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Possibilities of using granulocyte colony-stimulating factor in reproductive medicine. A literature review

© Cong T. Nguyen[1], Dariko A. Niauri[1, 2], Natalya I. Tapilskaya[2, 3], Aleksandr M. Gzgzyan[1, 2]

[1] Saint Petersburg State University, Saint Petersburg, Russia;
[2] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia;
[3] Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russia

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic glycoprotein that promotes proliferation, differentiation and activation of myeloid lineage cells. The abundant presence of G-CSF receptors in the female reproductive system highlights its possible importance in oogenesis, ovulation, implantation, and pregnancy development. This literature review describes the main aspects of G-CSF use in reproductive medicine, such as ovulation induction in women with the luteinized unruptured follicle syndrome, the improvement of folliculogenesis, overcoming repeated implantation failures, therapy of thin endometrium and recurrent pregnancy loss.

Keywords: granulocyte colony-stimulating factor; IVF / ICSI; pregnancy rate; repeated implantation failures; thin endometrium.

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Возможности применения гранулоцитарного колониестимулирующего фактора в репродуктивной медицине

© К.Т. Нгуен[1], Д.А. Ниаури[1, 2], Н.И. Тапильская[2, 3], А.М. Гзгзян[1, 2]

[1] Санкт-Петербургский государственный университет, Санкт-Петербург, Россия;
[2] Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта, Санкт-Петербург, Россия;
[3] Санкт-Петербургский государственный педиатрический медицинский университет, Санкт-Петербург, Россия

Гранулоцитарный колониестимулирующий фактор (G-CSF) —гемопоэтический гликопротеин, который способствует пролиферации, дифференцировке и активации клеток линии гранулоцитов. Присутствие рецепторов G-CSF в различных клетках органов репродуктивной системы женщин предполагает его значение в процессах оогенеза, овуляции, имплантации и развития беременности. В данном обзоре описаны основные аспекты применения G-CSF в репродуктивной медицине, такие как индукция овуляции у женщин с синдромом лютеинизации неовулирующего фолликула, улучшение фолликулогенеза, преодоление повторных неудач имплантации, терапия тонкого эндометрия и привычного невынашивания беременности.

Ключевые слова: гранулоцитарный колониестимулирующий фактор; ЭКО/ИКСИ; частота наступления беременности; повторные неудачи имплантации; тонкий эндометрий.

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General characteristics of granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF) is a cytokine of the colony-stimulating factor group, which also includes granulocyte macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor, and interleukin (IL)-3.

G-CSF (CSF-3) is a glycoprotein that promotes proliferation, differentiation, and activation of granulocyte cells. It was first discovered in the mid-1960s by scientists from Australia [1] and Israel [2]. In 1983, purified G-CSF was obtained from the lungs of mice injected with bacterial endotoxin [3]. Two years later, human G-CSF was isolated by Nicola et al. and Welte et al. [3, 4].

Human G-CSF consists of 174 amino acids and has a molecular weight of 18–19 kDa. G-CSF is encoded by one gene containing 5 exons and 4 introns, located on chromosome 17 (q11-22) [5].

The immune system cells, such as macrophages, monocytes, and peripheral blood cells, play an important role in G-CSF synthesis. G-CSF plays a crucial role in the proliferation and differentiation of neutrophils. In addition, it stimulates mitogenesis and differentiation of stem cells into mature polymorphonuclear leukocytes [6]. Moreover, it has an effect on the functions of mature neutrophils associated with the expression of CD11b/CD18, CD64, CD14, rTNFR, and IL-1 Rap as well as increases chemotaxis, phagocytosis, and antibody-dependent cellular cytotoxicity and delays apoptosis [7]. Studies conducted over the recent decade have demonstrated that G-CSF is also involved in the regulation of T-cell function of the immune system. Under experimental conditions, scientists from Australia demonstrated that G-CSF significantly improves the defense of the donor organism against graft versus host reaction [6].

In their review Rutella et al. (2005) demonstrated the contribution of G-CSF in stimulating the differentiation of regular T cells (Tregs) and proved that the efficiency of G-CSF is associated with an increase in IL-10 production by T cells [8]. At the same time, G-CSF reduces the toxicity of natural killer (NK) cells in various ways, including by reducing the generation of NK cell precursors ($CD34^+/CD2^+$, $CD34^+/CD7^+$, and $CD34/CD10^+$); decreasing the expression of activating receptors (e.g., NKG2D receptor) and inhibitory receptors (e.g., KIR2DL1 or KIR2DL2); and attenuating cytokine synthesis (interferon-γ, TNF-α, GM-CSF, IL-6, and IL-8) [9].

