/10.59299/2537-0928.1025)

This Original Study is brought to you for free and open access by Journal of Medicine in Scientific Research. It has been accepted for inclusion in Journal of Medicine in Scientific Research by an authorized editor of Journal of Medicine in Scientific Research. For more information, please contact m_a_b200481@hotmail.com.
Effect of empagliflozin metformin with clomiphene citrate versus metformin with clomiphene citrate on cases of polycystic ovary syndrome

Diaa S.E. El Gohary*, Mohammed M. Ismail, Ahmed M. El khayat, Sherin B. Elbohoty

Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

**Background:** Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age associated with long-term metabolic and cardiovascular consequences.

**Aim and objectives:** In this research, we aimed to assess the impact of Empagliflozin Metformin with Clomiphene Citrate versus Metformin with Clomiphene Citrate on weight reduction and its impact on folliculometry and ovarian volume in cases of Polycystic Ovary Syndrome.

**Subjects and methods:** This was a randomized clinical trial; in which 150 Patients were being randomly assigned into two equal groups; Group A: 75 cases received empagliflozin metformin 12.5/500 mg Continuously once daily plus clomiphene citrate 50 mg twice daily for 3 cycles from day 2 of the natural or the withdrawal cycle for 5 days. Group B: 75 cases received metformin 500 mg continuously once daily plus clomiphene citrate 50 mg twice daily for 3 cycles from day 2 of the natural or the withdrawal cycle for 5 days.

**Results:** There was a significant variation between the two studied groups regarding BMI hip circumference ovarian characteristics (ovarian volume and AFC), FBG, fasting insulin and ovulation rate.

**Conclusion:** Empagliflozin metformin with clomiphene citrate treatment had beneficial effects on anthropometric parameters (BMI and hip circumference), ovarian characteristics (ovarian volume and AFC), FBG, fasting insulin and ovulation rate in women with PCOS compared to metformin with clomiphene citrate, but no statistically significant variations were seen in number of dominant follicles, pregnancy rate and positive pregnancy.

**Keywords:** Anthropometric parameters, Empagliflozin, Metabolic, Metformin, Ovulation, Polycystic ovary syndrome

1. Introduction

A prevalent endocrine disease called polycystic ovary syndrome (PCOS) contributes to 8–13% of females in reproductive age [1,2]. This illness encompasses a wide range of ovarian dysfunction symptoms and signs, making it heterogeneous. The typical manifestation, as reported by Stein and Leventhal [2,3], includes characteristics of obesity, amenorrhea, and hirsutism with ultrasound-confirmed polycystic ovarian appearance [4].

Hence, a clinical diagnosis cannot be made only based on a single diagnostic factor, like polycystic ovaries (PCO) or hyperandrogenism. The updated criteria for diagnosis for the identification of PCOS from the 2003 Rotterdam Consensus were as follows, having two of the following being necessary: 1. Menstrual disturbance which can be described as either oligo or anovulation, or both; 2. hyperandrogenism which is determined by either clinical or biochemical signs or both; 3. PCO via ultrasound; and other causes of hyperandrogenism and menstrual disturbance are excluded (like androgen-secreting tumors, congenital adrenal hyperplasia, Cushing's syndrome) [5].

The diagnostic criterion for ultrasonography PCO morphology is either twenty or greater number of follicles per ovary or enlarged ovarian volume above 10 ml, when utilizing a transvaginal ultrasound scan,
according to a recent update to recommendations with regard of improving ultrasound technology and clarity [6]. Although PCOS is the most frequent etiology of anovulatory infertility [7], up to 70% of females with PCOS remain without a diagnosis [8].

The amount of data demonstrating that elevated resistance of insulin and compensated elevated concentrations of insulin (hyperinsulinemia) play a significant role in the pathophysiology of PCOS has expanded during the last 20 years [9]. Although it may also develop in non-obese women with the condition, insulin resistance is more prevalent in overweight women [10].

Metabolic abnormalities, such as insulin resistance, diabetes mellitus, hyperinsulinemia, and chronic anovulation may be effectively managed with the use of glucose-lowering medications like metformin [11,12].

A novel therapy option for individuals with type 2 diabetes, empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor; however, its impact on PCOS have not been previously investigated. Its main effect is to prevent the kidneys from reabsorbing glucose, which causes glucose to be excreted in the urine [13].

A biguanide called metformin has no impact on glucose levels in healthy participants but decreases levels of glucose in the blood in hyperglycemic individuals who have type 2 diabetes mellitus [14]. Metformin suppresses hepatic glucose production, lowers absorption of glucose intake from the gastrointestinal tract, and enhances peripheral insulin-stimulated glucose uptake, albeit the exact mechanism of action is yet unknown.

