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# Single Dose of Granulocyte-Colony Stimulating Factor Use to Improve Outcomes in Patient Undergoing Intracytoplasmic Sperm Injection.

**Aseel ALFil [1], Lubna A. AL-Anbari [1]**

[1] **High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq.**

aseelalfil@gmail.com

ABSTRACT

Receptive endometrium is essential for successful embryo implantation and is created by the synergistic activities of estrogen and progesterone, as well as support from other endocrine, paracrine, and autocrine pathways. Granulocyte Colony Stimulating Factor (G-CSF) may play a crucial role in modulating the immune response to enhance implantation. To estimate the role of granulocyte-colony stimulating factor on the clinical intracytoplasmic sperm injection (ICSI) outcome parameters. A prospective comparative study with random sample selection was carried out from 2021 to 2023 at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University. It included 80 women with infertility, with or without previous failure trials of intracytoplasmic sperm injection, who completed IVF and ICSI protocols and reached the day of embryo transfer. On the day of embryo transfer, patients were divided into two groups: 49 patients received no additional treatment (group 1), and 31 patients received granulocyte-colony stimulating factor subcutaneous injection within one hour of embryo transfer (group 2). The implantation rate was 13.3% in group 2 compared to 7.6% in group 1. The chemical and clinical pregnancy rates were 29.0% and 25.8% in group 2, while group 1 had 18.4% for both chemical and clinical pregnancy rates. The pregnancy and implantation rates were slightly higher in group 2, but the difference was not significant. More research is needed to support the use of G-CSF as a standard treatment in ICSI patients.

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**KEYWORD**

G-CSF, ICSI, Infertility, Endometrium Receptivity, Implantation

## 1. Introduction

Infertility is defined as the inability to conceive, maintain, or carry a pregnancy to live birth (Hameed *et al.*, 2018 [1]). Couples who are having problems with these issues can use reproductive medicine technologies to help them fix the problem (Ali, Jawad, and Al-Hilli, 2020 [2]). Assisted reproductive technology (ART), which includes in vitro embryo development, is one of the most groundbreaking treatments in this field (Remião *et al.*, 2018 [3]). Ovarian stimulation is commonly used in ART treatments to acquire a higher number of oocytes and raise the chances of embryo production (Yousif, Jwad, and Al-Hilli, 2020 [4]), allowing for the selection of the highest quality embryos for transfer (Cunha and Póvoa, 2021 [5]). Despite the fact that this method can produce a higher number of oocytes, some failure has been reported (Noël *et al.*, 2020 [6]). Receptive endometrium is essential for successful embryo implantation, and it is defined by a short window of time when the endometrium is conducive to embryo adhesion and subsequent attachment and invasion processes (Faisal *et al.*, 2019 [7]). Endometrial receptivity is created by the synergistic activities of the primary reproductive hormones estrogen and progesterone, as well as support from other endocrine, paracrine, and autocrine variables (Altmäe and Aghajanova, 2019 [8]). One of the most common causes of embryo implantation failure is impaired endometrial receptivity. G-CSF is a type of colony-stimulating factor that is produced by a variety of cell types (e.g., endothelial cells, fibroblasts, macrophages, lymphocytes) and has been shown to originate from reproductive tissue cells such as the human ovary and endometrium (Alvarez *et al.*, 2017 [9]). G-CSF and its receptors have been discovered in luteinized granulosa cells, placental trophoblastic cells, and

oocytes. G-CSF is thought to play a number of physiological roles during the pregnancy formation process, including promoting embryo cleavage and blastocyst formation, increasing regulatory T cells and dendritic cells, and appearing to influence endometrial expression of genes important for implantation, such as endometrial vascular remodeling, local immune modulation, cellular adhesion pathways, and targeting follicle development and ovulation (Cavalcante *et al.*, 2001 [10]).