G-CSF functions through a specific receptor located in different tissues and cells, namely myeloproliferative tissues and their cells (macrophages, NK cells, T cells, and platelets). In addition, G-CSF receptors are located in luteinized ovarian granulosa cells [10], placental cells [11], and trophoblasts [12]. This suggests the active participation of G-CSF in regulating the function of the reproductive system. G-CSF receptors are also present in almost all fetal tissues [13, 14]. Moreover, Liu et al. discovered G-CSF receptors in stem cells of hematopoietic organs and the nervous system [15].

Role of G-CSF in reproductive medicine

Role of G-CSF in ovulation induction in women with luteinized unruptured follicle (LUF) syndrome

Many types of cells of the reproductive system organs are additionally involved in the synthesis of G-CSF [16]. In the reproductive system, G-CSF synthesis primarily occurs in granulosa cells, luteal cells, and NK cells, especially endometrial NK cells ($CD56^{bright}$). The intensity of G-CSF synthesis during the menstrual cycle is different. As a result, while studying *in vitro* epithelial cells of the endometrium, endocervix, and fallopian tubes, Fahey et al. concluded that the epithelial cells of female genital organs can secrete various cytokines, including G-CSF [17]. During pregnancy, G-CSF is synthesized by the decidual cells as well as the chorionic villus cells. A high concentration of G-CSF is registered in the first trimester of pregnancy, which then decreases in the trimester II and increases again before childbirth. In addition, as a pro-inflammatory cytokine, G-CSF plays an important role in the implementation of ovulation. Some studies have shown that the concentration of plasma G-CSF in women with normal menstrual function changes during the menstrual cycle and reaches its highest values in the pre-ovular phase.

In the 1980s, studies were conducted to assess the efficacy of G-CSF for treating LUF syndrome. In 16 women with LUF syndrome, the administration of G-CSF increased the ovulation frequency from 53.5% to 88.9% [18]. Japanese scientists Shibata et al. enrolled 68 women with LUF syndrome and confirmed the positive effect of subcutaneous G-CSF on ovarian stimulation. Luteinization of the unruptured follicle was repeated only in three cycles (3/68 = 4.4%) among women who received G-CSF, which was significantly less frequent than that in women who did not receive G-CSF (observed in 13 cycles; 13/68 = 19.1%). The authors thus concluded that G-CSF may be used to treat LUF syndrome [19]. In 2013, Fujii et al. published the results of subcutaneous G-CSF administered to women undergoing ovulation induction with clomiphene citrate and human chorionic gonadotropin (hCG) using ultrasound markers of LUF syndrome. Comparative analysis showed that G-CSF increased the frequency of ovulation compared with that observed in previous cycles where the drug was not administered. In addition, no serious side effects were observed. Moreover, four of the 63 women included in the study became pregnant [20]. Thus, it can be concluded that G-CSF has a positive effect on ovulation induction in women with LUF syndrome.

Role of G-CSF in folliculogenesis

According to many experts, there exists a positive correlation between G-CSF concentration in the blood and follicular fluid and the number of mature oocytes and morphologically quality embryos in *in vitro* fertilization (IVF) protocols. Salmassi et al. determined the concentration of G-CSF in blood plasma and follicular fluid in 93 women (using enzyme-linked immunosorbent assay). They found that G-CSF concentration in the follicular fluid was higher than that in the blood plasma ($p < 0.01$) and that it increased to maximum values at the time of the ovulation trigger administration and then decreased gradually. Moreover, a significant correlation was noted between G-CSF concentration in the follicular fluid and the intensity of the ovarian response to stimulation ($p < 0.001$) and the frequency of pregnancy. Thus, the authors concluded that G-CSF is involved in the development of follicles and that G-CSF concentration in blood plasma and follicular fluid can be a predictor of the efficiency of assisted reproductive technologies (ARTs) [21]. The French researchers Fraydman et al. demonstrated that among women undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment, the concentration of G-CSF (high, medium, and low) in the follicular fluid clearly correlates with the frequency of pregnancy (14%, 43%, and 54% [$p = 0.003$ and $p = 0.006$]) and childbirth with live children (0%, 8%, and 51% [$p = 0.002$ and $p = 0.001$]), respectively [22]. The importance of G-CSF in the process of follicular growth and its effect on the quality of oocytes and embryos have been proven in various studies.