For the majority of patients with PCOS, clomiphene citrate (CC) continues to be the first-line pharmaceutical therapy for ovulation induction. CC is an antiestrogenic medication that has been used as an ovulatory inducer for more than 40 years. Anovulation occurs even after receiving regular CC treatment in around 15–20% of patients, which is referred to as CC resistance [15,16].

2. Aim of the work

To assess impact of Empagliflozin Metformin with Clomiphene Citrate versus Metformin with Clomiphene Citrate on weight reduction and its impact on folliculometry and ovarian volume in cases of Polycystic Ovary Syndrome.

3. Patients and methods

In this randomised clinical experiment, 150 participants were categorized equally into two groups and allocated at random.

Group A: 75 cases received empagliflozin metformin 12.5/500 mg once daily Continuously plus clomiphene citrate 50 mg twice daily for 3 cycles from day 2 of the natural or the withdrawal cycle for 5 days.

Group B: 75 cases received metformin 500 mg once daily Continuously plus clomiphene citrate 50 mg twice daily for 3 cycles from day 2 of the natural or the withdrawal cycle for 5 days.

3.1. Ethical considerations

(1) After receiving academic and medical ethics committee permission, the trial began.
(2) All patients who were involved gave their written, signed permission.
(3) The purpose of our research, risk factors, potential complications, and failure risk were all explained to all patients who were participating.

3.1.1. Inclusion criteria

(2) Age between 18 and 35 years.
(3) Normal semen analysis of the patient’s husband.
(4) Hysterosalpingography (HSG) should be normal.
(5) Patients with body mass index (BMI) equal or more than 27.

Exclusion criteria as following

(1) Patients with other pelvic pathology like endometriosis.
(2) Patients with history of 3 trials of failed ovulation induction.
(3) Patients with pelvic TVS showing pathology other than PCOS.

All patients were subjected to the following

(1) Taking a complete history.
(2) Full general and abdominal examination to exclude thyroid disorder and hyperprolactinemia.
(3) Patients got a comprehensive clinical examination locally, which included a vaginal examination.
(4) Weight, height, and waist circumference, hip circumference, Waist-hip ratio were assessed for all patients before and after treatment.
(5) Hormonal profile including venous blood samples were obtained and stored at −20 °C till analysis. Testosterone was measured with radioimmunoassay while LH and FSH were measured with immunoradiometric assay before and after treatment.
Table 1. Anthropometric parameters after treatment of the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>30.81 ± 2.22</td>
<td>34.19 ± 7.86</td>
<td>3.427</td>
<td>0.001</td>
</tr>
<tr>
<td>N (n = 75)</td>
<td>N (n = 75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>96.6 ± 8.59</td>
<td>100.89 ± 16.57</td>
<td>1.993</td>
<td>0.05</td>
</tr>
<tr>
<td>Hip circumference</td>
<td>110.86 ± 6.62</td>
<td>115.51 ± 11.88</td>
<td>2.971</td>
<td>0.004</td>
</tr>
<tr>
<td>SHBG (IU/l) Mean</td>
<td>0.857 ±0.068</td>
<td>0.853 ± 0.082</td>
<td>0.325</td>
<td>0.746</td>
</tr>
</tbody>
</table>
| FBG, fasting blood glucose; FSH, follicular stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin.

BMI, body mass index. Data is presented as mean (SD).

(6) Protocol of drugs administration

All the patients of 2 groups received ovulation induction by stimulation protocol, clomiphene citrate 50 mg twice daily from day 2 of the natural or the withdrawal cycle for 5 days.

Transvaginal sonography was done for folliculometry during each cycle and for measuring ovarian volume before and after treatment.

3.2. Statistical analysis

The sample size and power analysis were determined using version 2002 of the Epi-Info statistical software program developed by the World Health Organization and the Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

4. Results

There is a substantial variance among both studied groups regarding BMI and hip circumference but there is no significant difference in WC and W/H Ratio (Table 1).

Table 2. Ovarian characteristics after treatment of the two studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFC Mean ± SD</td>
<td>17.38 ± 3.31</td>
<td>15.52 ± 3.24</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovarian volume (ml) Mean ± SD</td>
<td>10.68 ± 1.81</td>
<td>9.75 ± 1.34</td>
<td>4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N (n = 75)</td>
<td>N (n = 75)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data is presented as mean (SD).

There is a significant decrease in AFC and ovarian volume in both groups after treatment (Table 2).