Recent studies have proposed the use of G-CSF as immune therapy in cases of repeated pregnancy losses of unknown cause as well as in cases of implantation failure in women with RIF (Kamath, Kirubakaran, and Sunkara, 2018 [11]). Würfel and his colleagues explored the therapeutic effect of G-CSF in patients with RIF as early as 2015, and the results demonstrated that systematic injection of G-CSF can considerably improve the implantation rate (Würfel, 2015 [12]). Since then, a slew of similar studies has been carried out for RIF, but the results have been mixed. Only around half of the thoroughly randomized control trials conclude that G-CSF can enhance endometrial thickness, implantation rate, or clinical pregnancy rate after IVF treatment, while the other half remains negative. This discrepancy could be due to differences in administration methods (systemic or local), time and duration of application, or clinical situations between trials (Kalem *et al.*, 2020 [13]).

## *2. Patients and Methods*

The High Institute for Infertility Diagnosis and Assisted Reproductive Technologies prospectively approved the present comparative study. All participants received detailed instructions on the administration of G-CSF, and patients who received systemic G-CSF treatment provided signed consent. Eighty women, ages 18 to 42, complained of infertility and

underwent IVF/ICSI procedures. Women with a history of autoimmune disease, endocrine disorder, hydrosalpinx, moderate to severe endometriosis, intrauterine pathology (polyp, fibroid), and autoimmune disease were excluded from this study. A complete medical, surgical, and obstetrical history is taken, and height and weight are evaluated to determine the body mass index (BMI). To exclude any anomalies, clinical and gynecological checks were conducted. FSH, LH, E2, prolactin, and TSH hormone analysis for female partners on day 2 of the menstrual cycle for each patient in both groups; the antagonist protocol was used; transvaginal US-guided oocyte retrieval is carried out approximately 35–36 hours after hCG triggers ovulation. Depending on the quantity and quality of the embryos, embryo transfer was carried out two to three days following the oocyte retrieval. On the day of embryo transfer, the patients were divided into Two groups :

Group 1: Included 49 patients who did not receive G-CSF.

Group 2: Included 31 patients who had 300 µg of recombinant human G-CSF subcutaneous injection (Reliance®, Filgrastrim TM, Life Sciences Ltd., India) within an hour of embryo transfer .Luteal phase support and follow-up were performed using a progesterone suppository. Chemical pregnancy was assessed using a positive serum hCG test two weeks after embryo transfer (Michikawa et al., 2022 [14]). Clinical pregnancy was evaluated as the ultrasound appearance of gestational sacs five weeks after ET (Eftekhar et al., 2020 [15]). The total number of transferred embryos was divided by the number of gestational sacs seen by transvaginal ultrasonography at the fifth week of pregnancy; these are used to calculate the implantation rate (Li et al., 2022 [16]) .

**Statistical analysis:** The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26. The data is presented as means and standard deviations. Categorical data is presented as frequencies and percentages. A chi-square and independent t-test was used to compare the two groups. P values less than 0.05 were considered significant.

## *3. Results*

The demographic features, which include females' age, infertility causes (male cause, female cause, unexplained, and combined), and infertility kinds, whether primary or secondary, are shown in (Table 1). There were no significant differences between the two groups. Embryo characteristic is shown in (Table 2). There were no significant differences between the two groups in embryo characteristics. The ICSI outcome (implantation, chemical, and clinical pregnancy rates) in group 2 patients were 13.3%, 29.0%, and 25.8%, respectively, compared to 7.6%, 18.4%, and 18.4%, respectively, in group 1. The p values > 0.05, as seen in (Table 3), indicate that the differences were not statistically significant.

***Table 1:*** Demographic Features

| Parameters Mean ± SD | Control (N=49) | G-CSF (N=41) | P- value |
|---|---|---|---|
| **Age (years)** | *31.84 ± 5.96* | *31.49 ± 5.55* | *0.77 ∀ NS* |
| **Causes of infertility n. (%)** | | | |
| **Male factors** | *14 (28.6 %)* | *7 (22.6 %)* | *0.263 € NS* |
| **Female causes** | *20 (40.8 %)* | *10 (32.3 %)* | |
| **Combined causes** | *10 (20.4 %)* | *7 (22.6 %)* | |
| **Unexplained infertility** | *5 (10.2 %)* | *7 (22.6 %)* | |
| **Infertility Types n. (%)** | | | |
| **Primary** | *39 (79.6%)* | *35 (85.3%)* | *0.267 € NS* |
| **Secondary** | *10 (20.4%)* | *6 (14.7%)* | |

