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Does the combination of myo-inositol improve pregnancy outcomes in obese polycystic ovary syndrome women undergoing ovarian stimulation with clomiphene citrate?

Klomifen sitrat ile over stimülasyonu yapılan yüksek kilolu polikistik over sendromlu hastalarda myo-inositol kombinasyonu gebelik sonuçlarını iyileştirir mi?

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Abstract

Aim: Recent evidence has shown that Myoinositol (MI), a nutrient belonging to vitamin B family, may improve hormone profile, and the metabolic disorders accompanying polycystic ovary syndrome (PCOS), probably through the amelioration of preexisting insulin resistance. This study aimed to compare the ovulation and pregnancy outcomes of clomiphene citrate (CC) and its combination with MI in obese PCOS women with infertility.

Methods: Data concerning 80 obese, PCOS women with infertility who had undergone ovarian induction were retrieved from the institutional digital database. Controlled ovarian stimulation (OS) was performed using CC 100 mg or CC (100mg) + MI (4 g). The primary outcome measure of this study was the difference in the ovulation and the pregnancy rates of the women receiving CC (CC group) or CC+MI (combination group) for ovarian stimulation. There were 40 patients in each group.

Results: Endometrial thickness was significantly higher in the combination group than in the CC group (8.4 (1.1) mm vs. 7.7 (1.2) mm, *P*=0.006) and the number of the follicles>17 mm following OS was significantly higher in the combination group compared to that of the CC group (1.6 (0.5) vs. 1.4 (0.5), *P*=0.036). However, the rate of ovulation following OS [37 (92%) vs. 37 (92%), *P*=1.000] and the rate of the pregnancy were similar in CC and combination groups [6 (15%) vs. 11 (27.5%), *P*=0.172, respectively].

Conclusions: Compared to ovarian stimulation with CC alone, the combination provides a beneficial effect on endometrial thickness and the number of mature follicles. However, ovulation rates are similar with the two regimens. Although not statistically significant, there was a trend towards higher rates of pregnancy on CC+MI combination compared to CC alone. Further prospective and randomized trials are required to clearly address the role of the MI in management of the PCOS women with infertility.

Keywords: Polycystic ovary syndrome, Ovarian stimulation, Clomiphene citrate, Myo-inositol

Öz

Amaç: Güncel kanıtlar, B vitamini ailesine ait bir besin maddesi olan miyoinositolün (MI), muhtemelen önceden var olan insülin direncinin iyileştirilmesi yoluyla hormon profilini ve polikistik over sendromuna (PKOS) eşlik eden metabolik bozuklukları düzenleyebileceği gösterilmiştir. Bu çalışmada klomifensitrat (CC) ile CC ve MI kombinasyonunun infertil obez PKOS'lu kadınlarda ovülasyon ve gebelik sonuçları üzerine etkisinin karşılaştırılması amaçlandı.

Yöntemler: Obez ve infertil 80 PCOS hastası kadın dijital veri tabanı aracılığıyla çalışmaya alındı. Kontrollü over stimülasyonu (OS), CC (100 mg) veya CC (100mg) + MI (4 g) kullanılarak yapıldı. Bu çalışmanın birincil sonuç ölçütü, ovülasyondaki fark ve overstimülasyonu için CC (CC grubu) veya CC + MI (kombinasyon grubu) alan kadınların gebelik oranları olarak alındı. Her bir grupta 40'ar hasta bulunmaktaydı.

Bulgular: Kombinasyon grubunda endometriyal kalınlığın (8,4 (1,1) mm ve 7,7 (1,2) mm, *P*=0,006) ve 17 mm'den büyük folikül sayısının (1,6 (0,5) vs. 1,4 (0,5), *P*=0,036) CC grubundan anlamlı olarak daha yüksek olduğu görüldü. Bununla birlikte, OS'yi takiben yumurtlama oranı [37 (%92) vs. 37 (%92), *P*=1,000] ve hamilelik oranı [6 (%15) vs. 11 (%27,5), sırasıyla *P*=0,172] açısından CC ve kombinasyon grupları benzerdi.

