Efficacy of ovulation induction with clomiphene citrate and metformin in women with polycystic ovary syndrome – Pilot study

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Introduction: When other causes are excluded, polycystic ovary syndrome (PCOS) refers to a state of chronic hyperandrogenemia and anovulation. There are four basic treatment goals: to treat hirsutism and its equivalents, treat anovulation, reduce insulin resistance and possible metabolic sequelae and reduce the risk of endometrial cancer. Approach in the treatment of anovulation should be gradual - from simple to more complex methods. Aim: To determine the effectiveness of ovulation induction in women with polycystic ovary syndrome in relation to given pharmacologic therapy. Patients and methods: The study included 30 women with a PCOS diagnosis. Patients were randomized in three study groups. The first study group included patients who used clomiphene citrate 50 mg 2-7 day of the cycle, the second study group included patients who used metformin 2 x 850 mg daily, while the third group included patients who used metformin 2 x 850 mg daily and clomiphene citrate 50mg 2-7 days of the cycle. Folliculometry was performed on each patient. Results: The average number of basal antral follicles bilaterally compared between study groups is not statistically significant, F=0.220, p = 0.804. The average number of basal antral follicles bilaterally was 15.40 ± 3.93. The difference in average size of follicles during the last folliculometry was not statistically significant between the study groups, F = 1.369, p = 0.271. Each induction at which the follicle size is less than 18 mm we consider a failed induction. At last measurement, patients who used clomiphene citrate and metformin had the most successful inductions. Combined use of clomiphene citrate and metformin also affected the thickness of the endometrium. Patients in the third test group had a thicker endometrium than patients from the first and second group to a degree that is statistically significant. Conclusion: If there are no problems with other factors (tubal patency, spermogram etc.), in ovulation induction the combination of metformin and clomiphene citrate in women with polycystic ovary syndrome can be successful and achieve pregnancy.

Key words: clomiphene citrate, metformin, polycystic ovary syndrome
### Introduction

When other causes are excluded (congenital adrenal hyperplasia, hyperprolactinemia, adrenal or ovarian carcinomas), polycystic ovary syndrome (PCOS) refers to a state of chronic hyperandrogenemia and anovulation. This syndrome is variably associated with menstrual irregularity, hirsutism and obesity: around 66% of patients experience menstrual irregularities manifesting themselves as anovulation (amenorrhea, oligomenorrhea, dysfunctional bleeding), about 66% suffer from hirsutism and about 50% are obese. Only 33% of them have a full clinical presentation (1, 2). Symptoms usually begin around menarche (3). Generally this syndrome can be suspected in every hirsute adolescent if accompanied by menstrual irregularity or obesity. Even acne refractory to conventional therapy should be considered as PCOS, just as sudden obesity parallel with menarche, especially if it is accompanied by acanthosis nigricans signs or a family history of type 2 diabetes (4). Treatment of PCOS requires a multidisciplinary approach and is very demanding and time consuming. A significant number of medications are available, as well as different physical and chemical interventions, even surgical ones. The treatment must be conceived strategically and in reasonable order. Therapeutic combinations are numerous and must be defined in relation to the predominant symptomatology, age, expectations from both patient and physician, and considering the metabolic status (5). There are four basic therapeutic goals: to treat hirsutism and its equivalents, treat anovulation, reduce insulin resistance and possible metabolic sequelae and reduce the risk of endometrial cancer. The approach to anovulation treatment should be gradual - from simple to more complex methods. Obesity can compromise the success of any pharmacological treatment modality, so body weight loss remains the main method of fertility induction.

First-line treatment for ovulation induction in PCOS remains Klomid® (clomiphene citrate), although recently its primacy is shared with metformin. Treatment starts with 50 mg Klomid® daily (1 tablet) for 5 days. Metformin at a dose of 1500-1700 mg daily significantly increases the percentage of spontaneous ovulations. In about 70% ovulatory cycles are established, while in almost 90% of the treated regularity of the menstrual cycle is established (6). The combination of metformin with clomiphene is superior to clomiphene monotherapy. In 95-100% of adolescents with PCOS resistant to clomiphene, ovulation is induced with human gonadotropins, wherein the recombinant FSH has an advantage over menopausal gonadotropin (HMG). Low doses (37.5 to 50.0 IU daily) are superior to standard doses because hyperstimulation is avoided (7).

**AIM:** To determine the effectiveness of ovulation induction in women with polycystic ovary syndrome in relation to given pharmacologic therapy.

### Patients and methods

This is a retrospective study. It included patients with polycystic ovary syndrome in whom ovulation induction and targeted intercourse has been prescribed as first-level assisted reproduction.

**Subjects**

The study included 30 women with a PCOS diagnosis. The basic criteria for inclusion in the study stipulated that patients be younger than 35 years and have had no previous attempts of assisted reproduction. Patients who have not responded to treatment with clomiphene citrate were excluded from the study. Using the random sample method, 30 patients were chosen.

**Methods**

Depending on the treatment, patients were randomized in three study groups. The first
study group included patients who used clomiphene citrate 50 mg 2-7 day of the cycle, the second study group included patients who used metformin 2 x 850 mg daily, while the third group included patients who used metformin 2 x 850 mg daily and clomiphene citrate 50mg 2-7 days of the cycle. Folliculometry is performed on each patient and, after the last ultrasound examination, when the follicles were over 18 mm, injection of Ovitrella® (choriogonadotropin alfa) was applied and sexual intercourse in the next four days was recommended. The induction procedure was repeated for 3 months and then discontinued, or if pregnancy occurred. The retrospective study was conducted at the IVF center Bahceci B&H.