***Table 2:*** Embryo Characteristic

| Parameters Mean ± SD | Group 1 (N=49) | Group 2 (N=31) | p-value ∀ |
|---|---|---|---|
| **Total Embryos** | 6.92 ± 4.05 | 5.48 ± 3.65 | 0.54 NS |
| **Grade I Embryos** | 3.08 ± 2.22 | 2.15 ± 1.58 | 0.13 NS |
| **Grade II embryos** | 1.71 ± 1.61 | 1.79 ± 1.16 | 0.89 NS |
| **Grade III Embryos** | 2.15 ± 1.54 | 1.52 ± 1.39 | 0.16 NS |
| **Transferred Embryos** | 2.88 ± 1.2 | 2.52 ± 1.0 | 0.23 NS |

***Table 3:*** ICSI Result

| ICSI Outcome % (N) | Group 1 (N= 49) | Group 2 (N= 31) | p-value € |
|---|---|---|---|
| **Implantation Rate (%)** | 7.6 % (11/145) | 13.3% (10/75) | 0.169 NS |
| **Chemical Pregnancy Rate** | 18.4% (9/49) | 29.0 % (9/31) | 0.266 NS |
| **Clinical Pregnancy Rate** | 18.4% (9/49) | 25.8% (8/31) | 0.485 NS |

## *4. Discussion*

The reproductive system produces the hematopoietic cytokine G-CSF after embryo implantation close to the maternofetal interface, where it stimulates granulocyte proliferation and differentiation. Therefore, it has been suggested that this cytosine may have an impact on both the decidua and placental function (Martin *et al.*, 2021 [17]). Through a variety of mechanisms, such as the key genes that regulate embryo attachment, cell migration, tissue remodeling, and angiogenesis, G-CSF can affect the implantation and pregnancy processes (Banerjee, Singla, and Verma, 2022 [18]). GCSF promotes trophoblast invasion and proliferation during pregnancy. For proper implantation and the continuation of pregnancy, these events are essential (Kashani *et al.*, 2021 [19]). According to numerous studies, subcutaneous treatment of G-CSF improves the frequency of clinical pregnancy and implantation in people with unexplained infertility (Jiang *et al.*, 2020 [20])**.**

Further research has shown that administering G-CSF to people

undergoing in vitro fertilization can boost pregnancy rates (both chemically and clinically) as well as live birth rates (Wu, Xu, and Hu, 2022 [21]). This contradicts our findings, which show that group 2 has a higher implantation and pregnancy rate (both chemically and clinically); however, the difference may not be statistically significant due to the small sample size, unequal group sizes, or the fact that a single dose of G-CSF contains insufficient G-CSF to improve implantation or sustain pregnancy. Al-Jubouri, Al-Obaidi, and Hussaini in 2021 [22] and Zhang *et al.* in 2022 [23] discovered that intrauterine injection of G-CSF might increase endometrial thickness and embryo implantation.

According to several researchers, pregnancy loss can be caused by immune rejection and endometrial or embryonic issues (Rawlings *et al.*, 2021 [24]). The most effective approach to address the immunological problem is still unresolved. In order to improve endometrial receptivity, several studies have focused on using G-CSF to treat the self-immune problem (Ojosnegros *et al.*, 2021 [25]). GCSF plays a crucial role in pregnancy in modifying the immune response that results in immunological tolerance (Maksym *et al.*, 2021 [26]). During pregnancy, the mother's immune system is challenged. By altering T cells' cytokine profiles, GCSF encourages Th2 actions, the growth of tolerant dendritic cells, and the production of IL-10-producing T regulatory cells (Kolanska *et al.*, 2021 [27]). Both before and after implantation in the uterus, these crucial immune regulatory phases occur (Günther *et al.*, 2021 [28]). According to Gao *et al.*, in 2022, G-CSF reduced the rate of abortion, making it a potential treatment for individuals who have had repeated abortions. Contrarily, Torky and his colleagues in 2022 [29] come to the conclusion that G-CSF has no impact on abortion rates but can boost implantation and

pregnancy rates. Additionally, Maneta and his associates in 2022 [30] discovered that G-CSF is essential for maintaining pregnancy. Within days of fertilization, the peripheral blood's granulocyte count starts to rise sharply, aiding in embryo implantation. Early in pregnancy, there is an increase in peripheral blood granulocyte activity that is crucial to the maintenance of the pregnancy. This was similar to our result: the implantation and pregnancy rates increased in the second group of women who took a single dose of G-CSF, but the difference was not significant.

