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Original article

Evaluating the efficacy of granulocyte-macrophage colony-stimulating factor in improving implantation rates in frozen embryo transfer cycles: a blind randomized-controlled study

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Abstract

Background: Implantation failure in assisted reproductive technologies (ART) remains a challenge. Granulocyte-macrophage colony-stimulating factor (GM-CSF) may enhance embryo implantation, but its efficacy needs more investigation. This study aimed to assess if adding GM-CSF to thawed embryo culture could improve implantation rates in frozen embryo transfer cycles.

Methods: One hundred rats were randomly assigned to GM-CSF or control groups at Avicenna Infertility Clinic, Tehran. Control group had standard embryo culture; GM-CSF group had embryos cultured in Embryogen® with GM-CSF. Pregnancy outcomes were assessed via serum β-HCG levels post frozen embryo transfer (FET) and ultrasonography at gestational week seven.

Results: No significant difference in blastocyst formation rates was found between groups. Positive beta-HCG levels were 36% in control and 40% in GM-CSF groups. Gestational sacs were detected in 36% of control and 34% of GM-CSF group during weeks 5-6. Clinical pregnancy rates were 32% in control and 30% in GM-CSF groups.

Conclusion: GM-CSF in embryo culture of thawed embryos shows no significant impact on blastocyst formation or pregnancy outcomes. However, interventions like these may enhance fertility treatments, warranting larger-scale clinical trials for further exploration.

Keywords: Assisted Reproductive Technologies (ART), Frozen embryo transfer (FET), Granulocyte-macrophage colony-stimulating factor (GM-CSF), Implantation rates, Clinical pregnancy

Introduction

In the female reproductive tract, embryos encounter a milieu rich in growth factors and cytokines, including (granulocyte macrophage-colony stimulating factor) (1). Studies on animal models have underscored the significance of autocrine and paracrine factors secreted by reproductive tracts and pre-implantation embryos for embryonic development and implantation (2, 3). These growth factors and cytokines play pivotal roles in normal blastocyst development and embryo implantation. Notably, human embryos express mRNA and protein of the GM-CSF receptor alpha subunit from the first cleavage through the blastocyst stages, with blastocysts cultured in GM-CSF demonstrating fewer apoptotic nuclei and increased viability of inner cell mass cells, mediated through a receptor independent of the beta receptor (4). GM-CSF has been proposed to mitigate the detrimental effects of embryo culture on embryo development and fetal viability (5). It is suggested that the detrimental

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influence of embryo culture on embryo development and fetal viability may be largely alleviated by GM-CSF (6). Blastocyst transfer has been associated with improved uterine and embryonic synchronicity and higher implantation rates, necessitating optimal in vitro culture conditions (7). In vitro experiments have revealed increased blastulation incidence in human embryos without compromising chromosomal constitution with the addition of 2 ng/ml GM-CSF in the culture medium, leading to significant enhancements in implantation and survival rates to week 12 gestation and live birth rates (8,12) However, studies on mouse embryos have yielded conflicting results regarding blastocyst formation and total cell count in blastocysts after the addition of GM-CSF in embryo media culture. Notably, GM-CSF supplementation during embryo culture has been linked to improved ongoing pregnancy rates in women undergoing intracytoplasmic sperm injection (ICSI) (8-10). This study aims to assess the effect of GM-CSF addition in thawed embryo media culture on developmental competence, blastulation rate, implantation, and clinical pregnancy rates. It has been described that embryo culture in the presence of GM-CSF can improve ongoing pregnancy rate in women undergoing ICSI (11). Specifically, we evaluated the clinical efficacy and pregnancy outcomes of frozen embryo transfer cycles wherein thawed embryos were cultured in BlastGen, a commercially available medium containing 2 ng/mL GM-CSF, compared with sequential Blast medium as a control group. Thus, the aim of this study was to evaluate the effect of granulocyte-macrophage GM-CSF in embryo culture medium of thawed embryos on implantation rate. The aim of this study was evaluation of the effect of granulocyte-macrophage GM-CSF in embryo culture medium of thawed embryos on implantation rate.

Materials & Methods

This research constitutes a randomized, controlled, blinded, prospective design investigation conducted at the Avicenna Fertility Clinic within the Avicenna Research Institute. The clinical trial was registered under the identifier IRCT 2014021611430 N4 on March 17, 2014, and the registration details can be accessed via the website https://en.irct.ir/trial/11703.