Statistical analysis

After analyzing case histories of patients and collecting data on the procedures of assisted reproduction, a database in MS Excel was created. After sorting variables, data were exported to the statistical and mathematical program SPPS version 20. Because therapy success was monitored at group level, group analysis of quantitative data was performed using ANOVA, while qualitative data were analyzed using the chi-square test. For the distribution of data order the Shapirowilk test was used. The level of significance was \( p = 0.05 \).

Results

The study included women with a PCOS diagnosis. The average age of patients was 32.8 ± 3.04 years. Ovarian volume is analyzed in Table 1 before the first ovulation induction. Applying ANOVA test we showed that the average ovarian volume in all patient groups is 8.39 ± 1.08 cm³ and there is no statistically significant difference between the study groups, \( F = 2.852, p = 0.078 \).

The difference in the average number of basal antral follicles bilaterally compared between the study groups is not statistically significant, \( F = 0.220, p = 0.804 \). The average number of basal antral follicles bilaterally was 15.40 ± 3.93 (Table 2).

The difference in average size of follicles during the last folliculometry was not statistically significant between the study groups, \( F = 1.369, p = 0.271 \) (Table 3). Each induction at which the size of the follicles is less than 18mm we consider a failed induction.

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**Table 1. Ovarian volume between study groups.**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>95% Confidence Interval for Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene citrate</td>
<td>10</td>
<td>8.89</td>
<td>0.68</td>
<td>0.21</td>
<td>8.4020 - 9.3780</td>
<td>7.50</td>
<td>9.50</td>
</tr>
<tr>
<td>Metformin</td>
<td>10</td>
<td>7.81</td>
<td>1.06</td>
<td>0.33</td>
<td>7.0474 - 8.5726</td>
<td>6.60</td>
<td>9.20</td>
</tr>
<tr>
<td>CC+Metformin</td>
<td>10</td>
<td>8.47</td>
<td>1.23</td>
<td>0.38</td>
<td>7.5893 - 9.3507</td>
<td>6.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>8.39</td>
<td>1.08</td>
<td>0.19</td>
<td>7.9858 - 8.7942</td>
<td>6.00</td>
<td>10.00</td>
</tr>
</tbody>
</table>

**Table 2. Number of basal follicles before starting ovulation induction**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>95% Confidence Interval for Mean</th>
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<tr>
<td></td>
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<td>Lower Bound</td>
<td>Upper Bound</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene citrate</td>
<td>10</td>
<td>14.80</td>
<td>3.22</td>
<td>1.01</td>
<td>12.4930 - 17.1070</td>
<td>10.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Metformin</td>
<td>10</td>
<td>16.00</td>
<td>4.02</td>
<td>1.27</td>
<td>13.1188 - 18.8812</td>
<td>10.00</td>
<td>20.00</td>
</tr>
<tr>
<td>CC+Metformin</td>
<td>10</td>
<td>15.40</td>
<td>4.74</td>
<td>1.49</td>
<td>12.0076 - 18.7924</td>
<td>6.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>15.40</td>
<td>3.93</td>
<td>0.71</td>
<td>13.9304 - 16.8696</td>
<td>6.00</td>
<td>20.00</td>
</tr>
</tbody>
</table>
At last measurement patients who used clomiphene citrate and metformin had the most successful inductions (Table 4).

Combined use of clomiphene citrate and metformin also affected the thickness of the endometrium. Patients in the third test group had a thicker endometrium than patients from the first and second group to a degree that was statistically significant, as shown in Table 5.
In the first three attempts of ovulation induction followed by sexual intercourse, pregnancy occurred in two cases in the first and second group of patients, while there were four pregnancies in women in whom ovulation was induced with clomiphene citrate and metformin.

Discussion

Ovulation induction is probably the most common therapeutic procedure that has made significant progress in the treatment of infertility in the second half of the 20th century. Twenty years ago, this procedure was performed mainly in women who could not conceive due to ovulatory and menstrual disorders. However, after the introduction of assisted reproduction methods in the treatment of infertility, the number of women with induced ovulation has increased. Although the drugs used during the induction of monofolliculogenesis in anovulatory women are often the same drugs that are used in controlled ovarian hyperstimulation in assisted reproduction methods, the protocols and objectives of such therapies are different. Since metformin was introduced for ovulation induction in women with polycystic ovary syndrome, there is a dilemma whether metformin is the drug of choice for treatment of such women, or clomiphene citrate. So far, published studies gave contrary results, mostly in favor of clomiphene citrate (5). The journal Fertility & Sterility published a study conducted by Jungheim and Odibo, which compared three types of treatment in these women. The efficacy of metformin, clomiphene citrate and combinations in achieving live birth in women with PCOS was analyzed. Results showed that the combination of metformin and clomiphene citrate was most efficient and has led to the highest rates of live birth. Authors concluded that this combination should be considered as first-line treatment in infertile women with PCOS (8). At the same time, New Zealand researchers published the results of a large multicenter, randomized study in the journal Human Reproduction. This study also compared metformin, clomiphene and their combination in women with polycystic ovary syndrome and with a BMI less than 32. In this study, priority is not given to any mode of treatment because live birth rate with metformin was 29 %, 36 % with clomiphene citrate and 43 % with the combination, which was not statistically significant (9).

Conclusion

Our research showed that the induction of ovulation in women with polycystic ovary syndrome who plan to become pregnant is a necessity. Monotherapy or a combination of drugs is becoming a challenge for gynecologists, considering that treatment success depends on the applied protocol. It was found that drugs such as clomiphene and metformin have a very important place in the treatment of patients with PCOS, but their disadvantages can sometimes be the cause of induction failure.

If there are no problems with other factors (tubal patency, spermiogram etc.), in ovulation induction the combination of metformin and clomiphene citrate in women with polycystic ovary syndrome can be successful and achieve pregnancy.

References


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