Original Article

Is There any Role for Granulocyte Colony Stimulating Factor in Improvement of Implantation in Intrauterine Insemination? A Prospective Double-Blind Randomized Control Trial

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Abstract

Background: Granulocyte colony stimulating factor (GCSF) has been introduced as an immunomodulatory agent by increasing implantation rate *in vitro* fertilization (IVF) patients but it has not been studied in intrauterine insemination (IUI) patients. The aim of this study is to answer the role of GCSF in implantation rate of IUI.

Materials and Methods: In this prospective double-blind randomized control trial, 320 eligible patients were enrolled, who were referred to the referral infertility clinic of Shiraz University of Medical Sciences from February 2018 till the end of 2019. They were divided into two groups randomly. After collecting the demographic data, all patients received clomiphene citrate from the 5th day of the menstruation cycle for 5 days. 50-150 units of recombinant purified follicle-stimulating factor (FSH) were started from the 8th day of the cycle. Follicle monitoring was done by transvaginal sonography till a mature follicle of 18 mm or more was developed. Human chorionic gonadotropin (HCG) injection was done in both groups with intrauterine administration of 300 µg GCSF in the case group and normal saline in the control group simultaneously. After 36 hours, IUI was performed. The clinical pregnancy, miscarriage, and ongoing pregnancy rates of both groups were calculated by SPSS software.

Results: The results showed improvement of clinical pregnancy rate [15.38% vs. 13.81% OR=1.17 (0.62-2.21)], miscarriage rate [3.84% vs. 5.26% OR=0.74 (0.25-2.20)] and ongoing pregnancy rate [11.53% vs. 8.55% OR=1.37 (0.65-2.92)] in the GCSF group compared to the control. However, the results revealed no statistically significance (P>0.05).

Conclusion: Although it was not statistically significant, 300 µg Intrauterine GCSF administration simultaneously with hCG injection in standard IUI procedure might increase the pregnancy outcomes. Further studies are warranted (registration number: IRCT201212079281N2).

Keywords: Embryo Implantation, Granulocyte Colony-Stimulating Factor, Pregnancy Rates

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Introduction

Nowadays, unexplained subfertility is an issue of concern in infertility clinic visits among 30-50% of couples (1, 2). Expectant management controlled ovarian hyper-stimulation with intrauterine insemination (IUI) as a less invasive method, or the more aggressive technique of *in vitro* fertilization (IVF) are the accepted practices for managing unexplained subfertility (3-5). Although treatment strategies should be selected individually, some authors recommend stimulated IUI as the first method of therapy with a success rate of 12% per cycle that is followed by IVF after three cycles of failure (1, 2). In addition, some authors indicated that the success rate of IUI is defined to be more similar to IVF than previously recognized (6).

It is logical to manage unexplained subfertility patients stepwise and gradually start with inexpensive, less invasive, and low-risk treatments (2). As IUI is less invasive and more economic than IVF with considerable benefits, it is reasonable to improve the success rate of IUI in these patients. Normal semen analysis and patent uterine tubes of unexplained subfertility patients highlight the role of the uterus as the main target of therapy for IUI improvement of success rate by affecting the implantation rate (7).

Granulocyte colony stimulating factor (GCSF) is introduced as an effective cytokine in reproduction and fertility via overcoming immunologic factors by the final consequence of altering the implantation rate (8, 9). This cytokine is derived from the bone marrow and cells like the monocyte, macrophage, and fibroblasts; it triggers the proliferation of the neutrophils and promotes releasing them into the blood circulation (10). It plays a role in inflammatory prohibition, angiogenesis, and prevention

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The results of this study showed no statistically significant improvement in fertility rate in patients who received GCSF on the day of hCG injection in the IUI cycle. To the best of our knowledge, we found no previous study on testing GCSF to improve the IUI success rate study. There are some articles in the literature focusing on GCSF in assisted reproductive techniques (ART) success among patients suffering from recurrent miscarriage (10, 25) or thin endometrium in ARTs (9, 26) although there are some non-specific side effects like nausea and vomiting, anorexia, and headache; moreover, chest pain, hypoxemia, and syncope are mentioned as its side effects (12).

