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# Impact of granulocyte colony stimulating factor infusion on the implantation rate in women with unexplained previous intracytoplasmic sperm injection failure: a case control study

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**ABSTRACT**

**Objective.** We studied the granulocyte colony stimulating factor (G-CSF)'s effect on women with unexplained infertility and previous intracytoplasmic sperm injection (ICSI) failure. Unexplained infertility is a condition when couples are not able to conceive despite normal semen analysis and absence of female infertility factor(s). Cytokines, transcription factors and signaling pathways are essential for complex interactions of decidualization. G-CSF is a glycoprotein with growth factor and cytokine functions, which are produced in many tissues.
**Patients and Methods.** The study was done on a total of 200 women with only 196 women who ended the study (99 women as a study group, 96 women as a control group). All women were complaining of unexplained infertility with previous history of failed ICSI. All cases proceed through ICSI procedure while study group only undergone G-CSF infusion intrauterine at time of ovum pickup.
**Results.** We found that intrauterine G-CSF injection at time of ovum pickup in the study group, in comparison with control group, did not improve neither implantation rate (16.68% *vs* 19.66%, p = 0.243) nor the chemical (54.5% *vs* 67%, p = 0.074), clinical pregnancy (51.5% *vs* 62.9%, p = 0.108) rates as well as live birth rates (31.0% *vs* 39.8%, p = 0.227).
**Conclusions.** Intrauterine infusion of G-CSF may not improve implantation rate in women with unexplained previous intracytoplasmic sperm injection (ICSI) failure. Further studies are needed to conclude if the dose, route and timing of the drug administration can give better results.

## INTRODUCTION

Unexplained infertility is a condition in which couples are unable to conceive despite normal semen analysis and the absence of any female infertility factors. While the results of intracytoplasmic sperm injection (ICSI) procedures have generally been positive, there is a new challenge that couples face: recurrent implantation failure (RIF). Roughly 10% of women seeking ICSI experience RIF [1]. This can leave couples feeling confused and frustrated. Coughlan and colleagues have proposed a definition of RIF, which states that it is the inability to achieve a clinical pregnancy after three fresh or frozen cycles with four Class A embryos transferred in a woman under the age of 40 [2, 3].

While there is now an international consensus on the definition of RIF, managing it requires a multidisciplinary approach beyond just evaluating the quality of embryos and endometrium. Other outcome parameters related to ICSI must also be considered to effectively manage RIF [3].

Sperm fragmentation [4], oocyte quality, chromosomal structure, immunologic and thrombophilic factors, endometrial sonographic parameters [5] and even living conditions can affect the success rate of the ICSI procedure [6]. While numerous ICSI "add-ons" have been developed and are widely believed to be safe and effective, the scientific evidence supporting these techniques is either strongly contradictory or, at best, unclear. From these innovations, aiming not to reach RIF, are endometrial scratching, assisted hatching, embryo glue and elective freeze all cycles [7].

In recent times, there has been an increasing recognition of the importance of immunological factors in embryo implantation. However, the effectiveness of immunological treatments for women with RIF remains a topic of debate as conflicting results have been reported in studies up to the present day [8]. Additional research is necessary to explore the clinical significance of emerging immunotherapy approach [9], cytokines, transcription factors and signalling pathways are essential for complex interactions of decidualization. A proper immune reaction is essential for embryo attachment and invasion [10]. Granulocyte Colony Stimulating Factor (G-CSF), also known as filgrastim, is a type of haematopoietic cytokine that is produced by bone marrow cells, macrophages, stromal cells, and fibroblasts. The phagocytosis and oxidative reactions induced by G-CSF are believed to play a crucial role in the process of implantation [11]. The G-CSF receptor has been detected in non-haematopoietic cell types such as trophoblastic, endothelial, placental, and granulosa lutein cells [8]. G-CSF appears to play a significant role in the regulation of endometrial gene expression, vascular remodelling, cellular adhesion mechanisms, and local immune modulation, all of which are crucial to the process of implantation [11]. Studies have shown that systemic administration of G-CSF can have an impact on embryonic development and trophoblastic growth [12]. However, local administration of G-CSF is believed to be crucial for endometrial remodelling and receptivity, particularly when administered intra-uterine [13]. G-CSF supplementation has emerged as a potential new therapy in the field of reproductive medicine, and is currently an area of active investigation [6].

