May Intrauterine Granulocyte Colony Stimulating Factor Improve Clinical & Ongoing Pregnancy & Live Birth Rates in Unexplained Repeated Implantation Failure Patients? A Randomized Clinical Trial

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ABSTRACT

Introduction & Objective: To study whether intrauterine granulocyte colony stimulating factor (G-CSF) improves the rates of clinical and ongoing pregnancy and live birth rates in unexplained repeated implantation failure (RIF) patients on their new ICSI-ET program.

Study Design: In University affiliated, Avicenna specialized center for fertility and repeated miscarriages 93 consenting unexplained RIF patients with normal endometrium and without any history of malignancy or uncontrolled background disease were enrolled in a registered, computer generated randomized double blinded placebo-controlled clinical trial. Patients underwent intrauterine perfusion of G-CSF or Placebo before ET and were monitored to calculate the Clinical & ongoing pregnancy and live birth rates in each group.

Result: The mean age was 32.85±5.02 years in G-CSF and 33.57±4.63 years in placebo group. There were no differences in baseline characteristic of patients and the ICSI protocols in groups. clinical and ongoing pregnancy and live birth rates were 17%, 14.9% and 12.8% in G-CSF group and 21.4%, 17.4 %and 13 % in control group respectively and did not show any statistically significant difference between the two groups. No adverse side effect was seen in the study groups.

Conclusions: In the study, intrauterine G-CSF did not affect clinical and ongoing pregnancy and live birth rates There was a non- significant improvement in clinical and ongoing pregnancy rate and also a reduction in the first trimester abortion in G-CSF patients. Non-significant higher ongoing pregnancy and lower abortion rates in the G-CSF group may be due to limited sample size or low G-CSF dosage. So further multicenter studies with larger sample size or higher doses of G-CSF is recommended. Clinical Trial Registration Number: IRCT2013063011653N2.

Keywords: G-CSF, Recurrent Implantation failure, Pregnancy rate, Randomized controlled trial.

INTRODUCTION

Recurrent implantation failure (RIF) is a major problem in most infertility treatment centers. The definition of implantation failure is not clear yet. It was defined as patients with at least two unsuccessful consecutive IVF/ICSI or frozen embryo transfer cycles while the cumulative number of cleavage stage embryos should not be less than four or the blastocyst embryos should not be less than two and all embryos have good quality and proper developmental stage (Polanski et al. 2014). Three categories of RIF were explained by (Timeva et al. 2014). : I) *Multifactorial RIF* is defined when different factors cause RIF. These factors include uterine (congenital or acquired) abnormalities, male factor (severe oligo-astheno-zoospermia or sperm DNA fragmentation), genetic disorders, uncontrolled background diseases (e.g., diabetes mellitus, thyroid dysfunction, infectious disease, thrombophilia, immunological or Psychological disorder, lifestyle),. *II) Endometrial RIF* or thin endometrium (<6^{mm}) is one of the main causes of RIF and usually resistant to various treatment *III) Idiopathic or unexplained RIF*: when nothing is detected to explain the failed outcomes (in spite of good quality embryo, normal endometrium and healthy parents) (Simon & Laufer. 2012).

Various algorithms are designed for evaluation and treatment of RIF's patients (Coughlan et al. 2014; Das & Holzer. 2012). Meanwhile Human Granulocyte colony-stimulating factors (G-CSF) was used in multiple clinical trials studies to treat RIF (Wurfel et al. 2014; Scarpellini & Sbracia. 2009) and in 2009 G-CSF treatment patented for treatment of RIF and recurrent pregnancy loss (RPL) patients, presuming that G-CSF may change the endometrium (Eftekhar et al. 2016; Sayadi & Arabjahvani.

2014).

GSCF prescription in IVF patients is controversial whereas it has been showed beneficial in many studies especially in RIF patients (Würfel. 2015) but on contrary few RCTs showed no significant positive effect on outcomes of the treatment (Zhang et al. 2018). At the time of study design there were no powerful meta-analysis assessing the G-CSF prescription outcome to solve the controversy (Zhang et al. 2018). During the study period many meta-analysis have been published which mostly have emphasized on effective role of the intra-uterine G-CSF perfusion on clinical pregnancies (Xie et al. 2017; Zhao et al. 2016) although it might not affect the endometrial thickness (Li et al. 2017; Kamath et al. 2017).