Based on the available data, Lédée et al. developed a classification system for assessing oocytes based on G-CSF concentration in the follicular fluid: oocytes were categorized as class I, II, and III when the C-CSF concentration in the follicular fluid was >30 pg/ml, ≤30 pg/ml to ≥18.4 pg/ml, and <18.4 pg/ml, respectively. Embryos obtained from class I oocytes were characterized by a higher implantation rate (36%) than those from class II (16.6%) and III (6%) oocytes ($p < 0.001$). Moreover, the implantation frequency of embryos from class I oocytes with optimal morphology was 54% [23]. Thus, it can be assumed that the determination of G-CSF concentration in the follicular fluid helps additionally select embryos for subsequent transfer. A group of Belgian authors reached similar conclusions and noted that along with the quality of embryos determined by morphological characteristics, the concentration of G-CSF in follicular fluid helps predict IVF/ICSI success [24].

In 2009, based on the results published by scientists from Italy, 18 women with a weak response to ovarian stimulation who entered the IVF/ICSI protocol were treated with subcutaneous G-CSF. In these women, the number and quality of the obtained oocytes increased with improvement of ART outcome compared with those in control women. In addition, the authors noted that the G-CSF concentration in the follicular fluid correlated with the quality of oocytes and their ability to fertilize [25]. At the same time, Nole et al. found no correlation between G-CSF concentration in the follicular fluid, the degree of mature oocytes obtained, and the ability of embryos to undergo implantation [26].

Role of G-CSF in overcoming repeated implantation failures

G-CSF is known to be synthesized by many cells of the reproductive system organs, including endometrial cells and trophoblasts. G-CSF receptors are found on placental tissue cells and trophoblasts. These may indicate the possible role of G-CSF in implantation and prolongation of pregnancy. Würfel et al. have demonstrated the therapeutic effect of G-CSF in women with repeated IVF failures. According to the authors, the pregnancy rate was significantly higher in women who received G-CSF (filgrastim, 34 mIU) than that in women who did not receive G-CSF (50.7% and 19.8%, respectively) [27]. The latest 2020 Cochrane review by Kamath et al., also reported a positive effect of G-CSF preparations in women with repeated IVF failures (risk ratio [RR]: 2.11; 95% confidence interval [CI]: 1.56–2.85) [28].

In a multicenter randomized controlled trial, Aleyasin et al. administered G-CSF subcutaneously before implantation in 56 women with repeated IVF failures and compared the results with those of 56 women who were not administered G-CSF. They found that the frequency of implantation (18% vs. 7.2%; odds ratio [OR]: 2.63; 95% CI: 1.09–6.96; $p = 0.007$) and the rate of clinical pregnancy (37.5% vs. 14.3%; OR: 2.94; 95% CI: 1.23–8.33; $p = 0.005$) was significantly higher in women using G-CSF than in those not using it [29]. In this regard, the results of a randomized placebo-controlled study conducted among 89 women with repeated IVF failures are of interest. The study demonstrated a significant increase in the pregnancy rate among women who used G-CSF daily (16/45; 42.2%) from the day of embryo transfer to the day of β-hCG test and up to day 40 if the test was positive, compared with that among women who did not receive G-CSF (7/44; 15.9%). At the same time, the level of β-hCG at 14, 21, 28, and 35 days after embryo transfer in women using G-CSF was higher than in control women [30].

Davari-Tanha et al. proved that the intrauterine infusion of 1 ml (300 μg) of G-CSF during oocyte puncture in women with repeated IVF failure increased the incidence of implantation and the onset of biochemical pregnancy; however, the incidence of clinical pregnancy did not increase, and the incidence of spontaneous abortions did not decrease [31]. Studies have also reported that the use of G-CSF by intrauterine infusion in women with multiple implantation failures increases the incidence of implantation and clinical pregnancy [32]. However, a randomized, double-blind,

placebo-controlled study provided evidence that intrauterine infusion of G-CSF in women undergoing infertility treatment using IVF programs (129 women), including those with cryopreserved embryo transfer (12 women), did not affect the implantation rate (33/224 [14.73%]) and pregnancy rates (35/219 [15.98%]) (RR: 0.99; 95% CI: 0.54–1.80) [33].

