Srp Arh Celok Lek. 2016 Mar-Apr;144(3-4):146-150
ОРИГИНАЛНИ РАД / ORIGINAL ARTICLE
DOI: 10.2298/SARH1604146B
UDC: 618.11-006-085 : 618.177-085

Comparison of the efficiency of clomiphene citrate and letrozole in combination with metformin in moderately obese clomiphene citrate – resistant polycystic ovarian syndrome patients

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SUMMARY

Introduction Polycystic ovary syndrome is the most common endocrinopathy in women of reproductive-age. Therapy for those who want to get pregnant involves ovulation induction using clomiphene citrate, metformin, letrozole and gonadotropins.

Objective The aim of the study was to compare the efficacy of combinations of clomiphene citrate–metformin and letrozole–metformin in obese patients who are resistant to clomiphene citrate alone.

Methods The investigation was conducted as a retrospective study involving 60 moderately obese patients with polycystic ovary syndrome. Thirty-one of them received the clomiphene citrate–metformin, and 29 letrozole–metformin therapy. Stimulation was carried out for the procedures of intrauterine insemination (IUI).

Results The age of patients, duration of infertility, and body mass index in both groups were similar. There was statistically significant difference in the thickness of the endometrium in favor of the group having the letrozole–metformin therapy (8.9 ± 1.7 mm) compared with the group receiving the clomiphene citrate–metformin treatment (6.3 ± 1.3 mm). The number of follicles was not statistically significantly different. Pregnancy rate in the first cycle of IUI in the clomiphene citrate group was 6.4%, and 17.2% in the letrozole group, which also was not statistically different. After the third IUI cycle, the pregnancy rate was significantly higher in the letrozole group (20.6%), while in the clomiphene citrate group it was (9.6%).

Conclusion This retrospective study demonstrated the advantages of the use of letrozole over clomiphene citrate in combination with metformin in moderately obese patients with polycystic ovary syndrome who are resistant to stimulation with clomiphene citrate alone.

Keywords: clomiphene citrate; letrozole; polycystic ovarian syndrome

INTRODUCTION

Ovulatory dysfunction is a frequent problem as it is responsible for 40% of female infertility, and polycystic ovary syndrome (PCOS) is one of its main causes [1]. PCOS is a common endocrine disorder, which is characterized by anovulation, irregular menses, hyperandrogenism, and polycystic ovaries detected by ultrasound. The prevalence of PCOS varies depending on the criteria that are used to make the diagnosis, but is as high as 15–20% [2]. Ovulation induction is recognized as the main therapeutic procedure for patients with PCOS wanting to get pregnant [3].

For ovulation induction, clomiphene citrate is the most often used medicament. Other therapeutic options include the ovulation induction with gonadotropins, use of insulin sensitizers, such as metformin, as well as aromatase inhibitors and laparoscopic ovarian drilling [4].

Clomiphene citrate is a first-line treatment option for induction of ovulation [4, 5]. However, it can have some undesirable consequences, such as the antiestrogenic effect on the endometrium and cervical mucus, which decreases the possibility of pregnancy [3].

Metformin, a biguanide, is a medicament which is used for ovulation induction for women with PCOS, whose main disturbance is insulin resistance and compensatory hyperinsulinemia [5]. Moreover, numerous studies have confirmed that addition of metformin to clomiphene citrate for clomiphene citrate-resistant women is an efficient procedure in the induction of ovulation. Some authors claim that this combination is more efficient than clomiphene citrate or metformin given alone [6, 7]. Still, there are also studies that do not confirm this finding [8].

Letrozole, as a specific inhibitor of aromatase, has been in practical application since 2000, as a drug to treat advanced breast cancer. However, it has been noticed later that its action influences ovary induction, with significantly less undesired effects in comparison with clomiphene citrate. In contrast to clomiphene citrate, letrozole more often causes monofollicular response and does not affect endometrium and cervical mucus, which is due to the absence of blockade of peripheral receptors. Presently, letrozole is considered to be a second-choice drug in the therapy of PCOS with clomiphene citrate-resistant women. A question that has

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been frequently posed is whether letrozole is more efficient than clomiphene citrate, the first-choice drug. A convincing answer to this question is still missing, but it is believed that it would be of great importance for everyday clinical practice. According to some authors, the application of letrozole results in a significantly higher pregnancy rate compared to that of clomiphene citrate [1, 9].