There is a substantial variance among both studied groups regarding FBG and fasting insulin but there is no substantial variance in HOMA-IR, LH, FSH, SHBG and Testosterone (Table 3).

There is no substantial variance among both studied groups. Regarding number of dominant follicles >18 mm after three months of Treatment: Regarding group A, the 8 patients who has 1 follicle in the 2nd month they failed in the 1st month and the patients had 2 or 3 follicles in the three months with increasing cumulative rate. While in group B, the 14 patients who has 1 follicle 9 of them were in the 1st month and 5 were in the 2nd month and the patients had 2 or 3 follicles in the three months (Table 4).

5. Discussion

Our results revealed that anthropometric measurements such as hip circumference and BMI showed significant decrease in group A when comparing to group B after treatment while waist circumference and Waist/hip circumference were insignificantly different among both groups. Within group comparison revealed that in group A, BMI, waist circumference and hip circumference significantly reduced after treatment than baseline. In group B only hip circumference reduced significantly after treatment.

As far as we know, this is the first research to assess the efficiency of adding empagliflozin to metformin with clomiphene citrate on cases of PCOS.

In agreement with our findings, Javed et al. [17], reported in the empagliflozin group, hip circumference at 12 weeks substantially reduced when compared to baseline (P = 0.013). However, in contrast to our findings, they reported that waist circumference significantly reduced (P = 0.024), at 12 weeks compared to baseline, but no changes were seen in BMI (P = 0.069). The difference from our findings may be attributed to that they compared only empagliflozin with metformin whereas we

Table 3. Laboratory investigations after treatment of the two studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 75)</th>
<th>Group B (n = 75)</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dL) Mean ± SD</td>
<td>75.82 ± 14.9</td>
<td>80.18 ± 10.5</td>
<td>2.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml) Mean ± SD</td>
<td>17.81 ± 8.88</td>
<td>15.1 ± 7.57</td>
<td>3.15</td>
<td>0.002</td>
</tr>
<tr>
<td>HOMA-IR Mean ± SD</td>
<td>3.12 ± 1.98</td>
<td>3.06 ± 1.8</td>
<td>0.194</td>
<td>0.846</td>
</tr>
<tr>
<td>LH (IU/l) Mean ± SD</td>
<td>11.59 ± 0.074</td>
<td>11.57 ± 0.069</td>
<td>1.71</td>
<td>0.089</td>
</tr>
<tr>
<td>FSH (IU/l) Mean ± SD</td>
<td>5.43 ± 1.06</td>
<td>5.51 ± 1.39</td>
<td>0.396</td>
<td>0.692</td>
</tr>
<tr>
<td>SHBG (IU/l) Mean ± SD</td>
<td>6.18 ± 2.72</td>
<td>6.12 ± 3.43</td>
<td>0.119</td>
<td>0.906</td>
</tr>
<tr>
<td>Free Testosterone (ng/ml) Mean ± SD</td>
<td>0.576 ± 0.431</td>
<td>0.541 ± 0.207</td>
<td>0.531</td>
<td>0.563</td>
</tr>
</tbody>
</table>

Data is presented as mean (SD).

FBG, fasting blood glucose; FSH, follicular stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin.
Table 4. Number of dominant follicles >18 mm of the two studied groups after three months of Treatment.

<table>
<thead>
<tr>
<th>Number of dominant follicles &gt;18 mm</th>
<th>Group A (n = 75)</th>
<th>Group B (n = 75)</th>
<th>$X^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 follicle</td>
<td>8 (10.7%)</td>
<td>14 (18.7%)</td>
<td>2.52</td>
<td>0.284</td>
</tr>
<tr>
<td>2 follicles</td>
<td>23 (30.7%)</td>
<td>25 (33.3%)</td>
<td>0.123</td>
<td>0.726</td>
</tr>
<tr>
<td>3 follicles</td>
<td>44 (58.7%)</td>
<td>36 (48%)</td>
<td>1.714</td>
<td>0.191</td>
</tr>
</tbody>
</table>

Data is presented as number and percentage.

studied the combined effect of empagliflozin with metformin.

In the metformin group, Javed et al. [17], documented that after 12 weeks of therapy, BMI ($P = 0.024$), body mass ($P = 0.019$), and total fat percentage ($P = 0.015$), hip circumference ($P = 0.031$), and fat mass ($P = 0.005$) increased significantly.

