Original Article
Comparison of the effect of combined therapy of HCG ampule and letrozole tablet with each method separately on the spermogram parameters in the obese men with idiopathic infertility: a clinical trial

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Abstract: Introduction: Considering that the use of aromatase inhibitors in the treatment of infertile men is a new approach and obesity in men is one of the factors affecting infertility, we decided to compare the effect of combined therapy of Human chorionic gonadotropin (HCG) and Letrozole and either of the two methods alone on the spermogram parameters in obese men with idiopathic infertility. Materials and Methods: This clinical trial study was performed with the participation of 15 infertile and obese men from 2018 to 2019 in Tabriz (infertility clinics); Patients were randomly divided into three groups; The first group received treatment with Letrozole 2.5 mg daily alone, the second group received treatment with HCG ampoules at a dose of 5000 units twice a week, and the third group received combination therapy with HCG ampoules at a dose of 5000 units twice a week and letrozole tablets at a dose of 2.5 mg daily; The results of testosterone and sperm tests before and after the intervention were evaluated by t-test and linear regression tests in SPSS21 software. A p-value less than 0.05 was considered significant. Results: There was no statistically significant difference between semen indices and hormones studied before the intervention (P < 0.05), while after the intervention there were statistically significant differences between all variables compared to those before the intervention (P < 0.05); Also, the rate of change in the third group was much more favorable than the other two groups. Conclusion: The combination of HCG ampules with letrozole tablets compared to the use of these drugs alone improved sperm count, sperm motility, and sperm morphology.

Keywords: Obesity, infertility, male, letrozole, HCG

Introduction

Male idiopathic infertility is considered as a disorder of the spermogram parameters such as abnormality in the number, morphology, or motility of sperm, provided that there is no record of genital surgery, symptom of genitourinary tract infection, use of drugs harming the spermatogenesis, suspicious sexual contact, and abnormalities in hormonal, renal and liver tests. Infertility in men has increased dramatically in recent decades, with its prevalence quadrupling in the United States, doubling in Europe, and up to five times in the Persian Gulf [1]. One of the reasons for the high rate of infertility in men is the effect of progress observed in scientific and medical technology in infertility diagnosis in couples [2, 3]. Among the important causes of decreased fertility in men are oxidative stress, varicocele, a positive family history of infertility, and changes in the sperm genome [4]. Oxidative stress plays a key role in male infertility with destructive effects on sperm structure, leading to changes in the morphology, size, volume, amount, and pH of sperm. Factors increasing oxidative stress include the high consumption of high-fat foods, the non-consumption of fruits and vegetables, smoking for over 10 years, the consumption of alcoholic beverages more than twice a week, and a sedentary lifestyle. However, these factors can be changed and controlled by lifestyle.
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Modification, resulting in boosted fertility in men [5]. A study has shown that the risk of sperm DNA damage in obese, smoking, and alcoholic men is 5, 7, and 6 times higher than that in men without these risk factors, respectively. Therefore, the researchers in this study suggested that before treating infertility, patients reduce smoking, body weight, and alcohol consumption [6]. In recent years, the prevalence of obesity in men of infertility ages has been increasing. Obesity can increase the conversion of testosterone to estradiol via reducing SHBG (sex hormone-binding globulin) produced in the liver and increasing the aromatase of adipocytes, which can also lead to negative pituitary and hypothalamic feedback and hypogonadotropic hypogonadism. According to some epidemiological studies on the negative effects of obesity on male fertility, weight loss can contribute to improved male fertility [7]. Similarly, in several studies, a direct relationship between increased BMI (Body mass index) and decreased blood testosterone, plus a decrease in the number, motility, and fertility rate of sperms have been reported [8, 9].