This blinded randomized-controlled study aimed to assess the hypothesis that the addition of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) to the culture medium of thawed embryos enhances implantation rates. The study intended to enroll 100 participants, divided equally into a GM-CSF group and a control group. Conducted at the Avicenna Infertility Clinic (AIC) in Tehran, Iran, the study recruited women with a minimum of 5 high-quality frozen embryos undergoing frozen embryo transfer cycles. Approval for the study was obtained from the Ethical Committee of the Avicenna Research Institute (Ethic code = 93/1273), and informed consent was obtained from all participants. Inclusion criteria encompassed women under the age of 42 with normal levels of thyroid stimulating hormone (TSH) and Prolactin. Participants were required to possess at least 5 good quality frozen embryos according to the Gardner classification, all originating from the couples' own gametes. Exclusion criteria involved women with hydrosalpinx or anatomical uterine disorders, as well as those with a history of two or more failed embryo transfers.

In this investigation, a computer-generated randomization list was utilized to allocate participants randomly into experimental groups. Allocation was performed via a process of drawing slips of paper from a container, each slip representing one group, ensuring equal representation of each group. The study consisted of two distinct experimental groups: a control group, where post-thaw embryos were cultured in G2 embryo culture medium until reaching day 5 of embryo development, and a GM-CSF group, where embryos were cultured in Embryogen® (EG), a commercially available medium containing GM-CSF.

The primary outcome measure for pregnancy in this study involved assessing serum β-HCG levels 14 day post Frozen embryo transfer (FET). Implantation rates were calculated as the proportion of embryonic sacs detected via ultrasonography at gestational week 7 relative to the total number of embryos transferred per patient. Clinical pregnancy was defined as the presence of a fetus displaying cardiac activity as confirmed by vaginal ultrasonography at 7 weeks of gestation. Multiple pregnancies were identified as the presence of more than one fetus visualized during vaginal ultrasonography.

Statistical analysis was conducted using SPSS 11.5 software. The findings are presented as mean values accompanied by standard deviations. To compare the

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study groups, various statistical tests were employed, including the Chi-squared test, Student's t-test, Fisher's exact test, and Mann-Whitney U test. A p-value of less than 0.05 was deemed statistically significant.

Results

This research involved the participation of 100 rates, with 50 assigned to the GM-CSF group and 50 to the control group. Both cohorts exhibited comparable baseline characteristics, including follicle-stimulating hormone (FSH) levels, body mass index (BMI), duration of infertility, number of previous abortions at 12 weeks or less, and presence of polycystic ovary syndrome (PCOs) criteria. Parameters such as the transfer of frozen embryos, quantity of embryos from frozen, and grading of embryos upon introduction to the culture medium were evaluated as outlined in Table 1, which delineates the characteristics of the study groups along with their ovulation stimulation and controlled preparation of endometrium cycle attributes.

Table 1. Characters of the of the GM-CSF* group and control group

	GM-CSF group N=50 Mean ± SD	Control group N=50 Mean ± SD	P-value
FSH**	6.1 ± 2.3	5.8 ± 2.3	0.505
BMI***	24.8 ± 3.2	24.5 ± 3.1	0.692
Thawed embryos	4.7 ± 1.11	4.4 ± 1.3	0.327
Blastocyst	1.3 ± 1.3	1.24±1.18	0.93
Grade A after thawing	3.4 ± 1.2	3.0 ± 1.3	0.100
Transferred embryos	3.1 ± 0.5	3.0 ± 0.4	0.49
Transferred blastocyst	1.2 ± 1.2	1.2 ± 1.1	1.00

* GM-CSF: Granulocyte-macrophage colony-stimulating factor
**FSH: Follicle stimulation Hormone
***BMI: Body mass index

Following the introduction of embryos into the culture medium, the mean number of embryos cultivated in the GM-CSF and control groups were 1.2 ± 4.3 and 1.4 ± 4.1, respectively, demonstrating no statistically significant variance between the groups. Similarly, the mean numbers of blastocyst embryos, early blastocyst embryos, compact embryos, and various grades of embryos did not significantly differ between the GM-CSF and control groups.

Subsequent to embryo transfer, parameters including the number of transferred embryos, transferred blastocyst embryos, early blastocyst embryos, compact embryos, and various grades of embryos exhibited no statistically significant differences between the GM-CSF and control groups.

Further analysis involved investigating pregnancy outcomes, including pregnancy rate, embryo implantation rate, clinical pregnancy rate, and abortion rate at 12 weeks of gestation or less. Results revealed comparable rates of positive pregnancy tests (β-HCG), gestational sac formation, and fetal heart development between the GM-CSF and control groups, indicating no significant differences in these pregnancy-related parameters between the two study cohorts.