Our results came in line with Sanoe et al. [18], who investigated the effects metformin on the hyperandrogenism and ovarian volume in PCOS. Twenty-eight patients with infertility meeting the Rotterdam ESHRE/ASRM criteria for PCOS were studied. The plasma levels of follicle stimulating hormone, luteinizing hormone, testosterone, estradiol, 17-hydroxyprogesterone, and dehydroepiandrosterone sulfate as well as the mean bilateral ovarian volume and morphology by transvaginal sonography were measured before and after three months of being treated with 500 mg of metformin three times per day. There was a substantial decrease in the mean ovarian volume ($11.70 \pm 4.31$ ml vs $8.27 \pm 3.71$ ml, $P = 0.001$).

Also, Romuald et al. [19], conducted a randomized, double-blind investigation on the impact of metformin on endocrine-metabolic variables and ovarian morphology in normo-insulinemic PCOS patients. Patients were randomly assigned to take 500 mg metformin twice daily (group A, 15 patients) or a placebo (group B, 13 patients) for three months. At baseline and after 3 and 6 months of therapy, pelvic ultrasonography, hormone and lipid profiles, and an oral glucose tolerance test were done. At three months, Metformin, but not placebo, decreased ovarian volume and the ratio of stromal to total area.

In support of our findings, Liu et al. [20], evaluated the safety and effectiveness of SGLT2 inhibitors in persons with type 2 diabetes (T2DM). SGLT2 inhibitors improved glycemic control in those with T2DM, as proven by decreases in HbA1c ($-0.49\%$ and $-0.50\%$ after 1 and 2 years of therapy) and levels of fasting plasma glucose ($-0.81$ and $-0.77$ mmol/l after 1 and 2 years of therapy) compared to placebo in 13 randomized trials.

Also, Liakos et al. [21], performed a meta-analysis comparing the safety and effectiveness of the SGLT2 inhibitor empagliflozin to placebo or other antidiabetic medications in type 2 diabetes patients. Comparing empagliflozin to metformin, the researchers found that empagliflozin efficiently reduced blood glucose and boosted fasting insulin, according to 10 studies on 6203 participants.

As alone or in combination with other glucose-reducing medicines, empagliflozin has proven improvement in glycemic control. In a placebo-controlled 24-week trial, Roden et al. [22], found that when compared to placebo, empagliflozin at dosages of 10 mg and 25 mg significantly reduced HbA1c percent ($-1.43\%$ and $-1.44\%$, correspondingly).

However, in contrast to our findings, Javed et al. [17], reported that After 12 weeks of therapy, there were no variations in insulin sensitivity (insulin, HOMA-IR, fasting glucose) in either empagliflozin or metformin arms.

Basirat et al. [23] examined the efficacy of combining Met to CC in females with PCOS, despite the absence of comparison data from trials investigating the impact of SGLT2 inhibitors on PCOS. 334 PCOS patients participated in the multicenter, randomized, controlled experiment conducted by the researchers. Participants were randomly separated into two groups, CC alone or CC with Met were used to induce ovulation. After three cycles of therapy, the follicular maturation and pregnancy rates were assessed. 68% of the CC + Met group had at least one substantial dominant follicle in the first cycle which was significant ($P < 0.001$), and 31.7% in the 2nd cycle. In the CC group, 54.5% of women ovulated in the first cycle, 31.7% in their 2nd cycle, and 6.9% in the 3rd cycle.

In contrast to our findings, Palomba et al. [24] examined the reproductive impact of metformin treatment in a large group of infertile PCOS patients receiving gonadotropins ovary stimulation for in vitro fertilization. (IVF). Infertile Participants with PCOS who underwent ovarian stimulation with gonadotropins and IVF with (metformin group, $n = 191$) or without (control group, $n = 187$) metformin were assessed. In the metformin group, the number of prominent follicles on the day of ovarian maturation prompting and peak estradiol levels were considerably ($P < 0.05$) lower than in the control group. Different patients’ characteristics as older patients may be appropriate explanation for this difference.

5.1. Conclusions

Empagliflozin metformin with clomiphene citrate treatment have favorable effects on anthropometric parameters (BMI and hip circumference), ovarian characteristics (ovarian volume and AFC), FBG, fasting insulin and ovulation rate in females with
PCOS when compared to metformin with clomiphene citrate, but no statistically significant variations were seen in number of dominant follicles, pregnancy rate and positive pregnancy.

Authors’ contribution

Funding
No funding was obtained for this investigation.

Availability of data and material
The datasets utilized and/or analyzed for this work are accessible as MS Excel files (.xlsx) from the corresponding author upon reasonable request.

Ethical approval and protocol registration
The research was done after approval from the Ethical Committee Tanta University Hospitals. An informed written consent was obtained from relatives of the cases.

Institutional review board (IRB) approval number
Approval number: 34763/6/21.

Conflicts of interest
There are no conflicts of interest.

References