### *Aim of the study*

The objective of this study is to investigate the impact of intrauterine injection of G-CSF into the uterine cavity of women with unexplained infertility who have experienced previous ICSI failure. Specifically, the study aims to examine the effects of G-CSF on implantation rate, miscarriage rate, chemical and clinical pregnancy rates, as well as live birth rate.

## PATIENTS AND METHODS

This prospective randomized controlled study was conducted at the Bedaya IVF centre, a private IVF centre, in collaboration with the infertility clinic of the National Research Center over the course of a year. The study was carried out after obtaining approval from the Ethical Committee. This study involved a total of 200 women with unexplained infertility who had previously undergone a failed cycle of intracytoplasmic sperm injection (ICSI). The women were randomly divided into two groups: the G-CSF group and the control group, with 100 women in each group. Standard antagonist long protocol was used for ovarian stimulation in both groups. Once at least two follicles had reached a diameter of 18 mm, human chorionic gonadotropin (hCG) (Choriomon 10000 IU, IBSA Institute, Switzerland) was administered to induce final oocyte maturation. Transvaginal oocyte retrieval was carried out 36 hours after hCG injection, and the retrieved oocytes were fertilized using the intracytoplasmic sperm injection method.

### *Group I (G-CSF group) (n = 100)*

At the day of ovum pickup and after oocytes collection, 300 $\mu$g in 1 mL G-CSF (300 $\mu$g/mL rHu G-CSF, Neukine; Intas Pharmaceuticals Ltd., India) will be administered by slow transcervical intrauterine infusion with IUI catheter [12].

### *Group II (control group) (n = 100)*

Normal saline of 1 mL was infused into the endometrial cavity of patients in the control group at the day of ovum pickup.

Vaginal micronized progesterone was administered on the day of oocyte retrieval to provide luteal phase support. At least three good quality embryos (as per the Society for Assisted Reproductive Technology embryo grading system, 2010) were transferred into all patients using an embryo transfer catheter (Cook USA) five days after oocyte retrieval.

A positive serum βhCG test 14 days after embryo transfer was considered indicative of a chemical pregnancy, while the observation of a gestational sac on transvaginal ultrasound examination three weeks after a positive serum βhCG result was considered indicative of a clinical pregnancy. Implantation rate was calculated by dividing the number of gestational sacs by the number of transferred embryos in each group [14]. The ongoing pregnancy rate was defined as the presence of foetal heart activity on ultrasonography after 12 weeks of pregnancy. Miscarriage rate was assessed by dividing the number of miscarriages before 20 weeks gestation by the number of women with a positive βhCG test.

The women who were included in this study were between 18 and 40 years of age and had a complaint of primary or secondary infertility for more than one year. To be eligible, women had to have unexplained infertility, with no abnormalities in the uterine cavity, normal Fallopian tubes, normal ovulation, and normal semen analysis results according to WHO 2010 criteria for the male partner. They must also have had a previous failed ICSI procedure with an embryo transfer of at least 3 good quality embryos on day 5 (either fresh or frozen embryos). In terms of laboratory findings, women had to have an Anti-Müllerian hormone level of ≥ 1 ng/mL and/or follicle stimulating hormone levels of ≤ 13 IU/L in the early follicular phase. They should have had a regular cycle of 25-35 days, positive ovulation tests, and/or midluteal progesterone levels of ≥ 25 mmol/L in an unstimulated cycle. Women who were excluded from the study were below 18 or over 40 years of age, had a body mass index (BMI) of ≥ 35 kg/m$^2$, or had any contraindications for G-CSF (such as active infections, kidney disease, sickle cell anaemia, malignancies, or chronic neutropenia).

All women who participated in the study underwent a review of their medical records and assessment sheets, with a specific focus on their personal history, including age, residence, schooling level, socioeconomic status, fertility problems, obstetric history (including the number of pregnancies and living children), and ultrasound for any uterine or tubal anomalies, as well as antral follicle count and measurement of the dominant follicle. A simple, computer-generated randomization was carried out with the assistance of an impartial statistician at a 1:1 ratio. Written informed consent was obtained from each participant, and the women were blinded to which group they were assigned to, while the medical practitioner was not blinded.