## 6- Conclusion

Infertility patients getting ICSI experience marginally improved implantation rates and pregnancy rates (chemical and clinical) following a systemic dose of 300 µg GCSF in the days of embryo transfer in a fresh cycle. To support the regular use of G-CSF, more research is required.


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***Author Contribution***

The research was carried out by Aseel ALfil under the supervision of Lubna Al-Anbari.

***Conflict of Interest***

There is no conflict of interest.

***Ethical Clearance***

The Ethical Approval Committee approved the study.

***Financial Disclosure***

There is no financial disclosure.

***Ethical Clearance***

The study was approved by the Ethical Approval Committee

***References***


**[1]** Hameed, A.M., Abood, M.S., Ghazi, H.F. and Al-Anbari, L., 'Evaluation of Soluble L-Selectin (CD 62L) Level in Embryo Culture Media to Embryo Quality and Implantation Rate', Iraqi Journal of Embryos and Infertility Researches, 2018 Jan. 8 (2). DOI:10.28969/IJEIR.v8.i2.r2

**[2]** Remião, M.H., Segatto, N.V., Pohlmann, A., Guterres, S.S., Seixas, F.K. and Collares,

T. The potential of nanotechnology in medically assisted reproduction, Frontiers in Pharmacology, 2018, Jan 8, p. 1–9.
DOI: 10.3389/fphar.2017.00994.

**[3]** Yousif, A. A. A., Jwad, M. A. and Al-Hilli, N. 'Glycotoxins Relationship with Body Mass Index (BMI),' Iraqi Journal of Embryos and Infertility Researches, 2020, Dec. 10 (1), pp. 51–66.
DOI: https://doi.org/10.28969/IJEIR.v10.i1.r4

**[4]** Ali, A. A., Jawad, M. A. and Al-Hilli, N. 'Evaluation of Serum and Follicular Fluid Levels of Advanced Glycation End products (AGEs) on ICSI Outcome,' Prensa Med Argent, 2020, May.109 (4) pp. S1-003.

**[5]** Cunha, A. and Póvoa, A. M. 'Infertility management in women with polycystic ovary syndrome: a review,' Porto Biomedical Journal, 2021, Jan 6 (1), p. e116.
DOI: 10.1097/j.pbj.0000000000000116.

**[6]** Noël, L., Fransolet, M., Jacobs, N., Foidart, J.M., Nisolle, M. and Munaut, C.'A paracrine interaction between granulosa cells and leukocytes in the preovulatory follicle causes the increase in follicular G-CSF levels', Journal of Assisted Reproduction and Genetics, 2020, Feb 37 (2), pp. 405–416.
DOI: 10.1007/s10815-020-01692-y.

**[7]** Faisal, Al-Kawaz, U., Al-Anbari, L. and Hussaini, H., 'Evaluation of the Level of Stem Cell Factor in Follicular Fluid and its Effect on Oocyte Maturity, Embryo Quality, and Pregnancy Rate,' Iraqi Journal of Embryos and Infertility Researches, 2020, May. 9 (2), p. 65–77.
DOI: https://doi.org/10.28969/IJEIR.v9.i2.r5

**[8]** Altmäe, S. and Aghajanova, L. 'Growth hormone and endometrial receptivity,' Frontiers in Endocrinology, 2019, Sep. 10
DOI: 10.3389/fendo.2019.00653.