Due to good outcomes of G-CSF treatment in RPL and in endometrial or multifactorial RIF patients, we decided to investigate whether G-CSF may improve pregnancy outcomes in unexplained RIF patients. A double blinded clinical trial was designed in order to compare intrauterine G-CSF with placebo (normal saline) in unexplained RIF patients. The outcome of clinical (FHR activity in 5-7thw) & ongoing pregnancy (12th week) in the G-CSF and control groups was described.

MATERIAL AND METHODS

This randomized clinical trial was approved by scientific and ethical board of Avicenna research institute (university affiliated) before initiation and was registered in Iranian Registry of Clinical Trials (IRCT) numbered 2013063011653N2. Samples were selected from patients referred to Avicenna Fertility Clinic (A tertiary center for recurrent pregnancy loss and infertility treatments) between December 2015 and September 2018. All patients with at least two pervious unsuccessful IVF/ICSI cycles, who were going to start a new ICSI in the center, were assessed for eligibility. Patients older than 38 years old, those with BMI>30, FBS>110, FSH>12, congenital (eg, bi-curnate uterus) or acquired (e.g., Asherman syndrome, sub-mucosal myoma with endometrial pressure) uterine anomaly, systemic disease such as known thrombophilia or coagulation disorder, uncontrolled diabetes, Hypertension, thyroid, renal disease, TPO>500, abnormal karyotype, third party reproduction cycle, azoospermia with negative sperm in biopsy and ongoing cancer were excluded. As fresh embryo transfer was targeted in the study, patients with any preference for embryo freezing (such as poly cystic ovarian disease (PCOD) and history of severe ovarian hyper stimulation syndrome (OHSS) were excluded this also led us to eliminate the role of PCOD which acts as a confounding co-factor in recurrent failed implantation. Since heterogeneity of patients is the main cause of inconclusive results in previous studies we strictly emphasized on inclusion and exclusion criteria in order to choose only unexplained RIF patients (with normal endometrium) in this trial. Those patients who insisted on pharmacological intervention (such as IVIG, corticosteroids…) were not included the trial in order to eliminate other confounding or interactive. Based on previous studies (7, 8, 10) with power of 0.8, considering one sided confidence interval 95% and also effect size of 20% in pregnancy rate, the sample size of 54 patients (in each group) were calculated for the study although due to lack of patients it was extenuated to 50 in each group. 230 RIF patients were checked for the study criteria. To reach a real homogeneity, all patients were evaluated by only one definite infertility fellowship during the first visit, continued in patients follow up, ovarian puncture and embryo transfer. Whenever the physician was not available only another specified infertility physician followed the patients. 87 patients were excluded based on inclusion and exclusion criteria. 143 unexplained eligible RIF patients were offered to contribute in the trial and fill the informed consent, 43patients refused to participate in the study, mostly (36 patients) due to difficulty in transportation to Tehran. Also a few patients (n=7) did not have any interest for the trial. Finally, 100 patients consented to contribute in the trial (Figure 1).

A computer-generated randomization was performed and 100 numbered envelopes, each containing a randomization card were used in order to allocated the patients in the treatment or control groups of the trial randomly. The randomization was completely blinded for all patients& physicians. After signing the informed consent and randomization, new ICSI cycle (Antagonist or Long agonist) initiated for these unexplained RIF patients. Stimulation was performed with a combination of FSH (Gonal F: Merck-sereno company, Fostimon: IBSA) and HMG (Merional IBSA) injection. Dose of stimulants was individualized by using regular ultrasound monitoring of patients' ovarian response and AMH level. cetrotide (merck-sereno) and Cinnafact (Cinagen) were used in antagonist and long agonist cycles respectively. In the treatment group 300µgr G-CSF (300 µgr/0.5 ml pDgrastim Amp pooyesh darou co. Tehran IRAN) was perfused via a sterile IUI catheter just after ovarian puncture in the operation room and in the control group 0.5 ml sterile normal saline was perfused in the uterine cavity as placebo. Three days embryo with more than 6 blastomeres considered as a good quality embryo if the embryo fragmentation ratio was lesser 10% and the blastomeres were symmetric. BHCG test was checked 14 and 16 days after embryo transfer to assess Pregnancy. Positive βHCG test was considered as chemical pregnancy. All pregnant patients were followed up to delivery of the neonate. Clinical pregnancy was determined when fetal heart activity was observed in the ultrasound examination on the 5-7th gestation. Ongoing pregnancy was defined as a fetus with fetal heart activity in the ultrasound in the 12th week gestation. Statistical analysis $P<0.05$ was considered as statistically significant. Data was analyzed using SPSS version 13. Normal distribution of quantitative variables was assessed by the Kolmogorov–Smirnov test and in normally distributed variables student t-test was used for comparing means of groups. In cases of non-normal or ordinal variables, Mann- Whitney test was replaced. Comparison of percentages was done using Chi square and fisher exact test (in low case number e.g. clinical pregnancy percentage).