Currently, to improve fertility in men, approaches affecting testosterone levels are utilized, since the target cells for testosterone and dihydrotestosterone in the testis are Sertoli cells with a significant role in supporting spermatogenesis. Therefore, testosterone is an important factor in initiating and maintaining spermatogenesis [10, 11]. A new approach in the treatment of infertility in men is the use of an aromatase inhibitor, improving S/A status, increasing serum testosterone levels, and decreasing serum estradiol levels [12, 13]. Letrozole is a new non-steroidal aromatase inhibitor that reversibly inhibits aromatase. A study has shown that adding vitamin E to letrozole can improve motility, number, and pH of sperm in infertile men, Researchers suggested that vitamin E be used in addition to the letrozole diet therapy to achieve optimal therapeutic results [14]. Another method for the rehabilitation of male reproduction is the use of Human Chorionic Gonadotropin (HCG) for at least 6 months, whose injection causes an increase in the number, quality, and volume of sperm and an increase in the production of testosterone by Leydig cells A study has shown that to achieve the maximum fertility, it is better to take this drug between six months to one year [15]. Given the fact that the use of aromatase inhibitors in the treatment of infertile men
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is a new approach and obesity in men is one of the factors affecting infertility, the main objectives of the current study were to evaluate and compare the changes in the count, motility, and morphology of sperms, and compare the changes in the estradiol-to-testosterone ratio after treating the obese men with idiopathic infertility by HCG and letrozole separately and their combination.

Materials and methods

Study population

This study was a retrospective clinical trial in which infertile obese men referred to both the infertility clinic of Alzahra Educational and Medical Center in Tabriz and a private clinic in Tabriz were evaluated between 2017 and 2018. The protocol of the study was approved by the ethical committee of Tabriz of Medical sciences (IR.TBZMED.REC.1398.097). Also, the current study was registered in the Iranian Registry of Clinical Trials (IRCT201006140-04181N9, https://en.irct.ir/trial/42901). All patients have signed written consent for participation in the study.

Inclusion and exclusion criteria

Inclusion criteria were obese infertile men with a BMI of over 30, and obese 20- to 45-year-old men. Exclusion criteria were men with a history of genital surgery, a history or symptoms of an infectious disease in the genital tract, a history of suspected contact or urethritis, a history of spermatogenesis-damaging drugs such as sulfasalazine, a history of smoking and alcohol use, and/or drugs, family history of infertility in immediate relatives, the presence of testicular atrophy, the presence of varicocele, changes in the consistency and size of the cord, vas deferens and epididymis, and the presence of disorders in hormonal, renal and hepatic tests.

Procedure

The titles of the treatments were placed in sealed envelopes and each patient was asked to choose one of the envelopes by lot and the main researcher prescribed the selected treatment for the patient. Thus, patients were randomly (using random allocation software) divided into three treatment groups. For the first group, the treatment with letrozole tablets (2.5 mg daily). For the second group, the treatment with HCG ampoules (5000 units twice a week) and for the third group, the combined therapy of HCG ampoules (5,000 units twice a week) and letrozole tablets (2.5 mg daily) were administrated.

Evaluation

One day before commencing the treatment in all patients, spermogram tests (including assessment of volume, count, motility, and morphology of the sperm) were carried out and blood samples were taken to measure serum testosterone and estradiol. Finally, 3 months after treatment in all three groups, blood samples were taken again to measure serum testosterone, estradiol, and S/A. Besides, serum testosterone and estradiol levels and the spermogram parameters of patients before and after treatment of all groups were compared with each other.

Statistical analysis

The sample size was calculated using the following formula:

\[ N = \left( \frac{Z_{1-\alpha/2} + Z_{1-\beta/2}}{\mu_1 - \mu_2} \right)^2 \left( S_1^2 + S_2^2 \right) \]
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N is a sample size and Z is a constant (set by convention according to accepted α error) [16].

The data obtained in the present study were statistically analyzed by SPSS statistical analysis software (version 21). Demographic variables were analyzed by descriptive statistical methods and presented as mean ± standard deviation, frequency, and percentage. The Independent t-test was used for the comparison of age and BMI. To compare the variables among the three groups, ANCOVA, ANOVA, and Kruskal-Wallis tests were used. To establish a statistically significant relationship, the p-value value was considered less than 0.05.

Results

Preintervention data

Forty-nine infertile male patients were referred to infertility treatment centers, 15 of which met the inclusion criteria of the present study. After the random assignment of the patients to the relevant groups, they were present until the end of the intervention; In other words, the sample loss rate in this study was zero (Figure 1). The mean ± standard deviations of age in groups 1, 2, and 3 were 38/2±42/10, 38/2±10/12 and 38/2±39/15. The mean ± standard deviations of BMI in groups 1, 2 and 3 were 34/2±03/62, 33/2±12/29 and 33/2±63/19, respectively (Table 1).