**[9]** Alvarez, K.L.F., Beldi, M., Sarmanho, F., Rossetti, R.A.M., Silveira, C.R.F., Mota, G.R., Andreoli, M.A., Caruso, E.D.D.C., Kamillos, M.F., Souza, A.M. and Mastrocalla, H., 'Local and systemic immunomodulatory mechanisms triggered by Human Papillomavirus transformed cells: A potential role for G-CSF and neutrophils', Scientific Reports, 2017, Jul, 7 (1), p. 1–16.
DOI: 10.1038/s41598-017-09079-3.

**[10]** Cavalcante, M.B., Costa, F.D.S., Barini, R. and Júnior, E.A. 'Granulocyte colony-stimulating factor and reproductive medicine: A review,' *Iranian Journal of Reproductive Medicine*, 2015, Apr. 13 (4), p. 195–202.

**[11]** Kamath, M. S., Kirubakaran, R. and Sunkara, S. K. 'Granulocyte-colony stimulating factor administration for

subfertile women undergoing assisted reproduction,' Cochrane Database of Systematic Reviews, 2018 Dec. (12).

DOI: 10.1002/14651858.CD013226.

**[12]** Würfel, W., 'Treatment with granulocyte colony-stimulating factor in patients with repetitive implantation failures and/or recurrent spontaneous abortions,' *Journal of Reproductive Immunology*, 2015, Apr. 108, p. 123–135.

DOI: 10.1016/j.jri.2015.01.010

**[13]** Kalem, Z., Namli Kalem, M., Bakirarar, B., Kent, E., Makrigiannakis, A. and Gurgan, T., 'Intrauterine G-CSF Administration in Recurrent Implantation Failure (RIF): An Rct,' Scientific Reports, 2020, Mar.10 (1), p. 1–7.

DOI: 10.1038/s41598-020-61955-7.

**[14]** Michikawa, T., Morokuma, S., Yamazaki, S., Takami, A., Sugata, S., Yoshino, A., Takeda, Y., Nakahara, K., Saito, S., Hoshi, J. and Kato, K. Exposure to chemical components of fine particulate matter and ozone, and placenta-mediated pregnancy complications in Tokyo : a register-based study',2022, Jan. 32 (1) p. 135–145.

DOI: 10.1038/s41370-021-00299-4.

**[15]** Eftekhar, M., Mohammadi, B., Mangoli, E. and Mortazavi, M., 'Is there any correlation between estradiol supplementation, as luteal phase support, and clinical pregnancy in art cycles? A cross-sectional study, International Journal of Reproductive BioMedicine, 2020, Nov. 18 (11), p. 969–974.

DOI: 10.18502/ijrm.v13i11.7964.

**[16]** Li, X., Zeng, Y., He, J., Luo, B., Lu, X., Zhu, L., Yang, Z., Cai, F., Chen, S.A. and Luo, Y., 'The optimal FET strategy for the recurrent implantation failure patient: thawing Day 3 embryos and culturing to Day 5 blastocysts. Fertility and Sterility.2022, Jun.

**[17]** Martin, K.R., Wong, H.L., Witko-Sarsat, V. and Wicks, I.P. 'A double edge sword in neutrophil-mediated immunity. Semin Immunol. 2021 Apr; 54:101516.

DOI: 10.1016/j.smim.2021.101516.

**[18]** Banerjee, K., Singla, B. and Verma, P. 'Efficacy of subcutaneous granulocyte colony-stimulating factor infusion for treating thin endometrium,' Clinical and Experimental Reproductive Medicine, 2022, Mar. 49 (1),p. 70–73.

DOI: 10.5653/cerm.2021.04833

**[19]** Kashani, L., Moini, A., Esfidani, T., Yamini, N. and Mohiti, S., 'Effect of intrauterine granulocyte-colony stimulating factor administration on in vitro fertilization outcome in women with moderate-to-severe endometriosis: An rct,' International Journal

of Reproductive BioMedicine,2021, Aug. 19 (8),p.733–740.
DOI: 10.18502/ijrm.v19i8.9621.