A recent meta-analysis of 10 randomized controlled trials that included 1016 embryo transfer cycles in IVF (521 cycles in G-CSF group and 495 cycles in the control group) showed that G-CSF significantly increased the incidence of clinical pregnancy (RR: 1.89; 95% CI: 1.53–2.33). Moreover, subcutaneous administration was more effective (RR: 2.23; 95% CI: 1.68–2.95) than intrauterine infusion (RR: 1.46; 95% CI: 1.04–2.05). In general, the authors concluded that the systemic use and local infusion of G-CSF in any case improves the outcome of ART, especially among women with repeated failed transfers [34]. The combined route (subcutaneous and intrauterine) of G-CSF administration or the use of G-CSF in combination with platelet-rich plasma can increase IVF efficiency in women with repeated failures [35, 36]. The available literature also reports that G-CSF concentration in uterine flushing, obtained on the day of puncture, is a predictor of the outcome of ART programs in women with repeated IVF/ICSI failures. The receiver operating characteristic curve presented by the authors showed a sensitivity of 87.5% and specificity of 94.3% with a CSF threshold value of 0.151 [37].

Role of G-CSF in treating recurrent miscarriage

There exists evidence that G-CSF has a positive effect on embryo adhesion, cell migration, tissue remodeling, and angiogenesis during transfer, which allows its use in clinical cases of women with recurrent miscarriage. As early as 20 years ago, a randomized controlled trial by Scarpellini et al. proved that the frequency of healthy babies delivered by a women who used rG-CSF (filgrastim) from day 6 after ovulation to the week 9 of gestation was significantly higher than that in control women (29/35 [82.8%] vs. 16/33 [48.5%]; OR: 5.1; 95% CI: 1.5–18.4; $p = 0.0061$) [38]. It has been established that the administration of G-CSF to women with repeated spontaneous abortions increases the number of Tregs in the peripheral blood.

A randomized study conducted by a German group reported the result of a comparative analysis of the efficacy of G-CSF and various pharmacological drugs used in routine practice to treat recurrent miscarriage after ART programs. The results revealed a high therapeutic efficacy of G-CSF not only in comparison with the control group (pregnancy rate: 47% vs. 24%, $p = 0.016$; live birth rate: 32% vs. 13%, $p = 0.016$) but also in the comparison group, where traditional treatment regimens were used (pregnancy rate: 47% vs. 27%, $p = 0.016$; live birth rate: 32% vs. 14%, $p = 0.006$) [39]. Thus, there are grounds to believe that G-CSF may become one of the methods of treatment in women with repeated spontaneous abortions after an ART program.

However, the results of a randomized, multicenter, double-blind, placebo-controlled study conducted by colleagues from the UK did not confirm the reports that the subcutaneous administration of G-CSF to women with recurrent miscarriage has a positive effect on its prolongation beyond 20 weeks and the frequency of birth of viable fetuses compared with women who did not receive G-CSF (59.2% vs. 64.9%; RR: 0.9; 95% CI: 0.7–1.2; $p = 0.48$). Moreover, in contrast to previous studies, the authors administered G-CSF at later terms from 3 to 5 weeks of pregnancy [40]. In addition, a randomized study assessing the efficacy of G-CSF for treating recurrent miscarriage revealed that intrauterine infusion of G-CSF had no significant effect on the incidence of biochemical and clinical pregnancy, implantation, and spontaneous abortion [41]. In another study, the use of a short treatment regimen (two subcutaneous injections of G-CSF: on the day of transfer and after 2 days) of G-CSF also did not affect the efficiency of IVF/ICSI programs [42].