Sonuç: Sadece CC ile overstimülasyonu ile karşılaştırıldığında, CC + MI kombinasyonunun endometriyal kalınlık ve olgun folikül sayısı üzerinde olumlu etkileri olduğu görüldü. Ancak, yumurtlama oranları her iki rejimde birbirine benzerdi. İstatistiksel olarak anlamlı olmamakla birlikte, CC + MI kombinasyonunda sadece CC ile karşılaştırıldığında daha yüksek gebelik oranları yönünde bir eğilim vardı. İnfertilitesi olan PKOS'lu kadınların yönetiminde MI'nın rolünü açıkça ele almak için ileriye dönük ve randomize çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Polikistik over sendromu, Over stimülasyonu, Klomifensitrat, Miyoinositol

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Introduction

Polycystic ovary syndrome (PCOS) affects 4% to 18% of women of reproductive age and is one of the leading causes of women infertility [1]. PCOS is characterized by anovulation, hyperandrogenism, hirsutism and polycystic ovaries on ultrasonographic examination. This syndrome presents with several manifestations, including reproductive disorders, metabolic features, and psychological squeals [2]. Dyslipidemia and insulin resistance are common in women with PCOS, and it has been shown that these women are at a higher risk of developing type-2 diabetes than their age and weight-matched counterparts without PCOS [3]. Compensatory hyperinsulinemia resulting from the insulin resistance plays a critical role in the pathophysiology of PCOS [4]. The synergistic action of the insulin with luteinizing hormone (LH) increases androgen production from theca cells, which in turn leads to masculine phenotypic changes [5]. Male phenotypic changes existing in women with PCOS eventually affect psychological health. Anxiety, depression, and negative body image are frequent in PCOS women.

Obesity and insulin resistance also contribute to anovulation and menstrual irregularities in women with PCOS [6]. This syndrome is currently recognized as the leading cause of anovulatory infertility accounting for >80% of all cases [7]. It has been reported that 90% to 95% of the women referred for infertility treatment have PCOS [8]. In addition, the time to conception is increased in women with PCOS. The response to assisted reproductive technologies are also reduced in women with PCOS [9,10]. Obesity is observed in almost 90% of the infertile PCOS patients and reduces the success of infertility treatment [8].

Clomiphene citrate (CC) is a nonsteroidal selective estrogen receptor modulator and has long been assumed as the standard first-line agent in ovulation induction of PCOS patients due to the satisfying ovulation rates of 85% and pregnancy rates exceeding 35% [11]. CC is also used for ovulation induction in many other infertility problems [12]. Recent evidence has shown that myoinositol (MI), which is a nutrient belonging to vitamin B family, may improve hormone profile, and the metabolic disorders accompanying PCOS, probably through the amelioration of preexisting insulin resistance [13,14]. MI has also been shown to increase estradiol and thus can be used to eliminate the symptoms arising from decreased estrogen in PCOS [15]. A number of trials have revealed that D-chiro-inositol, which is a derivate of MI, increases the ovulation frequency and suppresses hyperandrogenism [16].

We hypothesized that implementation of MI in conjunction with CC might improve the outcomes expected from ovulation induction compared to CC alone. The present study, therefore, aimed to compare ovulation induction with CC alone or in combination with MI in obese PCOS patients.

Materials and methods

Subjects

Data concerning 80 obese, PCOS patients with infertility undergoing with ovarian stimulation (OS) in gynecology department of a tertiary center, between January 2016 and January 2019, were retrieved from the institutional digital database. Inclusion criteria for the current retrospective cohort study were as follows: age between 18 and 40 years, presence of PCOS according to Rotterdam criteria, ovarian stimulation in conjunction with either CC or CC + MI combination, and having a body mass index (BMI) ≥30 kg/m^2. The diagnosis of PCOS was based on the Rotterdam criteria, and accordingly patients having the two of the following three features: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries compatible with PCOS [17].

Sample size calculation was performed for two independent groups. We used the mean values of endometrial thickness which was reported in a study conducted by Nakamura et al. [18]. According to power analysis results, with 0.05 alpha error and 80% power level, each group had to contain at least 37 patients.

The total of 40 patients who received CC alone were defined as the "CC group" and the remaining 40 patients who received CC + MI combination were defined as the "combination group".

Written informed consents for inclusion into the study were obtained from all patients. The study protocol was approved by the Acibadem Mehmet Ali Aydınlar University Ethical Committee (2019-15/1) and the study was performed in accordance with the most recent version of the Helsinki Declaration guidelines.

Detailed medical history was obtained from all patients, and each patient underwent a gynecologic examination. Initial workup, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, and thyroid-stimulating hormone (TSH) levels was conducted the 3rd day of the menstrual cycle. Hysterosalpingography was performed to confirm the tubal patency.