Gonadotropins are also used in ovulation induction for women with PCOS, but only as a therapy of third or fourth choice with clomiphene citrate-resistant women [10]. This is because their application is associated with a high risk of the ovarian hyperstimulation syndrome. Their high cost may also be a reason for their infrequent application [2].

OBJECTIVE

The aim of the study was to compare the efficiency of clomiphene citrate–metformin and letrozole–metformin combinations application with obese clomiphene citrate-resistant women, in respect of the number of follicles, endometrium thickness, conception rates after the first insemination, and cumulative conception rate after three inseminations.

METHODS

This study is a retrospective analysis of data about stimulation cycles for IUI using clomiphene citrate and letrozole for obese women with PCOS that also take metformin. Ovulation stimulation, monitoring of the cycles, and IUI were carried out in the Department of Gynecology and Obstetrics of the Clinical Center of Vojvodina in the 2012–2013 period.

The analyses encompassed three insemination trials with 60 moderately obese women with PCOS, treated with the abovementioned stimulators.

The inclusions were based on the Rotterdam Criteria for PCOS and presence of obesity (body mass index > 30). An additional criterion for inclusion into the analysis was resistance to clomiphene stimulation. Namely, all the patients had at least two attempts of ovulation induction with clomiphene citrate in doses of 100–150 mg/day during five days to which they did not respond (no follicular growth could be verified in a series of ultrasound examinations in the period between 10 and 25 days of the cycle, after which further monitoring of the cycle was suspended). Also, an inclusion criterion was previous treatment with metformin for at least three months, after establishing resistance to the clomiphene citrate treatment in a dose of 1,500 mg/day. The existence of some other causes of sterility was an exclusion criterion.

The stimulators were administered one dose a day, viz. clomiphene citrate – 100 mg, and letrozole – 5 mg. Stimulation began three days after the menstrual cycle and lasted five days. The stimulator was selected by randomization.

After serial folliculometries, when at least one follicle attained the size of at least 18 mm, human chorionic gonadotropin (HCG) was administered in a dose of 5,000 IU. Insemination was performed 30–36 hours after the administration of HCG. The analyses encompassed three insemination attempts with the same subject.

The examination encompassed the following parameters: thickness of the endometrium on the day of HCG administration, total number of follicles longer than 18 mm, rate of clinical pregnancies verified by ultrasound after the first insemination attempt, and cumulative rate of pregnancies after three inseminations.

The obtained results were analyzed using the statistical package SPSS 22.0 (methods of descriptive statistics, Pearson's χ^2 test, and Student's t-test).

The study was conducted according to the ethical standards approved by the Ethical Committee of the Clinical Center of Vojvodina in Novi Sad.

RESULTS

The investigation encompassed 60 women divided into two groups of 31 and 29 patients. As can be seen from Table 1, the data on their age, duration of infertility, and body mass index were quite comparable, and there were no statistically significant differences between these parameters.

The endometrium was statistically significantly thicker in the group receiving letrozole than in that receiving clomiphene citrate (Table 2). With the group receiving letrozole, it was 8.9 ± 1.7 mm, and for that receiving clomiphene citrate it was 6.3 ± 1.3 mm. Statistically significant differences among the two groups were observed in the number of follicles that were larger than 18 mm. The difference between the number of pregnancies in the first insemination cycle was not statistically significant. However, after three IUI cycles, a statistically significant difference

Table 1. Characteristics of women in the groups treated with clomiphene–metformin and letrozole–metformin combinations

	clomiphene citrate + metformin	letrozole + metformin	p
Number of patients	31	29	0.267
Age	27.3	28.4	0.258
Sterility duration, years	3.9	4.2	0.129
BMI	33.1	31.9	0.317

BMI – body mass index

Table 2. Criteria for the effect assessment of the applied ovulation inductors in combination with metformin

	clomiphene citrate–metformin	letrozole–metformin	p
Endometrium thickness (mm)	6.3 ± 1.3	8.9 ± 1.7	0.001
Number of follicles larger than 18 mm	1.9 ± 0.9	1.7 ± 0.3	0.241
Clinical pregnancies after the first IUI cycle	2 (6.4%)	5 (17.2%)	0.257
Cumulative pregnancy rate after three IUI cycles	9 (9.6%)	20 (20.6%)	0.024

IUI – intrauterine insemination

in the cumulative number of pregnancies appeared. Namely, in the clomiphene citrate group there were nine, and in the letrozole group there were 20 pregnancies.