Role of G-CSF in treating a thin endometrium

In recent years, the urgency of the so-called resistant thin endometrium has increased. According to the accumulated experience of this condition, the treatment of infertility using the ART program is characterized by a very low efficiency [43]. Various methods have been used to solve this problem, including the use of growth hormones, sildenafil treatment, and platelet-rich plasma, including the administration of G-CSF [44, 45]. In 2011, Gleicher et al. reported that in four women with thin endometrium who received intrauterine perfusion of G-CSF, the thickness of the endometrium increased, and after transfer of 1 or 2 embryos, clinical pregnancy occurred [46]. Nevertheless, a number of researchers who did not confirm the positive effect of intrauterine G-CSF perfusion on changes in endometrial thickness showed that under these conditions, women with a thin endometrium (<7 mm) had an increased incidence of biochemical (39.3% vs. 14.3%) and clinical (32.1% vs. 12%) pregnancy after cryopreserved embryo transfer, compared with control women [47].

In 2015, Chinese colleagues Xu et al. conducted a prospective cohort study and found a significant increase in endometrial thickness in cycles when the women were treated with intrauterine G-CSF perfusion. Moreover, they proved that intrauterine G-CSF perfusion in cryoprotocols improves performance in women with thin endometrium compared with that in women who did not receive G-CSF (implantation rate: 31.5% vs. 13.9%; $p < 0.01$ and pregnancy rate: 48.1 vs. 25%; $p < 0.038$) [48]. Similar results were reported by Xie et al., based on a meta-analysis of

11 studies [49]. In recent years, these data have also been confirmed by several studies [44, 50, 51]. However, the discussion about the therapeutic role of intrauterine administration of G-CSF in women with thin endometrium continues, and to resolve this issue, randomized placebo-controlled trials are required [52, 53].

Safety of G-CSF in pregnancy

The safety issues of using G-CSF preparations during pregnancy are being actively discussed in the literature. Cruz et al. compared the results of biometric parameters (weight and body length) and the gestational age of 33 newborns from women who received G-CSF in the first half of pregnancy and of 3798 children from women who did not receive G-CSF. Based on these results, they reported no significant difference between the two groups. There were also no significant differences in these parameters when analyzing the frequency of preterm delivery up to 32 weeks and up to 36 weeks as well as the birth rate of children weighing <2500 g and <1500 g [54]. A US-based study reported interesting results regarding the use of G-CSF for treating chronic neutropenia during pregnancy without adverse effects on the fetus [55]. Obviously, only the results of further multicenter, controlled, randomized prospective studies can conclusively confirm the safety of using G-CSF-based drugs during pregnancy.

Thus, the prospect of using G-CSF-based drugs in the management of patients with reproductive disorders is obvious. At the same time, while designing further studies assessing the efficacy of G-CSF-based drugs, it is essential to provide for the fundamental possibility of obtaining convincing evidence of the safety of these drugs in the long term for ensuring the health of women and newborns.

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AUTHORS INFO

***Cong Tuan Nguyen**, MD, Post-Graduate Student;
address: 7-9, Universitetskaya nab.,
Saint Petersburg, 199034, Russia;
ORCID: https://orcid.org/0000-0002-4665-9025;
dr.tuan99999@gmail.com

Dariko A. Niauri, MD, PhD, DSci (Medicine), Professor;
ORCID: https://orcid.org/0000-0003-1556-248X;
eLibrary SPIN: 4384-9785; e-mail: d.niauri@mail.ru

Natalya I. Tapilskaya, MD, PhD, DSci (Medicine), Professor;
ORCID: https://orcid.org/0000-0001-5309-0087;
e-mail: tapnatalia@yandex.ru

Aleksandr M. Gzgzyan, MD, PhD, DSci (Medicine);
ORCID: https://orcid.org/0000-0003-3917-9493;
eLibrary SPIN: 6412-4801; e-mail: agzgzyan@gmail.com

ОБ АВТОРАХ

***Конг Туан Нгуен**, аспирант;
адрес: Россия, 199034, Санкт-Петербург,
Университетская наб., д. 7–9;
ORCID: https://orcid.org/0000-0002-4665-9025;
dr.tuan99999@gmail.com

Дарико Александровна Ниаури, д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0003-1556-248X;
eLibrary SPIN: 4384-9785; e-mail: d.niauri@mail.ru

Наталья Игоревна Тапильская, д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0001-5309-0087;
e-mail: tapnatalia@yandex.ru

Александр Мкртичевич Гзгзян, д-р мед. наук;
ORCID: https://orcid.org/0000-0003-3917-9493;
eLibrary SPIN: 6412-4801; e-mail: agzgzyan@gmail.com