The data were described statistically in terms of mean (standard deviation (SD)), median and range, or frequencies (number of cases) and percentages as appropriate. Numerical data were assessed for normality using the Kolmogorov-Smirnov test. A Student's t-test for independent samples was used to compare numerical variables between the study groups, while a chi-square ($\chi^2$) test was used to compare categorical data. In cases where the expected frequency was less than 5, an exact test was used instead. P-values less than 0.05 were considered statistically significant, and all statistical calculations were performed using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

## RESULTS

In total of 200 women, only 196 women with unexplained infertility who experienced previous ICSI failure were included in this study, with 99 patients (50.5%) in the G-CSF group and 97 patients (49.5%) in the control group. Four women discontinued the study upon their request either due to failure of fertilization or cancelation of embryo transfer (**Figure 1**).

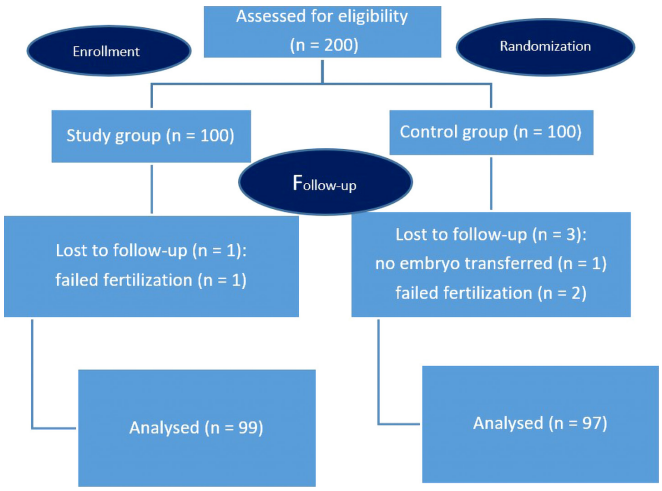


**Figure 1.** *Consort flow diagram.*

**Table 1.** *Demographic characteristics of the research groups.*

| | Control | Case | P-value |
|---|---|---|---|
| Age | 28.87 ± 4.482 | 29.87 ± 4.12 | 0.518 |
| Duration of infertility | 6.14 ± 4.913 | 5.87 ± 4.265 | 0.683 |
| FSH | 6.251 ± 1.242 | 6.018 ± 1.309 | 0.633 |
| AMH | 4.095 ± 1.8108 | 3.560 ± 2.1953 | 0.064 |
| AFC | 24.42 ± 9.086 | 25.13 ± 10.939 | 0.623 |
| Endometrial thickness | 9.41 ± 1.881 | 9.42 ± 1.467 | 0.977 |
| Previous IVF | 1.59 ± 0.910 | 1.40 ± 1.106 | 0.206 |
| Previous pregnancy | 0.92 ± 1.891 | 0.75 ± 0.993 | 0.430 |

All data are expressed by mean ± standard deviation; P-value significant < 0.05.

**Table 1** shows the demographic data and baseline characteristics of patients enrolled in the study. No differences were found in both groups regarding the women's age, duration of infertility, number of previous pregnancies, number of pervious IVF failures, antral follicle count and endometrial thickness. For the biochemical parameters, the mean follicle stimulating hormone (FSH) level was 7.22 ± 2.14 (G-CSF 6.242 ± 2.1833 and control 7.206 ± 2.0036) and the Antimullerian hormone was 3.824 ± 2.0269 (G-CSF 3.560 ± 2.1953 and control 4.095 ± 1.8108). The mean of endometrial thickness at the day of hCG trigger was 9.42 ± 1.680 mm (G-CSF 9.42 ± 1.467, control 9.41 ± 1.881 and P-value 0.977). **Table 2** shows no significance difference regarding induction of ovulation criteria. The mean gonadotropin (GN) duration was 10.51 ± 1.025 days (G-CSF 10.47 ± 1.043 days and control 10.55 ± 1.011 days) and the gonadotropin dose was 252.70 ± 83.104 IU (G-CSF 255.30 ± 85.660 IU and control 250.05 ± 80.769 IU). For the oocyte quality parameters, the mean number of retrieved oocytes 22.95 ± 11.474 (G-CSF 22.18 ± 10.797, control 23.73 ± 12.133 and P-value 0.346), the mean number of metaphase 2 oocytes (M2) was 14.67 ± 8.716 (G-CSF 13.61 ± 9.344, control 15.75 ± 7.928 and P-value 0.085), the mean number of injected oocytes (including metaphase 1 oocytes) was 15.18 ± 8.477 (G-CSF 14.43 ± 9.076, control 15.94 ± 7.793 and P-value 0.215) and the mean number of fertilized oocytes was 12.21 ± 7.302 (G-CSF 11.95 ± 7.715, control 12.47 ± 6.886 and P-value 0.616).