**[20]** Jiang, L., Qian, Y., Chen, X., Ji, X., Ou, S., Li, R., Yang, D. and Li, Y. 'Effect of early rescue ICSI and split IVF-ICSI in preventing low fertilization rate during the first ART cycle: A real-world retrospective cohort study', Reproductive medicine and biology, 2022, Dec. 21 (1), p. e12420.
DOI: 10.1002/rmb2.12420

**[21]** Wu, W., Xu, G.-F. and Hu, Y.-J. 'The therapeutic effect of granulocyte colony-stimulating factor (G-CSF) on potential biochemical pregnancy in patients with unexplained repeated transplantation failure (RIF): a case series and literature review,' Gynecological Endocrinology, 2022, May 38 (5), p. 443–447.
DOI: 10.1080/09513590.2022.2036716

**[22]** Al-Jubouri, W. M., Al-Obaidi, M. T. and Hussaini, H. A. 'Endometrial perfusion with granulocyte colony-stimulating factor in infertile women,' Pharmacology online, 2021, Aug.,2, p. 417–425.

**[23]** Zhang, A.W., Morjaria, S., Kaltsas, A., Hohl, T.M., Parameswaran, R., Patel, D., Zhou, W., Predmore, J., Perez-Johnston, R., Jee, J. and Daniyan, A.F. 'The Effect of Neutropenia and Filgrastim (G-CSF) on Cancer Patients With Coronavirus Disease 2019 (COVID-19) Infection', Clinical Infectious Diseases, 2022, Mar, 74 (4),p. 567–574.
DOI: 10.1093/cid/ciab534

**[24]** Rawlings, T.M., Makwana, K., Taylor, D.M., Molè, M.A., Fishwick, K.J., Tryfonos, M., Odendaal, J., Hawkes, A., Zernicka-Goetz, M., Hartshorne, G.M. and Brosens, J.J, 'Modelling the impact of decidual senescence on embryo implantation in human endometrial assembloids,' *Elife*, 2021 Sep 6;10:e69603.
DOI: 10.7554/eLife.69603.

**[25]** Ojosnegros, S., Seriola, A., Godeau, A.L. and Veiga, A., 'Embryo implantation in the laboratory: an update on current techniques,' Human Reproduction Update,2021, Apr. 27 (3), p. 501–530.
DOI: 10.1093/humupd/dmaa054

**[26]** Maksym, R.B., Hoffmann-Młodzianowska, M., Skibińska, M., Rabijewski, M., Mackiewicz, A. and Kieda, C. 'Immunology and immunotherapy of endometriosis,' *Journal of Clinical Medicine*, 2021, Dec. 10 (24),p. 1–12.
DOI: 10.3390/jcm10245879.

**[27]** Kolanska, K., Alijotas-Reig, J., Cohen, J., Cheloufi, M., Selleret, L., D'argent, E., Kayem, G., Valverde, E.E., Fain, O., Bornes, M. and Darai, E., 'Endometriosis with infertility: A comprehensive review on the

role of immune deregulation and immunomodulation therapy,' American Journal of Reproductive Immunology,2021, Mar. 85 (3), p. 0–3.
DOI: 10.1111/aji.13384.

**[28]** Günther, V., Otte, S.V., Freytag, D., Maass, N. and Alkatout, I., 'Recurrent implantation failure–an overview of current research,' Gynecological Endocrinology, 2021, Jul. 37 (7), p. 584–590.
DOI 10.1080/09513590.2021.1878136.

**[29]** Torky, H., El-Desouky, E.S., El-Baz, A., Aly, R., El-Taher, O., Shata, A., Hussein, A., Marie, H., Deif, O., Eldemery, A. and Abo-Louz, A. 'Effect of intrauterine granulocyte colony-stimulating factor vs. human chorionic gonadotropin at ovum pick up day on pregnancy rate in IVF/ICSI cases with recurrent implantation failure,' JBRA Assisted Reproduction, 2022, Apr. 26 (2), p.274.
DOI 10.5935/1518-0557.20210056.

**[30]** Maneta, E., Fultang, L., Taylor, J., Pugh, M., Jenkinson, W., Anderson, G., Coomarasamy, A., Kilby, M.D., Lissauer, D.M., Mussai, F. and De Santo, C 'G-CSF induces CD15+ CD14+ cells from granulocytes early in the physiological environment of pregnancy and the cancer immunosuppressive microenvironment', Clinical & Translational Immunology,2022, 11 (5), p.e1395.