Table 2. Outcome of the GM-CSF* group and control group

	GM-CSF group N=50 N (%)	Control group N=50 N (%)	P-value
Pregnancy	20 (40.0)	18 (36.0)	0.680
Implantation	17 (34.0)	18 (36.0)	0.834
Clinical pregnancy	15 (30.0)	16 (32.0)	0.829
Abortion ≤12 week	3 (6.0)	4 (8.0)	0.780**

* GM-CSF: Granulocyte-macrophage colony-stimulating factor
*Fisher´s Exact test

Discussion

The findings of this study demonstrate that the incorporation of GM-CSF into the embryo culture medium for thawed embryos resulted in deleterious effects on pregnancy outcomes when compared to the

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control group. Contrary to the anticipated positive outcomes based on prior research, the addition of GM-CSF yielded unfavorable results. It is noteworthy that various cells within the reproductive tract and gestational tissues contribute to the production of GM-CSF. The synthesis of GM-CSF is regulated by signaling molecules derived from both the conceptus, male seminal plasma, and ovarian steroid hormones (13-16) (17).

The examination reveals that granulocyte-macrophage GM-CSF functions as a trophic agent crucial for embryonic sustenance, exerting significant influence in both the process of embryo implantation and the subsequent stages of embryonic development. (4). The research findings indicate that granulocyte-macrophage GM-CSF, derived from either maternal or fetal sources, is indispensable for ensuring the optimal growth and survival of the fetus in murine models (18). Moreover, it is proposed that the adverse effects of embryo culture on both embryo development and fetal viability can potentially be mitigated to a significant extent through the supplementation of GM-CSF (6).

In murine models, exposure to granulocyte-macrophage GM-CSF during the post-thaw period has been observed to significantly enhance the re-expansion of blastocoeles (19). In certain investigations involving mouse embryos, the rates of blastocyst formation and the total cell count within blastocysts were found to be comparable across all treatment groups receiving recombinant murine GM-CSF (rm GM-CSF) supplementation in embryo culture media, in comparison to the control group (11). Conversely, in a separate study where GM-CSF was introduced into the culture media of frozen-thawed one-cell mouse embryos, no disparities were detected in blastulation rates, and GM-CSF did not exert any discernible influence on the overall cell count within developing blastocysts (20).

Several studies have highlighted varying impacts on embryo development across different species in response to varying concentrations of recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) (21, 22). In murine blastocysts, it was observed that GM-CSF did not alter the rates of mosaicism/aneuploidy; however, it augmented the proportion of aneuploid cells within mosaic embryos and exhibited a detrimental effect on blastocyst development at higher concentrations (5 and 10 ng/ml concentrations) (22).

Contrarily, heightened levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) found within hydrosalpingeal fluid have been linked to adverse impacts on embryo development (23). Thus, it appears that GM-CSF does not consistently exhibit beneficial effects on embryo development.

In the study conducted by Kazuhiro et al. (24), cryopreserved day 3 embryos were thawed and assessed based on their morphology. Following the exclusion of fragmented poor-quality embryos, the remaining good-quality embryos were categorized into optimal (6-cell-stage, grade 1 or 2) and suboptimal groups (6-cell-stage, grade 3; 3- to 5-cell-stage, grade 1 to 3). These embryos were then subjected to culture with or without various growth factors (GM-CSF, EGF, IGF-I, M-CSF, BDNF, artemin, and GDNF) for a duration of 72 hours. It was observed that a significantly higher proportion of blastocyst-stage embryos and the formation of high-quality blastocysts (graded 3AA to 5AA according to Gardner's criteria) occurred in embryos from the optimal group treated with growth factors. Conversely, no such effects were detected in suboptimal embryos treated with growth factors. Additionally, the study noted that the administration of growth factors to thawed cryopreserved day 5 embryos did not impact blastocyst adhesion. The concurrent use of multiple growth factors in the study resulted in overlapping effects, rendering it challenging to discern the specific influence of GM-CSF alone. Conversely, the absence of an effect of growth factors on suboptimal embryos suggests the necessity for further evaluations. It is posited that the optimal development of growth factor receptors in embryos may be more crucial than the mere presence of growth factors in the embryo culture media. In our own study, the number of thawed cultured embryos of A and B quality was similar between the two groups, and there was no significant difference in embryo development on day 5 based on embryo grade. The proportions of blastocyst-stage embryos were also comparable between the two groups (compact, early blastocyst, expanded blastocyst). Similar to the findings of Kazuhiro et al., the presence of growth factors in the embryo culture of thawed cryopreserved embryos did not affect blastocyst adhesion in our patients. Notably, in our patient cohort,

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a lower proportion of patients in the GM-CSF group (13.3%) exhibited positive beta-HCG levels compared to the control group (50%) (OR: 0.15, 95% CI: 0.03-0.87; P=0.024), suggesting a significant reduction in embryo implantation in the uterine cavity with GM-CSF treatment. This reduction in embryo implantation may be attributable to disturbances in adhesion factors or chromosomal abnormalities in embryos, necessitating further investigation.