There is a controversy on GCSF efficacy to treat RIF patients (20). Kamath et al. (27), in a recent systematic review, Kalem et al. (23) in a randomized control study on intrauterine administration of GCSF in normal endometrium patients (23), and Davari Tanha et al. (28), in a randomized double-blind placebo control trial presented GCSF as an ineffective treatment in RIF patients. They are all in line with the Practice Committee of the American Society for Reproductive Medicine which believes there is no effect of GCSF considering insufficient study on the issue (29). In contrast, the following mentioned studies indicated that GCSF was beneficial. Zhang et al. (15) revealed the positive effect of GCSF in either systematic or intrauterine root administration in RIF patients. Also, the potency of GCSF to increase fertility in RIF patients is shown in a systematic review as well as other immunotherapy methods (10). Zhao et al. (30), in a systematic review and meta-analysis presented this cytokine as a beneficial method of fertility improvement. These controversies occur due to national, ethical, and genetic variations as well as different sample sizes and study design studies, the dosage of administration, and root of injection (8, 31). In line with the Practice Committee of the American Society, Davari Tanha et al. (28), we found no significant improvement in the fertility rate although it was more in the groups that received GCSF. It may be attributed to the very short lag between the administration of GCSF and insemination (36 hours). More time might be needed to present the positive effects of GCSF. Also, we perfused GCSF once in the uterine cavity, with possible benefit in more times of administration of the cytokine.

The outstanding root of GCSF administration is uncertain. Zeyneloglu et al. (14) demonstrated the benefits of dual subcutaneous and intrauterine administration of GCSF in patients with recurrent implantation failure in the intracytoplasmic sperm injection process. Patients received GCSF subcutaneously for 15 days starting from the oocyte retrieval day. The intrauterine dose was injected on the day of ovulation induction. The result of the study revealed the effectiveness of combination therapy of GCSF as the best method of prescription. Kalem et al. (23) showed no effectiveness in intrauterine administration of GCSF daily on hCG. Recently, a systematic review emphasized the effectiveness of GCSF in both intrauterine and subcutaneous administration with more success for subcutaneous method (8). Cavalcante et al. (10) in a systematic review showed the subcutaneous root as the method of choice for recurrent miscarriage treatment purposes, while the intrauterine root was a suitable choice for RIF or thin endometrium. In a systematic review, the beneficial effect of GCSF was attributed to the subcutaneous root of administration (30). Incongruently, Xie et al. (32) presented the effectiveness of intrauterine administration of GCSF in patients suffering from thin endometrium. In the present study, although we presented a better outcome in patients who received intra-uterine GCSF, this improvement was not statistically significant in patients with normal endometrium thickness. Effects on the patients with thin endometrium were not studied in this survey, so the possible intrauterine positive effect of GCSF might have been ignored. The potential effects of systematic administration of GCSF on normal endometrium patients should be investigated in further studies.

The strength of our study is its large population with the study design of a double-blind randomized control trial. Sonographer, laboratory, and IUI performer were the same among all participants, leading to a reduction in bias. Also, to the best of our knowledge, there is limited data on the effect of GCSF administration on the IUI success rate. We focused on the possible effects of GCSF that could lead to altering the protocols of subfertility management. Finally, it is concluded that less expensive modalities with less invasive procedures should be used. Performing this study only on patients with normal endometrial thickness is the limitation of our study. It is recommended that further studies be conducted considering the thin endometrium group and those with normal endometrium. Also, considering different lags between GCSF prescription and insemination should be examined in future studies to evaluate the possible positive effects of the cytokine prescribed in systemic, intra-uterine, or both methods.

Conclusion

Intrauterine 300 μg GCSF administration simultaneously with hCG injection in standard IUI procedure has increased the pregnancy outcome although it was not statistically significant. More studies are warranted that focus on the root and day of administration and studied population.

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