**Table 2.** *Induction of ovulation criteria.*

| | Control | Case | P-value |
|---|---|---|---|
| Gonadotropins duration | 10.55 ± 1.011 | 10.47 ± 1.043 | 0.626 |
| Gonadotropins dose | 250.05 ± 80.769 | 255.30 ± 85.660 | 0.659 |
| Number of retrieved oocytes | 23.73 ± 12.133 | 22.18 ± 10.797 | 0.346 |
| Number of Metaphase 2 oocytes | 15.75 ± 7.928 | 13.61 ± 9.344 | 0.085 |
| Number of injected oocytes | 15.94 ± 7.793 | 14.43 ± 9.076 | 0.215 |
| Number of fertilized oocytes | 12.47 ± 6.886 | 11.95 ± 7.715 | 0.616 |
| No of ET | 3.59 ± 1.058 | 3.62 ± 1.057 | 0.850 |
| No of sacs | 0.67 ± 0.473 | 0.55 ± 0.500 | 0.075 |
| Implantation rate | 19.66 ± 16.232 | 16.68 ± 19.142 | 0.243 |

All data are expressed by mean ± standard deviation; P-value significant < 0.05.

As shown on **Table 3**, sixty-five women (67%) had a chemical pregnancy (positive βhCG titer) after embryo transfer in G-CSF group while 54 women (54.5%) was positive in control group. Only sixty-one women established clinical pregnancy in G-CSF group 62.9% (61 out of 99) and in control group 51.5% (51 out of 97 patients). The difference of chemical pregnancy as well as clinical pregnancy was not significant with a P-value 0.074 and 0.108 respectively. The live birth babies in G-CSF group to control group was 39.8% to 31% in order with a P-value 0.227.

From 588 embryos were transferred, the implantation rate was 16.68% in G-CSF group and 19.66 % in control group. Referring to **Table 2**, the implantation rate was not statistically different for G-CSF regarding control group (p = 0.243). There were

**Table 3.** *Pregnancy outcome parameters.*

| | Control | Case | P-value |
|---|---|---|---|
| Chemical pregnancy | 67% | 54.5 % | 0.074 |
| Clinical pregnancy | 62.9% | 51.5% | 0.108 |
| Live birth rate | 39.8% | 31.0% | 0.227 |
| Miscarriage rate | 16.5% | 9.1% | 0.120 |

Data expressed by percent of positive cases in each group; P-value significant < 0.05.

sixteen cases (16.5%) miscarriages in G-CSF group and nine cases (9.1%) in control group (p = 0.120).

## DISCUSSION

The results of our study showed that intrauterine G-CSF injection did not lead to a significant improvement in pregnancy outcome parameters. However, a systematic review published in 2018 concluded that G-CSF may have a positive effect on improving endometrial receptivity and pregnancy rates in women with thin endometrium. Nonetheless, the review recommended conducting more controlled randomized studies, as previous studies on this topic have produced conflicting results [15]. Another study investigated the impact of subcutaneous injection of G-CSF on women with repeated IVF failure and concluded that it resulted in better implantation rates and pregnancy rates [16]. Additionally, Zeyneloglu and colleagues found that a dual method of administration of G-CSF (both subcutaneous and systemic) was significantly more effective than the subcutaneous only method [17]. It is believed that subcutaneous injection of G-CSF just before embryo transfer could elicit a systemic immunological response that enhances the local effect of the drug.