Ovulation stimulation

Controlled ovarian stimulation was performed using CC (Clomen®; KocakFarma, Turkey) 100 mg (CC group) or CC (100mg) + MI (4 g) (combination group) from days 3 to 7 aiming at least one mature follicule > 17mm in diameter. Follicular growth and endometrial thickness were evaluated with transvaginal ultrasound during stimulation. When the presence of at least one mature follicle was confirmed, 250 μg of recombinant human chorionic gonadotropin (Ovitrelle®; Merck-Serono, Italy) was administered to trigger ovulation.

The primary outcome measure of this study was the difference in the ovulation and the pregnancy rates of the women receiving CC or CC+MI for ovarian stimulation.

Statistical analysis

All analyses were performed with SPSS v21. Shapiro-Wilk test was used for evaluation of normality. Data are given as mean (standard deviation) or median (minimum-maximum) for continuous variables regarding normality. Categorical variables are presented as frequency and percentage. Comparison of the normally distributed variables (endometrial thickness and >17 m follicle count) was performed using the Student's t-test. Non-normally distributed variables (age, BMI, infertility duration, FSH, LH, prolactin, and TSH) were compared using the Mann Whitney U test. Chi-square test was used to compare the

categorical variables. A *P*-value <0.05 was considered statistically significant.

Results

A total of 80 women with PCOS [median age 25 (19-34) years] and obesity [median BMI 32 (30-37) kg/m^2] were enrolled in this retrospective cohort study. The median duration of infertility was 15 (8-32) months. Forty women received CC, and other forty received CC+MI for ovarian stimulation. Demographic characteristics and laboratory measurements of the study groups are presented in Table 1. There were no significant differences between the two groups with respect to age, BMI, duration of infertility, and laboratory measurements. Anovulation before ovarian stimulation was recorded in 24 (60%) women in the CC group and in 22 (55%) women in the combination group (*P*=0.651).

As shown in Table 2, endometrial thickness was significantly higher in the combination group than in the CC group (8.4 (1.1) mm vs. 7.7 (1.2) mm, *P*=0.006) and the number of follicles >17 mm following OS was significantly higher in the combination group compared to that in the CC group (1.6 (0.5) vs. 1.4 (0.5), *P*=0.036). However, the rate of the ovulation following OS [37 (92%) vs. 37 (92%), *P*=1.000] and the rate of the pregnancy were similar in CC and combination groups [6 (15%) vs. 11 (27.5%), *P*=0.172, respectively].

Correlation analysis revealed that there was no significant relationship between endometrial thickness and presence of the pregnancy (*P*=0.265). However, the number of the follicles >17 mm following OS was significantly correlated with the presence of the pregnancy (*P*=0.001).

Table 1: Demographic features and the laboratory measurements of the study group

	OS with CC n=40	OS with CC+MYO n=40	*P*-value
Age, years	25 (21-32)	25 (19-34)	0.755
Body mass index, kg/m2	32.2 (30.3-37.0)	32.0 (30.0-36.7)	0.129
Infertility duration, months	15 (8-32)	15 (9-24)	0.845
FSH, mIU/ml	5.4 (3.4-9.9)	5.6 (3.4-9.8)	0.478
LH, mIU/ml	9.7 (6.0-16.0)	10.4 (5.6-17.0)	0.112
Estradiol, pg/ml	43.5 (21.4-72.2)	43.4 (22.1-67.0)	0.689
Prolactin, ng/ml	11.1 (5.5-18.7)	10.4 (6.0-18.7)	0.857
TSH, uIU/ml	3.2 (0.9-5.2)	2.6 (0.9-5.2)	0.901
Pretreatment anovulation, n	24 (60%)	22 (55%)	0.651

Data given as mean (standard deviation) or median (minimum - maximum) for continuous variables regarding normality and frequency (percentage) for categorical variables, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, OS: Ovarian stimulation, TSH: Thyroid-stimulating hormone

Table 2: Comparison of the outcomes of the ovarian stimulation in the two groups

	OS with CC n=40	OS with CC+MYO n=40	*P*-value
Endometrial thickness , mm	7.7 (1.2)	8.4 (1.1)	0.006
Follicles >17 mm, n	1.4 (0.5)	1.6 (0.5)	0.039
Ovulation following OS, n	37 (92%)	37 (92%)	1.000
Pregnancy, n	6 (15%)	11 (27.5%)	0.172

Data given as mean (standard deviation) and frequency (percentage) for categorical variables, OS: Ovarian stimulation

Discussion

This study was based on the hypothesis that implementation of MI in conjunction with CC, would improve the outcomes expected from ovulation induction compared to CC alone. Our findings demonstrate that compared to ovarian stimulation with CC alone, CC+MI combination provides a beneficial effect on endometrial thickness and the number of the mature follicles. However, ovulation rates are similar with the two regimens. Although not statistically significant, there was a trend towards higher rates of pregnancy on CC+MI combination compared to CC alone.