DISCUSSION

Induction of ovulation is a procedure of crucial importance for women with PCOS [3]. Clomiphene citrate is the drug most often prescribed to such patients [11]. Although it is still used as a traditional means for ovarian induction, there are reports on the resistance to this drug. This is observed as persistent anovulatory cycles after applying the standard clomiphene citrate therapy, appearing in 20–25% of cases [3]. Clomiphene citrate initiates or stimulates ovulation by binding to the estrogen receptors. The capacity to play this role is due to its structural similarity to natural estrogen. The difference is seen in the fact that binding of clomiphene citrate to the receptors lasts longer (several weeks), whereas the binding of estrogen lasts only several hours [11]. Pharmacologically, clomiphene citrate is a mixture of two stereoisomers, enclomiphene and zuclomiphene, which have different properties. The level of enclomiphene increases somewhat after drug administration, and then falls very rapidly, and after several days it is not detectable in the blood. On the other hand, the level of zuclomiphene increases much slower and it remains in circulation even one month after the drug administration [6]. This prolonged binding causes depletion of endometrial estrogen receptors, which is reflected on the normal estrogen-binding process. The depletion of the receptors in the hypothalamus leads to an erroneous explanation of the estrogen blood level and increased secretion of gonadotropin-releasing hormone and subsequent increase in the level of gonadotropins. The increase in the level of follicle-stimulating hormone initiates maturation of the ovarian follicles in anovular women. Ovulation is restored in 70–80% of cases, but pregnancy occurs in only 30–40% of cases. This decrease in the percentage of pregnancies is attributed to the peripheral antiestrogenic effect of clomiphene citrate. Zuclomiphene, which due its long half-life causes prolongation of the mentioned antiestrogenic effects, plays a significant role in this process. One of the antiestrogenic effects is the condensation of the cervical mucus, which appears in 15% of patients. It can be overcome by IUI. Another side effect is inhibition of endometrium proliferation. This can be also seen from this study, where endometrium thickness was significantly smaller compared to that observed in the application of letrozole in the therapy. One of previous studies demonstrated that pregnancy did not occur if the endometrium thickness in the middle of the cycle was less than 6 mm, and that the percentage of pregnancies increased significantly in women with endometrium thickness in the middle of the cycle between six and 8 mm [9]. This finding was also partly confirmed in our study, since the letrozole-treated group was characterized by thicker endometriums and a higher number of pregnancies after the third IUI cycle.

The number of follicles that attained 18 mm does not show a statistically significant difference between the two groups examined in this paper. A similar study by Al-Fozan et al. [12], also showed no statistically significant differences. In a study in which authors measured and compared follicles between 14 and 18 mm in size, a statistically significant difference was observed in favor of the letrozole-treated group [13].

Letrozole belongs to the third generation of non-steroid aromatase inhibitors, which act on the aromatase inhibitors and prevent transformation of androgen to estrogen. It is assumed that letrozole acts on the ovaries by reducing the amount of estrogen, which influences the negative feedback in the hypothalamus, thus leading to increased production of gonadotropin and an increase in the number of maturing ovarian follicles. It has been noticed that letrozole acts in almost the same way as clomiphene citrate, but without depleting the estrogenic receptors, and causing no antiestrogenic effects [11]. Because of their short half-life, aromatase inhibitors exert less antiestrogenic effects, especially during the late follicular phase, as they do not act on the endometrium and cervix. This also increases the possibility of the occurrence of pregnancy [9]. Some of the studies have pointed out the advantages of letrozole in the ovarian induction for women with PCOS. However, such patients often over-reacted to this type of stimulation, so there is significant risk for the development of hyperstimulation syndrome. In our study, all pregnancies were mono-fetal, whereas some other studies reported a higher number of multi-fetal pregnancies after administering clomiphene, compared to the therapy with letrozole [11]. These data were explained in terms of the fact that letrozole induces a limited number of ovarian follicles if compared to clomiphene citrate and some other stimulators.

