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Pregnancy and live birth rate in idiopathic male infertility treated with Human Menopausal Gonadotropin: A pilot clinical trial

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ABSTRACT

Background & aim: Idiopathic male infertility refers to the condition in which there is no clear cause for the diagnosis of infertility. Human menopausal gonadotropin (HMG) containing the follicle-stimulating hormone and luteinizing hormone is a medication that causes ovarian follicles to grow in women. This medication can also induce spermatogenesis in men. The present study was conducted to investigate and compare the rates of pregnancy and live birth in partners of men with unexplained infertility after the injection of 8 and 12 ampules of HMG.

Methods: This clinical trial study was carried out on 22 men with unexplained infertility who referred to the Urology Clinic of Rafsanjan University of Medical Sciences, Rafsanjan, Iran, during March 2016 and December 2018. The patients were randomly divided into two groups each of which included 11 cases. For one group 8 HMG injections and for the other group 12 HMG injections were administered (two injections per week). Afterward, the results of clinical pregnancy were assessed, and the cases were followed up to live birth after the clinical pregnancy. Data analysis was carried out using the Chi-square test.

Results: In this study, the rate of positive pregnancy was reported as 62.5% in the group with 12 HMG injections in comparison to 37.5% in the group with 8 HMG injections. Although the pregnancy rate was higher in the 12-injection group, statistically there was no significant difference (P=0.7).

Conclusion: According to the results of the present study, it can be concluded that for couples with unexplained male infertility, the administration of 8 to 12 HMG injections can increase the chance of pregnancy and live birth. Since this study was the first attempt to evaluate the pregnancy rate after treatment with HMG, it is suggested to perform further studies for the assessment of HMG effect on hormonal profile and chromatin quality.

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Introduction

Infertility refers to a situation in which a couple fails to experience pregnancy despite having enough sexual intercourse without using contraceptive methods after a year (1). On average, 15% of couples have reproductive problems half of which goes back to male infertility problems. Infertility can be due to male, female, and combined factors of both, as well as unknown causes (2). Despite significant evidence-based medicine in the diagnosis of infertility

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causes, there is no clear cause for the diagnosis of infertility in 15-30% of cases, and this situation is referred to as unexplained infertility (3).

Human menopausal gonadotropin (HMG) is a medication used for ovulation induction in women with hypogonadism caused by the lack of gonadotropin and stimulation of spermatogenesis or sperm production in men. Menotropin or HMG containing the follicle-stimulating hormone (FSH) and luteinizing hormone is a medication that causes ovarian follicles to grow in women. This medication causes spermatogenesis in men (both in primary hypothyroidism and in the pituitary lower extremity) (4).

According to the literature, various interventions are used for the treatment of infertility, ranging from invasive approaches, such as varicocelectomy and in vitro fertilization (IVF), to pharmacological methods, lifestyle changes, special diets, reduced use of smoking and alcohol, and even physical activity for weight loss, especially in men (5-7). Noninvasive treatments are preferred if there is no clear explanation for infertility (8).

According to the results of a study performed by Guzick, the fertility rate in cases with unexplained infertility was reported as 1.8-3.8% (9). Hull also reported a fertility rate of 50-80% over a 3-year period in cases with unexplained infertility without any treatments among whom pregnancy did not occur within 3 years. This reported rate decreases by 2% for each year of age after 25.7 years (10).

Hormonal therapy has been used for the treatment of male infertility in recent years (3). In a study performed by Madhukar et al. in India (2009), it was observed that hormone therapy was carried out in order to stimulate spermatogenesis and provide reproductive capacity in infertile men. They stated that various treatments, including IVF and intracytoplasmic sperm injection, are useful for infertility; however, some medical studies also considered the option of hormone therapy in the treatment of unexplained infertility (11).

Majority of the studies carried out on hormone therapy have investigated the effect of hormonal therapy on sperm parameters, and they have failed to consider the outcomes of pregnancy. Therefore, for the first time, the present study was conducted to investigate the rates of pregnancy and live birth in men with unexplained infertility after HMG therapy.

Materials and Methods

The present clinical trial was conducted on 40 infertile men enrolled after screening in the Urology Clinic of Rafsanjan University of Medical Sciences during March 2016 and December 2018. The participants were selected through convenient sampling method. Therefore, all infertile men within the age range of 25-40 years who referred to the Urology Clinic with unknown causes for male infertility were chosen for the present study. Sperm analysis, FSH, testosterone, and prolactin tests were performed in order to determine the cause of infertility. If the results of all above-mentioned tests were normal, the subject was enrolled in the study as a case with an unknown cause of infertility.