Analysis of blood characteristics

Before the intervention, blood samples were taken from all patients to measure the levels of estradiol and testosterone hormones. The mean ± standard deviations of testosterone and estradiol levels before the intervention were 3.59 89±0.89 and 30.69±0.32, respectively. Before the intervention, there was not a statistically significant difference between the three groups in terms of levels of FSH (P-Value: 0.447), LH (P-Value: 0.225), Testosterone (P-Value: 0.443), Estradiol (P-Value: 0.129), and Estradiol-to-Testosterone ratio (P-Value: 0.240). Although, the status of the hormones studied after the intervention showed that the intervention could be useful in all three groups, the therapeutic approach in the third group (combination of HCG ampoule and letrozole) was associated with better results than the other two groups (Figures 2 and 3).

Analysis of semen characteristics

Before the intervention, the statistical studies showed no significant difference between the three groups in terms of semen characteristics.
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such as percentage of normal morphology (P-Value = 0.144), and percentage of motile sperm (P-Value = 0.238), percentage of progressive sperm (P-Value = 0.421), percentage of rapidly progressing sperm (P-Value = 0.375), semen volume (P-Value = 0.215), and number of sperm (P-Value = 0.221). The assessment of sperm indexes after the intervention also showed that the rate of improvement and success of the third group was much better than the other two groups. In addition, comparing the statistical difference between each group before and after the invention confirmed the occurrence of the most statistically significant changes in the third group after the invention (Figures 4-6).

Discussion

In the present study, the rate of change in sperm count in all three groups increased significantly in the following order: the third group (HCG ampules and letrozole tablets) was more than the second group (HCG ampule group) and the second group was more than the first group (letrozole tablets). The results of this study were consistent with those reported by Patri et al. (2009), Shuling et al. (2019), Gregoriou et al. (2012), Zhao et al. (2014), Bibancos et al. (2015), Roth et al. (2010), Nieschlag et al. (2017) [17-23]. According to these studies, both HCG and letrozole could increase the chance of fertility in men; HCG injections also could increase the number of sperms by a more successful mechanism compared to letrozole, and the combination of both drugs could be even more effective in treating male infertility. In addition, it was reported in the mentioned studies that the sperm count of obese men is higher than normal-weight men due to their high testicular temperature, and these drugs are effective in treating infertility in obese people, in line with the results of our study.

In our study, the changes in the sperm motility index in the third group (HCG ampules and letrozole tablets) were higher than those in the second group and the changes in the second group (HCG ampules group) were higher than those in the first group (letrozole tablets), meaning that the combination of these drugs could increase sperm motility more. The results of the present study agreed well with those carried out by Bauman et al. (2017), Roth et al. (2010), Farhat et al. (2010), Wang et al. (2018), Plessis et al. (2010), and Rambhatla et al. (2016) [22, 24-28]. In these studies, letrozole and HCG were shown to increase sperm motility by increasing energy production in sperm intracellular energy-producing mechanisms, thereby increasing the likelihood of fertility in men. According to the mentioned researchers,
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Obese people had lower sperm motility than normal-weight men, and using this drug could increase sperm motility in obese men.

In the present study, the rate of sperms’ morphological changes in the third group (HCG ampules and letrozole tablets) was higher than that of the second group and the changes in the second group (HCG ampules) were greater than that of the first group (letrozole tablets). In other words, the combined administration of HCG and letrozole led to the most favorable changes in sperm morphology. The results of the present study were in line with those of studies conducted by Ribeiro et al. (2016), Salehpour et al. (2010), Nieschlag et al. (2017), and Zenzmaier et al. (2011) [23, 29-31]. The researchers said that the use of stimulant drugs and aromatases caused favorable changes in sperms’ morphology.

**Conclusion**

As one of the causes of infertility in men, obesity harms the number, motility, and morphology of sperm. The use of stimulant drugs such as letrozole and HCG can improve the fertility of obese men. The present study showed that the combined use of letrozole and HCG, compared to the use of them separately, resulted in greater success in increasing the number, motility, and morphology of sperm.

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**Disclosure of conflict of interest**

None.

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