When the percentage of pregnancies in the first IUI cycle is concerned, it appeared that it was higher for the group receiving letrozole (17.2%) than in the clomiphene citrate group (6.4%), but this was not a statistically significant difference. Similar results (with no statistically significant difference) in therapies also using these two drugs were obtained in some other studies [14, 15]. However, some randomized studies reported a significant difference in the percentages of pregnancies also using letrozole and clomiphene citrate [16]. In one of the studies, women were divided according to criteria similar to those in our own study, but they had the average endometrium thickness of 9.3 ± 0.9 mm and 10.2 ± 1.03 mm, respectively. However, their results showed no statistically significant differences in the efficiency of effecting pregnancies in the first IUI cycle [17].

In the present study, statistically significant difference was obtained only after the third IUI cycle, as in the group treated with the letrozole–metrformin there were 20.6% of pregnancies, compared to 9.6% for the clomiphene citrate–metformin group. The presented data are related to the PCOS subgroup of women that are moderately obese and resistant to stimulation with clomiphene citrate. The results

doi: 10.2298/SARH1604146B

indicate that the resistance to clomiphene citrate may be overcome to some extent by adding metformin in the period of at least three months before starting new stimulation with clomiphene citrate. Nevertheless, it should be pointed out that, regarding the cumulative period of three months, better results are achieved by using letrozole as an ovulation stimulator.

CONCLUSION

The present retrospective study showed certain advantages of using letrozole in combination with metformin for moderately obese women with PCOS which are resistant to the stimulation with clomiphene citrate. The results indicate that both combinations, i.e. letrozole–metformin and camphene citrate–metformin, resulted in the same number of follicles, but with no antiestrogenic effects on the endometrium, as well as in a larger number of pregnancies after the third IUI cycle. Having in mind these differences, it can be concluded that the inclusion of metformin in the therapy and choice of letrozole as an inductor is an efficient procedure for ovarian induction for moderately obese PCOS women resistant to clomiphene citrate.

A more extensive study would be needed to obtain more reliable guidelines for the use of the letrozole–metformin combination in everyday clinical practice.

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Компарација ефикасности кломифен цитрата и летрозола у комбинацији са метформином код умерено гојазних кломифен цитрат резистентних пацијенткиња са синдромом полицистичних јајника

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КРАТАК САДРЖАЈ

Увод Синдром полицистичних јајника једна је од најчешћих ендокринопатија у репродуктивном периоду жена. Терапија за пацијенткиње које желе да затрудне подразумева индукцију овулације, за коју се користи више медикамената: кломифен цитрат, метформин, летрозол и гонадотропини.

Циљ Циљ ове студије био је да се упореди ефикасност примене комбинације кломифен цитрат – метформин и летрозол – метформин код гојазних пацијенткиња које су резистентне на стимулацију само са кломифен цитратом.

Методе Истраживање је спроведено као ретроспективна студија којом је обухваћено 60 умерено гојазних пацијенткиња са полицистичним оваријалним синдромом, од којих је тридесет једној дата терапија кломифен цитрат – метформин, а других 29 добило је терапију летрозол – метформин. Стимулација је спроведена за поступке интраутерине инсеминације.

Резултати Старост пацијенткиња, трајање стерилитета и индекс телесне масе у обе групе били су слични. Забележена је статистички значајна разлика у дебљини ендометријума у корист групе која је као терапију имала летрозол – метформин (8,9 ± 1,7 *mm*) у поређењу са групом која је у терапији имала кломифен цитрат – метформин (6,3 ± 1,3 *mm*). У броју фоликула који су достигли величину од 18 *mm* и више није забележена статистички значајна разлика. Проценат трудноћа у првом циклусу инсеминације је у кломифен цитрат групи био 6,4%, док је у летрозол групи износио 17,2%, што није статистички значајна разлика. Након трећег циклуса интраутерине инсеминације проценат трудноћа је био статистички значајно већи у летрозол групи (20,6%), док је у кломифен цитрат групи износио (9,6%).

Закључак Ова ретроспективна студија показује предности употребе летрозола у комбинацији са метформином код умерено гојазних пацијенткиња са полицистичним оваријалним синдромом које су резистентне на стимулацију са кломифеном.

Кључне речи: кломифен цитрат; летрозол; синдром полицистичних јајника

Примљен • Received: 04/03/2015 **Прихваћен • Accepted:** 18/01/2016

doi: 10.2298/SARH1604146B