Partners of the subjects were examined and evaluated in terms of fertility by a gynecologist. After examination, the results of ultrasound and hormone tests revealed that their partners had no problem regarding fertility. Men with spermatic disorders, varicocele, hormonal disorders, systemic diseases, chemotherapy and radiotherapy, as well as those with the administration of antioxidant during the last 3 months before the initiation of the study, were excluded from the study. Out of these 40 patients, 18 cases with mild spermatic disorders were excluded, and finally 22 men with unexplained infertility were included in the next step.

In this step, the patients were randomly divided into two groups each of which with 11 subjects. For one group 8 HMG injections (Merional, IBSA, Lugano, Switzerland) and for the other group 12 HMG injections were administered (two injections per week). The subjects were asked to report the results of the injections and pregnancy information. If the results of beta human chorionic gonadotropin test were positive, they waited until the fetal heart rate was diagnosed in ultrasound. Moreover, the results of clinical pregnancy were recorded, and the cases were followed up to live birth after the clinical pregnancy. The patients were contacted and followed up every 2 months for 2 years. Data were extracted by a questionnaire, including demographics,

treatment, and follow-up information.

Data analysis was carried out using SPSS software (version 18). Data were analyzed using the Chi-square test, and qualitative variables were presented in numbers and percentages. P-value less than 0.05 was

Results

Out of 22 eligible men in the present study, the outcomes of 3 treated patients were not complete due to lack of follow-up data. These three cases were in the 8-injection group (Figure 1).

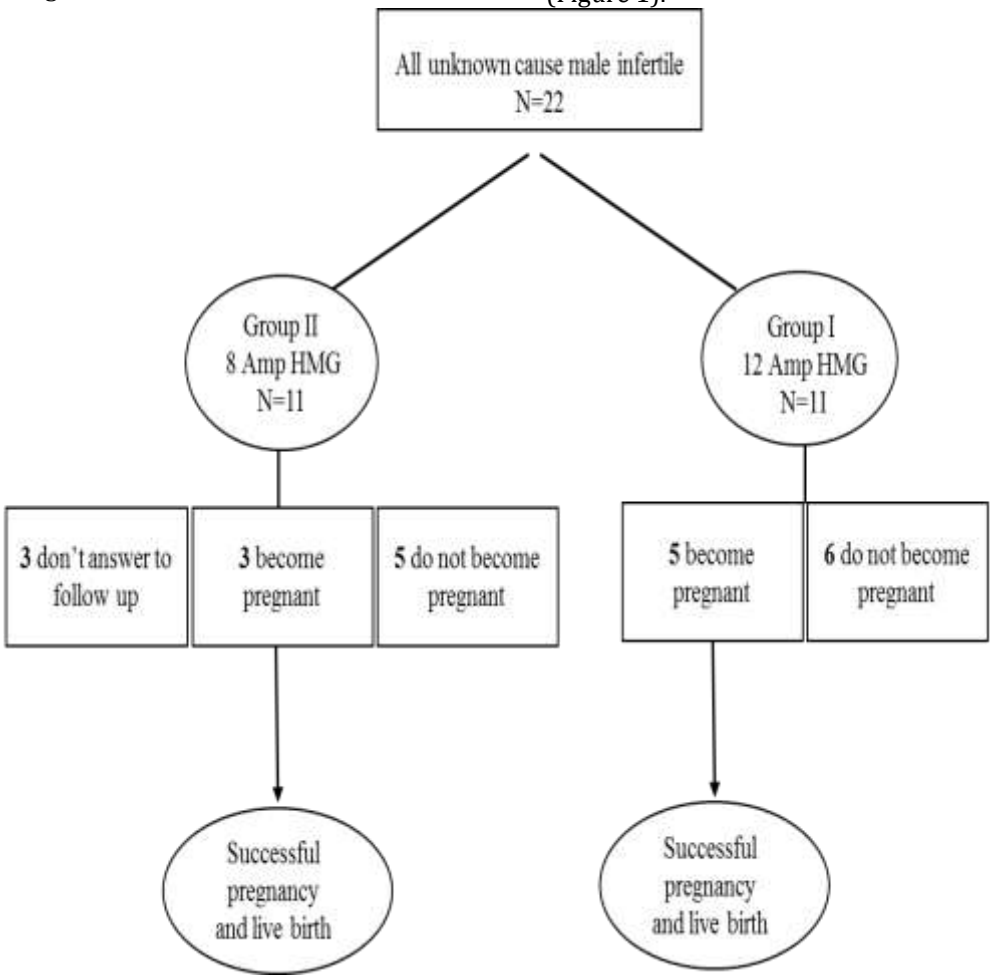

Figure 1. Pregnancy rate in couples with idiopathic male infertility treated with human menopausal gonadotropin (HMG: Human menopausal gonadotropin)

Considered statistically significant. Demographic characteristics, including male and female ages, as well as duration of infertility, were shown in Table I. Mean age of male participants in the present study was reported as 4.36± 34.35 years. Results of pregnancy rate showed that overall 8 (36.4%) patients in the two groups become pregnant. In addition, the progress of pregnancy was followed up to live birth (Table 1).