In a study conducted by Eftekhar and colleagues, they investigated cases of recurrent implantation failure despite normal endometrial thickness and found that intra-uterine infusion of G-CSF did not increase endometrial thickness or significantly improve pregnancy rates [18]. Barad and colleagues showed the same results as well [19]. While Eftekhar and other researchers were unable to demonstrate that G-CSF improves endometrial thickness, they did find that it may result in better chemical and clinical pregnancy rates in women with thin endometrium after a frozen-thawed embryo transfer cycle [20]. The observed differences in results may be attributed to differences in the timing and route of administration, endometrial thickness, and sample size. Administering G-CSF at the time of ovum pick-up may provide a stable environment for the attached embryos at the early stage of implantation.

A recent meta-analysis by Kamath *et al*. suggested that G-CSF may induce an unknown immunological process that allows embryo implantation without showing endometrial regeneration [21]. However, a Turkish research group found no statistically significant difference in endometrial thickness, implantation, and pregnancy rates with the use of G-CSF. They excluded women with thin endometrium by freezing embryos in cases where the endometrium was less than 7 mm in thickness [6]. Similarly, our study found that intrauterine injection of G-CSF did not play a role in the implantation process in women with normal endometrium.

Studies have shown that different routes of G-CSF administration can yield varying results. Those using the systemic subcutaneous route have reported an increase in pregnancy rates [6, 22, 23]. However, studies using endometrial infusion, including our study, as well as those conducted by Kalem *et al*. and Eftekhar *et al*., found no significant difference in implantation and pregnancy rates between the study and control groups [6, 20]. Singal and colleagues claimed in 2020 that both intrauterine and subcutaneous routes can improve endometrial thickness, with intrauterine infusion being more beneficial for assisted reproductive techniques [24]. In 2021, Jindal *et al*. compared subcutaneous and intrauterine infusion of G-CSF starting on day 14 of the cycle. Although they found a difference in clinical pregnancy rates between the two groups in favour of the intrauterine group, it was not statistically significant [25]. In 2022, the same research group focused on intrauterine infusion of G-CSF on the day of trigger in women with thin endometrium. Although they found a significant increase in endometrial thickness and implantation and clinical pregnancy rates, they recommend more multicentre trials to assess its potential for improving implantation rates [26].

In studies comparing subcutaneous and local uterine application of G-CSF, ovulation parameters tend to be better in the subcutaneous route [21]. This may explain why our study did not show a change in pregnancy rates, as we administered G-CSF locally and did not benefit from the claimed systemic effects of G-CSF.

Our randomized case control study showed no statistical significance in clinical pregnancy as well as live birth rates. Most of the studies did not comment on live birth rates and this is why we consider our study to be more accurate as we are concerned with the "To Go Home Baby" which is considered the main aim of all infertility related studies. Long-term follow-up of children born after ICSI is an important issue that should be addressed in future research, as the available data on this topic is still limited [27]. We also selected cases of unexplained

infertility with previous ICSI failure to examine the immunomodulatory part of G-CSF. We considered the patient selection and standardization of the ICSI protocols is the main limitation for the study. Also, the economic inflation was a big limitation due to lack of cases as most of infertility procedures is not covered by insurance in our country.

## CONCLUSIONS

In conclusion, we have doubts about the effectiveness of G-CSF in cases of unexplained infertility. However, future studies are needed to investigate the effects of different doses and routes of administration of G-CSF that may have a beneficial effect. Uterine perfusion of G-CSF could be a promising new tool for addressing the intractable problem of unexplained ICSI failure in women.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contribution*

M.M.: Conceptualization, methodology, supervision. E.S.: Data curation, formal analysis, validation, writing – original draft, writing – review & editing. A.O.: Data curation, formal analysis, investigation, methodology, validation.

### *Funding*

None.

### *Study registration*

None.

### *Disclosure of interests*

The authors declare that they have no conflict of interests.

### *Ethical approval*

Ethical approval has been obtained from the Research Ethics Committee of Faculty of Medicine, Cairo University. The research involved human participants. The research data that support the findings of this study are available upon request. We declare that this manuscript adheres to the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network guidelines.

### *Informed consent*

Written informed consent was obtained from each patient before being enrolled in the present study.

### *Data sharing*

Data are available under reasonable request to the corresponding author.

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