Oligo or anovulation is one of the cardinal features of the PCOS. Consequently, menstrual irregularities also accompany PCOS frequently; however, they can be masked by the use of oral contraceptive drugs. The endocrine and metabolic abnormalities existing in patients with PCOS may also deteriorate uterine function and lead to abnormal endometrial cellular proliferation which in turn causes challenges in implantation. PCOS accounts for >80% of all cases with anovulatory infertility and eugonadotrophic hypogonadism. Pregnancy usually takes longer than expected in PCOS women. However, population-based studies have revealed that lifetime fertility is likely not impaired in these women [19].

Weight loss and drugs that induce monofollicular ovulation are the primary treatment of infertility related to PCOS. CC followed by the exogenous gonadotropins in conjunction with intrauterine insemination (IUI) is the most common treatment in PCOS related infertility [20]. Assisted reproductive techniques, including in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are reserved for women in whom IUI has failed [21]. Controlled stimulation is challenging in PCOS and resistance to stimulation is more frequent [22]. Oocyte quality and maturity, which complicates the adoption of assisted reproductive techniques, may also be compromised in PCOS [23].

Clomiphene citrate has selective estrogen receptor modulator properties and it is by far the most commonly used drug for infertility worldwide. While ovulation rates with CC are about 85%, pregnancy rates range between 35% to 40% [24]. The divergence between the ovulation rates and the pregnancy rates is attributed to the peripheral anti-oestrogenic actions of CC on endometrial development and cervical mucus [18, 25]. A recent randomized study conducted by Ozay et al. [26] revealed that MI has improved pregnancy rates in PCOS patients undergoing controlled ovarian hyperstimulation with recombinant FSH and IUI. Another trial by Benelli et al. [15] has documented that combination therapy with MI and D-chiro inositol in young overweight PCOS women leads to a significant reduction in LH, free testosterone, fasting insulin, and HOMA index and increases 17-beta-Estradiol levels. With this in mind, we hypothesized that combining MI with CC could ameliorate the pregnancy outcomes obtained with CC alone, through the suppression of the peripheral anti-estrogenic actions of the CC.

This retrospective cohort study, which investigated the impact of the CC + MI combination on ovulation and the pregnancy outcome in obese PCOS women, demonstrates that the addition of MI to CC for ovulation induction improves endometrial thickness and the number of the mature follicles. Ovulation rate, however, was similar in the two regimens. Although not statistically significant, adding MI to CC also led to a favorable trend in pregnancy rate. Nevertheless, despite the combination of MI with CC, the pregnancy rate was still lower than those indicated in previous data [27]. A possible explanation for this might be that we enrolled only the first cycles after the induction with CC and CC+MI. Findings of the present study also demonstrated a significant correlation between the mature follicle count and presence of the pregnancy. As follicle count reflects the normalization of the hormone levels, the close relationship between the follicle count and the pregnancy rate

observed in this study may be explained by the improvement in the hormone profile, which is essential for both ovulation and implantation [28-30]. Despite the lack of the statistical significance the trend towards a higher pregnancy rate in the combination group might be explained by the increase of mature follicle count of this group. We consider that prospective data, including more cycles of the ovulation induction with CC+MI combination and a larger sample size may provide additional evidence concerning the benefits of this combination, not only in mature follicle count but also in the ovulation and the pregnancy rates.

Limitations

There are some limitations concerning the presents study. First, we analyzed the retrospective data of the post-induction period and therefore could not provide the causal relationships. Second, we could not present data regarding the degree of the insulin resistance, HOMA-IR and the androgen levels. We suggest that prospective, randomized trials with larger sample size are required to clearly address the role of the MI in PCOS women with infertility.

Conclusions

This retrospective analysis demonstrates that compared to CC alone, CC+MI combination improves endometrial thickness and oocyte maturation in obese PCOS women undergoing ovarian induction. However, our findings failed to show any additional benefit of MI in terms of the ovulation rate and the pregnancy rate, although there was a trend towards a higher rate of pregnancy in the combination group. Further prospective and randomized trials are required to clearly address the role of the MI in management of the PCOS women with infertility.

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