Table 1. Demographic characteristics of study participants

Characteristics	Mean±standard deviation	Range
Male age (year)	34.35±4.36	28-40
Female age (year)	26.53±3.38	17-31
Infertility duration (year)	2.40±5.20	2-10

Pregnancy rates of patients in the two study groups are summarized in Table II. In this study,

the rate of positive pregnancy was reported as 62.5% in the group with 12 HMG injections in comparison to 37.5% in the group with 8 HMG injections. Although the pregnancy rate was higher in the 12-injection group, statistically there was no significant difference (Table 2).

Table 2. Pregnancy rate based on human menopausal gonadotropin-injection groups

	12-HMG injection Group n (%)	8-HMG injection Group n (%)	P-value
Negative pregnancy	6 (54.5%)	5 (45.5%)	0.77
Positive pregnancy	5 (62.5%)	3 (37.5%)	
Live birth	5 (62.5%)	3 (37.5%)	

Data analysis using Chi-square test; presentation of qualitative variables in numbers and percentages; P<0.05 statistically significant.

Discussion

According to the obtained results of the present study, it seems that the injection of HMG for men with unexplained infertility can increase the pregnancy rate, as well as chance of successful pregnancy and live birth. Many factors can cause unexplained infertility unlikely to be controlled and examined for the identification of a proper explanation regarding infertility. Generally, if the couples are not fertilized without any specific and known physiologic or anatomical causes, they are categorized as cases with unexplained infertility (12).

Different medical methods are implemented for the treatment of infertility. Use of hormones and medication supplements, as well as lifestyle changes, has revealed controversial results (5, 6, 11). Brandes in his review study examined 15 clinical trials on the administration of FHS, compared to the use of other medications for male idiopathic infertility, which is consistent with the present study. Results of the aforementioned study showed that the use of FSH improved sperm parameters and fertility rate in the couples who had undergone various infertility treatments, such as IVF (13).

Usui et al. investigated the treatment of a 29-year-old infertile male with pituitary tumor by the administration of HMG. It was shown that the sexual dysfunction of the patients improved soon after the treatment, and his partner became pregnant 5 months after the initiation of the treatment (14); therefore, the results are consistent with the findings of the present study. In another study, contrary to the results of the present study, Knuth et al. studied the effect of human chorionic gonadotropin/HMG on the fertility rate of the cases who had idiopathic male infertility with normal gonadotropin and sperm concentration below 10 million per ml. Accordingly, there was no difference between the HMG and placebo groups in fertility rate (15).

Although the present study was not conducted to evaluate sperm parameters, the main focus of this study was on the rates of positive pregnancy and live birth. In a study carried out by Dabaja et al. in 2014, given the high prevalence of male infertility, various treatments were experimentally applied without the approval of related authorities, such as Food and Drug Administration, some of which were proved to be effective. In the aforementioned study, they considered the role of hypothalamus-pituitary-gonadal axis and high estrogen levels on the treatment of infertile men. In addition, they stated that the administration of some medications leads to improved sperm parameters, such as sperm concentration and sperm motility (16).

Siddiq et al. also observed that the use of hormones, such as HMG, were effective in the improvement of sperm parameters in the United States. However, in the aforementioned study, it was shown that these changes were not statistically significant 3 to 6 months following the use of HMG (17). In 2002 in Italy, Rocchietti March reported that idiopathic male infertility was a complex complication with a variety of therapies. Therefore, there is a possibility of treating such individuals through the application of various pharmacological methods by clinical specialists (18).

Conclusion

According to the findings of the present study, it can be concluded that 8 to 12 injections of HMG in couples with unexplained male infertility can increase the chance of pregnancy and live birth. Since this study was the first attempt for the evaluation of pregnancy outcomes after the treatment with HMG, the main objective was to focus on pregnancy outcomes, not hormonal profile or sperm parameters. However, the next study, which is currently being performed, focused on the assessment of HMG effect on sperm parameters, hormonal profile, and pregnancy outcomes in couples with unexplained male infertility. Sample size of the present study was reported as 22; therefore, it is suggested to perform future studies with a larger sample size.

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Conflicts of interest

The authors declare no conflicts of interest.

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