INPLASY PROTOCOL

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Corresponding author:
Yushi Meng

mengyushi0102@163.com

Author Affiliation:
The Second Affiliated Hospital of Kunming Medical University.

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Conflicts of interest:
None declared.

What is the impact of granulocyte colony-stimulating factor (G-CSF) in subcutaneous injection or intrauterine infusion and during both the fresh and frozen embryo transfer cycles on recurrent implantation failure: A systematic review and meta-analysis?

Hou, Z[1]; Jiang, F[2]; Yang, J[3]; Yang, L[4]; Hao, Z[5]; Yang, X[6]; Jia, B[7]; Meng, Y[8].

Review question / Objective: **The aim of this systematic review and meta-analysis was performed to further explore the effects of G-CSF according to embryo transfer cycle (fresh or frozen) and administration route (subcutaneous injection or intrauterine infusion) among RIF patients.**
Condition being studied: **Among recurrent implantation failure (RIF) patients, the rate of successful implantation remains relatively low due to the complex etiology of the condition, including maternal, embryo and immune factors. Effective treatments are urgently needed to improve the outcomes of embryo transfer for RIF patients. In recent years, many researchers have focused on immunotherapy using granulocyte colony-stimulating factor (G-CSF) to regulate the immune environment. However, the study of the G-CSF for RIF patients has reached conflicting conclusions.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 July 2021 and was last updated on 13 July 2021 (registration number INPLASY202170040).

INTRODUCTION

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METHODS

Search strategy: We will search the following database for literature published in English before October 2020: PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) , the search string will be built as follows: ((recurrent implantation failure) OR (repeated implantation failure) OR (mif) OR (rif)) AND ((Granulocyte Colony-Stimulating Factor[) OR (G-CSF) OR (Granulocyte colony stimulating factor) OR (Granulocyte-colony stimulating factor) OR (colony-stimulating factor) OR (CS) OR (Lenograstim) OR (Filgrastim).

Participant or population: Patients under the age of 40 years who failed to achieve clinical pregnancy after the transfer of at least four good-quality embryos in a minimum of two IVF Fresh or frozen cycles who was treated with subcutaneous injection or intrauterine infusion of G-CSF before a fresh or frozen embryo transfer cycle will be included, those with uterine factors such as uterine anomalies, myoma, endometrial polyps and systemic diseases or contraindications of G-CSF will be excluded.

Intervention: Patients included was treated with subcutaneous injection or intrauterine infusion of G-CSF before a fresh or frozen embryo transfer cycle.

Comparator: Patients in control group received placebo or no treatment.

Study designs to be included: Randomized controlled trials (RCT) will be included.

Eligibility criteria: A study was included when it met all of the following criteria: 1. Patients under the age of 40 years who failed to achieve clinical pregnancy after the transfer of at least four good-quality embryos in a minimum of two IVFresh or frozen cycles. 2. Subcutaneous injection or intrauterine infusion of G-CSF before a fresh or frozen embryo transfer cycle. 3. RCT with a control group that received placebo or no treatment. 4. Reporting of one of the following outcomes: clinical pregnancy rate, live birth rate, miscarriage rate, biochemical pregnancy rate. Studies that did not meet all the criteria above were excluded.

Information sources: Literature published in English before October 2020 was searched from PubMed, Embase and Cochrane Central Register of Controlled Trials(CENTRAL).

Main outcome(s): Clinical pregnancy rate.

Additional outcome(s): Live birth rate, biochemical pregnancy rate, and miscarriage rate.

Quality assessment / Risk of bias analysis: Risk of bias were assessed using the Cochrane 'Risk of bias' tool according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0). The following domains were assessed by two researchers independently: 1.Selection bias (random sequence generation and allocation concealment); 2. Performance bias (blinding of participants and personnel);3. Detection bias (blinding of outcome assessors); 4. Attrition bias (incomplete outcome data); 5. Reporting bias(selective reporting); 6. Other bias (including unplanned interim analysis).

Strategy of data synthesis: Stata software (Version 15.0; Stata Corporation, College Station, TX, USA) was employed to perform all data analysis. The influence of G-CSF treatment on the outcomes of IVF-ET for

RIF patients was assessed with pooled risk ratios (RRs) and their 95% confidence intervals (CIs).

Subgroup analysis: Subgroup analysis was performed in terms of embryo transplantation cycle and administration route. We will not assess publication bias across studies if the number of included studies are under 10.

Sensitivity analysis: The pooled RRs were calculated through a Mantel–Haenszel fixed-effects model if there was no heterogeneity; otherwise, a random-effects model was adopted. Statistical heterogeneity across studies was formally tested using Cochran's Q test. The I2 statistic was examined, and I2 > 50% was considered to represent significant heterogeneity between studies.

Country(ies) involved: All of the authors of this systematic review and meta-analysis are from China.

Keywords: Granulocyte colony-stimulating factor, repeated implantation failure, intrauterine infusion, subcutaneous injection, fresh embryo transfer, frozen embryo transfer, clinical pregnancy rate.

Contributions of each author:

Author 1 - Zhijin Hou - Provided the idea and design of this research, searched the literature and extracted data, drafted the manuscript.
Email: 948362809@qq.com
Author 2 - Fangjie Jiang - Provided the idea and design of this research, check the manuscript.
Email: jiangfangjiess@yeah.net
Author 3 - Jie Yang - Check the manuscript.
Email: yangh0110@163.com
Author 4 - Liu Yang - Check the manuscript.
Email: 13518735544@163.com
Author 5 - Zha Hao - Check the manuscript.
Email: zhahao_211@126.com
Author 6 - Xiaoling Yang - Check the manuscript.
Email: kmdyxl@163.com
Author 7 - Bie Jia - Check the manuscript.
Email: 791630202@qq.com
Author 8 - Yushi Meng - Corresponding author, Provided the idea and design of this research, check the manuscript.
Email: mengyushi0102@163.com