OBSERVATIONS AND RESULTS

During the trial period among the 100 allocated patients in two groups seven patients dropped out of the study: four patients in control group (two patients due to poor cooperation for scheduled visits, two due to request of using IVIG, and three patients in case group (one case due to request of using IVIG, and two patients because of poor cooperation for scheduled visits).

The demographic characteristics of both groups was compared and there was no statistical difference in age, BMI, number of previous IVF/ICSI cycles, baseline FSH or baseline AMH between the two groups (Table 1).

Moreover statistical analysis did not show any significant differences in the characteristics of ICSI cycle including mean gonadotropin dosage, mean E2 before OPU, mean number of Follicles and oocytes between the two study groups. In particular endometrial thickness in all patients of both groups, was normal (8.3±1.9 vs. 7.9± 1.7 p=0.279).

βHCG test was positive in 18 patients:8 patients in G-CSF group (17%) and 10 patients in placebo group (21.6%), means chemical pregnancy rate was not significantly deferent in the G-CSF and control group.

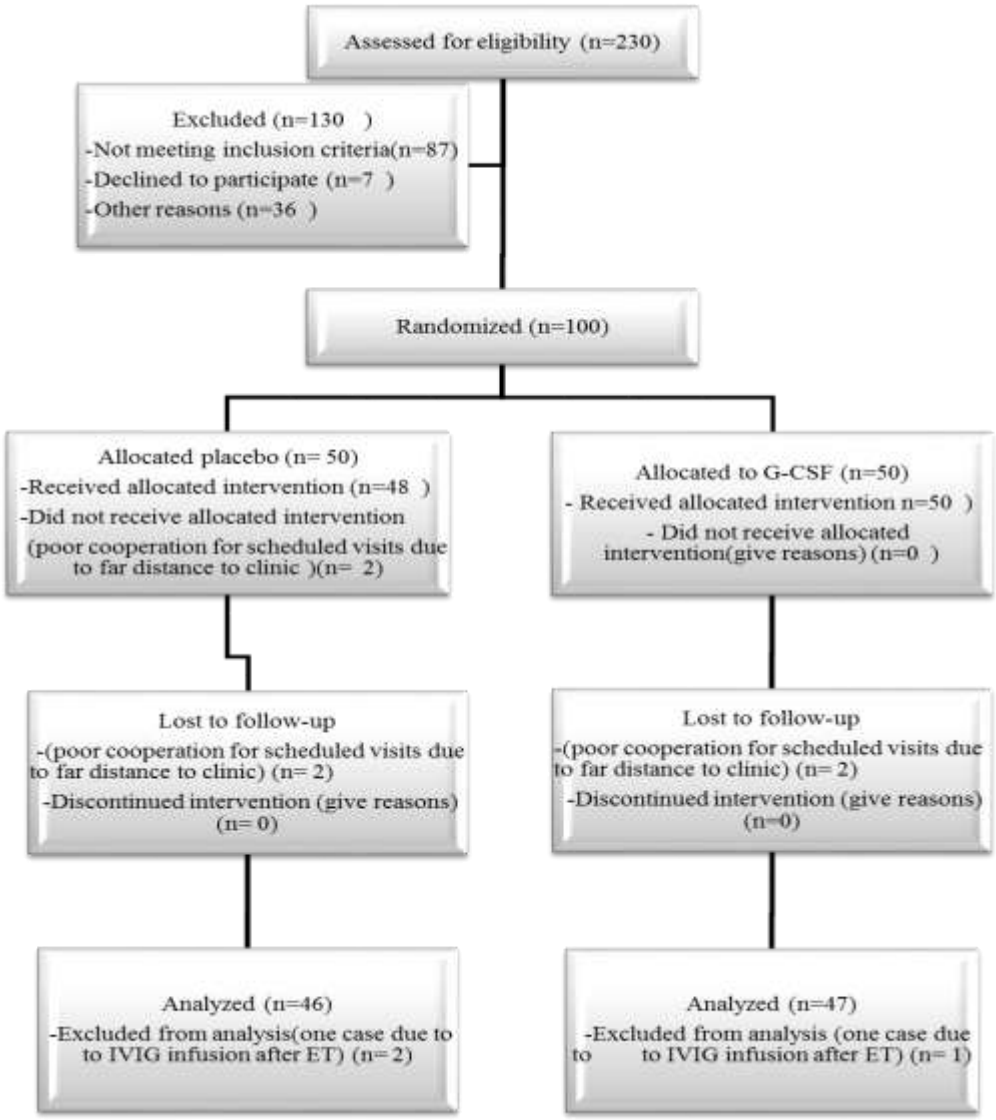

Figure 1: Diagram for Patient's enrollment

Table 1: Demographic characteristics of patients in Treatment and control groups

Variables	Treatment Group (n=47)	Control Group (n=46)	P-value	Result
Age	32.85 ± 5.02	33.57 ± 4.63	0.478	N.S[1]
BMI	26.14 ± 3.16	25.25 ± 3.24	0.186	N.S
Infertility Duration	8.03 ± 4.84	7.22 ± 4.36	0.395	N.S
Number of previous IVF/ICSI	2.72 ± 1.73	2.72 ± 1.00	0.984	N.S

cycles				
Baseline FSH	7.36 ± 2.81	7.63 ± 2.56	0.623	N.S
Baseline AMH	3.67 ± 2.50	2.81 ± 2.43	0.259	N.S
Sperm Count (count/ml)	(40±45)×10^6	(43±42)×10^6	0.743	N.S

1-N.S: Not Significant

In G-CSF group, only one chemical pregnancy occurred and all other 7 pregnant patients progressed to 7th (clinical pregnancy) and 12th (ongoing pregnancy) week of gestation .Therefore clinical and also ongoing pregnancy rates were 14.9 % (7/47) and 87.5% (7/8) respectively within pregnant patients of GCSF group. In the placebo group, one chemical pregnancy, one ectopic pregnancy and two abortions (after FHR detection, in 6.5th and 10th week) were observed. Therefore 8 clinical pregnancy (17.4%) and 6 ongoing pregnancy (13.10%) were detected. One and two twin pregnancies were seen in the G-CSF and placebo groups respectively which had no significant differences (Table 2).