Ziebe et al. (25) conducted a study involving fertilization, embryo culture, and transfer using Embryo Assist either without cytokine (control) or formulated with 2 ng/mL GM-CSF (test), provided by ORIGIO. Embryos were transferred on day 3, with either one or two embryos transferred. The study found no significant difference in the implantation rate between the two groups. Moreover, there was no discernible variance in the percentage of top-quality embryos (15.6% [GM-CSF] vs. 16.8% [control]) or in the percentage of normally developed day 3 embryos (42.0% [GM-CSF] vs. 43.9% [control]). When low HSA (human serum albumin) concentration (2 mg/mL) was present in the test or control medium, 23.0% (GM-CSF) and 18.7% (control) of embryos reached gestational week 12. However, with a high HSA concentration (5 mg/mL), the rates were 22.4% (GM-CSF) and 21.1% (control). The study revealed that the benefit of adding GM-CSF was only evident in the culture medium containing the lower concentration of 2 mg/mL HSA. As the HSA concentration increased to 5 mg/mL, ongoing implantation and live birth rates escalated in the control group but remained unchanged in the GM-CSF group. This observation may be attributed to a potential protective effect against culture-induced stress conditions in the GM-CSF group. Similar to our study, top-quality embryos and implantation rates were comparable between the two groups in this study.

Sjöblom et al (8) conducted an investigation into the development of frozen 2–4-cell human embryos, which were cultured in media supplemented with 2 ng/ml recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF). These embryos were thawed after reaching or exceeding their 1-year storage limit in liquid nitrogen. The authors assessed embryo development using both G1.2/G2.2 and IVF-50/S2 sequential media combinations. No statistically significant differences were observed in blastulation rates between the two distinct culture media systems. However, the progression of 2–4-cell embryos to the blastocyst and hatching blastocyst stages was markedly enhanced upon the addition of rhGM-CSF to the culture medium. It was noted that the favorable effect of rhGM-CSF on blastocyst development seemed to stem from the rescue of embryos lost at the 4–16-cell stage. In our study employing sequential media in both control and GM-CSF groups, blastulation rates were comparable between the two groups. Notably, the authors did not assess implantation in their study; therefore, the evaluation of the impact of GM-CSF on pregnancy outcomes is not feasible based on their findings.

The insufficiency of morphological assessment in discerning between viable and nonviable embryos is evident, as numerous embryos may exhibit ostensibly normal morphological characteristics while harboring significant cellular aberrations indicative of compromised viability. Within the context of assisted reproductive technology (ART) and embryo culture, the primary objective is to facilitate successful implantation and the development of a healthy, full-term infant. Consequently, interventions aimed at enhancing the likelihood of implantation and promoting optimal fetal development, such as the incorporation of granulocyte-macrophage GM-CSF into embryo culture protocols, are deemed acceptable. However, it is noted that extant investigations concerning the impact of GM-CSF supplementation in embryo culture remain insufficient, warranting further inquiry and scrutiny.

Limitation: Despite the intention to enroll 100 rates, the actual sample size was not specified, which may limit the statistical power of the study and increase the risk of type II errors. While the study employed objective outcome measures, the personnel conducting outcome assessments were not explicitly described as blinded, raising the possibility of bias in outcome assessment. The study primarily focused on short-term outcomes up to 7 weeks of gestation, providing limited insight into the potential long-term effects of GM-CSF supplementation on pregnancy outcomes. The use of Embryogen®, a commercially available medium containing GM-CSF, introduces the potential for conflicts of interest, as the manufacturer may have vested interests in the study outcomes. Exclusion criteria such as hydrosalpinx and anatomical uterine

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disorders may limit the generalizability of the findings to populations with these conditions, potentially reducing the external validity of the study.

Conclusion

In conclusion, this research, encompassing the examination of 100 rats with equal allocation to GM-CSF and control groups, meticulously evaluated various parameters spanning ovulation stimulation, controlled preparation of the endometrium cycle, embryo culture, transfer, and subsequent pregnancy outcomes. Findings consistently indicated a lack of statistically significant differences between the GM-CSF and control groups across all assessed parameters, including embryo quantity, quality, transfer outcomes, and pregnancy-related metrics. These results suggest that the addition of GM-CSF to embryo culture did not yield discernible advantages in terms of embryo development, transfer success, or early pregnancy outcomes in the context of this experimental model. Further investigations are warranted to elucidate potential nuances or alternative applications of GM-CSF supplementation in assisted reproductive techniques.

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Conflicts of Interest

None declared.

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