Table 2: ICSI cycle characteristics in treatment and control groups

Variables		Treatment Group(n=47)	Control Group (n=46)	P-value †
Cycle Protocol*	Antagonist	53.2%	52.2%	0.989
	Long agonist	46.8%	47.8%	
Mean Endometrial Thickness**		8.3±1.9	7.9±1.7	0.279
Mean Number Of Oocytes		10.5±6.3	11.2±6.5	0.597
Mean Number of*** Embryos		4±7	5±6	0.663
Good Quality Embryos*		57/1%	64/3%	0.184
Mean Number Of Frozen Embryos**		2.06±3.05	2.35±3.77	0.690
Mean Number Of Transferred Embryos ***		3±1	3±1	0.422

*Data was presented as percentage
**Data was presented as (Mean ±SD)
*** Data was presented as (Median± IQR)
† Independent t test and Man-Whitney tests' P-values ≤ 0.05 was considered statistically significant

According to our exclusion criteria, those patients with history of previous severe ovarian hyper stimulation syndrome (OHSS) were excluded. Nevertheless, in this study 10.6% of G-CSF group and 6.5 % of placebo group showed mild OHSS and were managed by lower dose of HCG injection (5000IU) and some other conservative management, insofar embryo transfer could be done safely. There was no case of severe OHSS in either group. No other adverse side effect was seen in this study (Table 3).

Table 3: Pregnancy outcome in treatment and control groups

Variables	Treatment Group(n=47)	Control Group (n=46)	P-value†
βHCG+	8/47 (17%)	10/46 (21.7%)	0.68
Clinical Pregnancy rate	7/47(14.9%)	8/46(17.3)	0.78
Live Birth Rate	6/47(12.8%)	6/46(13%)	0.96
Clinical pregnancy Rate(per HCG+)	7/8 (87.5%)	8/10 (80%)	0.69
Ongoing pregnancy per HCG+ (12th week)	7/8 (87.5%)	6/10(60%)	0.60
Abortion before 12th week[B]	0	2/10 (20%)	0.15

Data was presented as ratio (percentage)
† Chi square P-value≤ 0.05 was considered statistically significant

DISCUSSION

This study was designed to evaluate the effect of intrauterine G-CSF on improvement of pregnancy rate among patients with unexplained recurrent failure. The main outcomes of the study showed no significant statistical difference between G-CSF or control group although the clinical pregnancy rate was higher in intervention group.

Many cytokines are involved in the interaction of the trophoblasts and endometrium or the same feto-maternal dialog (Kauma, 2000). Human Granulocyte colony-stimulating factors (G-CSF) is a multi-potential cytokines which has specific receptors on variety of tissues in human body, especially in placenta, trophoblast, luteinized human granulosa and human endometrial cells (Daiter et al. 1992). Thus G-CSF suggested as an effective treatment reducing pre-eclampsia and recurrent abortion, treatment of resistant thin endometrium and RIF patients (Zeyneloglu et al.

2013; Gleicher et al. 2013). In a case control study of 138 RIF patients in IVF 69 patients received single dose of G-CSF sub-cutaneously (34×10^6 IU)on the day of ET and 69 patients received no treatment as control group and clinical pregnancy rate was significantly higher in the treatment group (50.7% vs 19.8 %). Also in another clinical trial, 61 RIF/long infertility patients, received 13 $\times10^6$ IU of G-CSF every 3 days after ET. The clinical pregnancy rate was 73.8% and 42% in blastocyst and 2th days ET respectively; these rates were significantly higher than routine ART outcomes. Meanwhile in this trail, clinical abortion rate was not decreased (38.7% and 37.5%) in blastocyst and 2th days ET respectively (Santjohanser et al. 2013).

In two other studies frequent subcutaneous injection of G-CSF, in RPL patients resulted in significantly lower miscarriage rate (Zafardoust et al. 2017) however there are many studies reject these finding (Gleicher et al. 2011). In another clinical trial, intrauterine G-CSF infusion did not improve endometrial thickness, implantation rates, or clinical pregnancy rates in a heterogeneous sample of IVF patients (Kunicki et al. 2017).

On the other hand, intrauterine infusion of G-CSF in patients with resistant thin endometrium or recurrent pregnancy failure resulted in higher pregnancy outcomes in a few clinical trials but similarly it has been shown ineffective in some other studies (Li et al. 2014).

None of the human clinical trials of G-CSF on pregnant women reported any teratogenicity or congenital anomaly, nevertheless G-CSF is considered in category "C" of FDA. Since the half-life of G-CSF is only 3.5 hours, In order to be more careful about safety of G-CSF, we used only local (intrauterine) single dose of G-CSF just after ovarian pick up (almost 2 or 3 days before ET) . Moreover intrauterine infusion of G-CSF in the operating room just after OPU (while the patient was still sedated) was more convenient for patients and using single dose infusion was less expensive, although the dosage, number and route of injection are controversial like other issues about G-CSF (Zhang et al. 2018).

This study was extremely strict in patient selection and implementation to reduce the heterogeneity of the samples (which might be problematic and cofounding) and helped us to be more conclusive. Firstly, choosing unexplained RIF patients with normal (not thin) endometrium deletes the role of other clinical factors lead to RIF, especially thin endometrium (Xu et al. 2015). Secondly, young patients with normal AMH and good ovarian reserve eliminate the age effect which was a major obstacle in RIF's patients sampling (Barad et al. 2014). Additionally follow up of patients up to delivery and determination of live birth rate makes this study more accurate than other ones. The patients of this study were selected, managed and consulted exclusively with a single infertility fellowship which made the protocols and sampling more homogeneous. The main limitation of the study was sampling while unexplained RIF patients with normal endometrium are not frequent enough. On the other hand due to disappointing nature of the disease, the patients who accept participation in a trial with placebo injection are rare too.

CONCLUSIONS

In accurately evaluated unexplained RIF's patients, intrauterine G-CSF infusion could not significantly improve clinical &ongoing pregnancy and live birth rates, although a non-significant improvement was achieved in the clinical and ongoing pregnancy raets. In other words, intrauterine G-CSF might potentially decreases first trimester pregnancy loss in unexplained RIF patients. Non- significant outcomes in clinical and ongoing pregnancies and first trimester abortion rates may be due to small sample size or low dose of G-CSF in the study ; thus further multicenter clinical trials with larger sample size and probably higher doses of G-CSF is suggested to determine clinical and ongoing pregnancy improvement in unexplained RIF patients.

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CONFLICT OF INTEREST

There was nothing detected as conflict of interest by authors.

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