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The Efficacy and Safety of Granulocyte Colony-Stimulating Factor in Pregnant Women at High Risk of Preeclampsia

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Backgrounds: This study aims to explore the efficacy and safety of Granulocyte Colony-Stimulating Factor (G-CSF) in preventing pre-eclampsia at high risk and its effectiveness in correcting the imbalance of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PIGF).
Methods: A retrospective study was conducted on high-risk pregnant women treated with G-CSF between January and December 2021. G-CSF was administered in conjunction with standard prophylactic treatments, including aspirin, heparin, calcium supplements, and folic acid. The incidence of PE, serum levels of PIGF, and the sFlt-1/PIGF ratio were monitored. Statistical analyses were performed using SPSS 25.0.
Results: Among 60 high-risk women, the incidence of PE was 1.8% (1/56). G-CSF treatment resulted in a 316.2% increase in PIGF levels and a 70.0% reduction in the sFlt-1/PIGF ratio, with 96.7% of patients returning to normal biomarker levels. Adverse effects were minimal and manageable. Pregnancy outcomes included a cesarean section rate of 78.6%, with no perinatal deaths or cases of fetal growth restriction.
Conclusions: G-CSF shows potential as an adjunctive treatment for preventing PE in high-risk pregnancies, significantly improving key biomarkers and pregnancy outcomes with a tolerable safety profile. Further research is needed to validate these findings and assess long-term safety and efficacy.
Keywords: G-CSF; Pre-eclampsia; PIGF; sFlt-1/PIGF; Pregnancy outcomes.

Introduction

Pre-eclampsia (PE) is a common risk factor for morbidity and mortality among pregnant women and perinatal infants worldwide[1]. Standardized prenatal examinations, including close follow-up of high-risk patients during and after mid-pregnancy, can help detect pre-eclampsia in its early stages[2]. Early diagnosis and appropriate treatment, including delivery, can prevent some severe sequelae of the disease, such as eclamptic seizures and multi-organ failure. A systematic review found that 4.6% (95% CI 2.7–8.2) of pregnancies worldwide are complicated by pre-eclampsia[3]. Differences in incidence rates between countries may reflect, at least in part, differences in the age distribution of pregnant women and the proportion of nulliparous women. In the United States is approximately 5%[4,5]. As there is no cure other than delivery, taking preventive measures against PE is essential for the health of pregnant women and newborns globally[6].

Currently, effective predictive methods for preeclampsia remain limited; therefore, risk factors for preeclampsia are still important clinical indicators for screening high-risk pregnant women in early pregnancy. According to the 2019 recommendations of the International Federation of Gynecology and Obstetrics (FIGO)[7], a "two-stage" screening strategy can be adopted in early pregnancy. Specifically, all pregnant women undergo primary screening, followed by more precise secondary screening for those with moderate or higher risk. Among these, placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) are currently recognized as biomarkers for secondary screening of preeclampsia[8–10]. In patients with preeclampsia, elevated levels of sFlt-1 and decreased levels of angiogenic factors, such as PlGF and VEGF, destabilize the vascular environment, leading to placental insufficiency and elevated maternal blood pressure[11]. sFlt-1 inactivates and reduces PlGF and VEGF, causing endothelial dysfunction, which can be detected in maternal blood up to 5 weeks before the clinical onset of preeclampsia[12,13]. In Europe, sFlt-1 and PlGF have been used for clinical screening and auxiliary diagnosis of preeclampsia. The ratio of sFlt-1 to PlGF has shown good predictive and evaluative value for early-onset preeclampsia, with a sensitivity of up to 89% and a specificity of 97%[14].

Several randomized trials have investigated various strategies for preventing PE, with low-dose aspirin emerging as the most effective pharmacological preventative method[15–18]. However, the degree of benefit varies among patients depending on numerous factors, such as the timing of initiation and dosage. The pathogenesis of PE is complex, involving multiple etiologies or pathways that lead to the clinical syndrome, making simple preventive methods largely unsuccessful.

The placenta plays a crucial role in the maternal adaptive regulation during pregnancy. Trophoblast cells are the foundation of placental function. The invasion of trophoblast cells into the uter-

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ine endometrium during early pregnancy is essential for placental formation and healthy embryonic development. In normal pregnancies, trophoblast cells invade the uterine spiral arteries and remodel them to meet the demands of pregnancy. However, in patients with preeclampsia, insufficient trophoblast invasion leads to failed vascular remodeling and reduced uteroplacental blood flow[19]. Shallow placentation caused by inadequate trophoblast infiltration is a key pathophysiological mechanism underlying the development of preeclampsia. Recent studies have shown that G-CSF plays a vital role in reproductive medicine. Studies have demonstrated that G-CSF promotes the activity of trophoblast cells, enhancing their proliferation and invasion abilities[20–22]. Randomized controlled clinical studies suggest that G-CSF treatment for patients with unexplained recurrent pregnancy loss can increase live birth rates, reduce miscarriage rates, and elevate hCG levels[23]. Immunohistochemical studies indicate that G-CSF plays a crucial role in embryo implantation and trophoblast invasion during the first trimester[24]. G-CSF treatment restores the growth and development of trophoblast cells in patients with recurrent pregnancy loss. Additionally, Treg cells in the placenta of pregnant women receiving G-CSF treatment significantly increase.

Furthermore, abnormal maternal-fetal interface immune status significantly impacts the pathogenesis of PE. In pre-eclamptic patients, Tregs in the placenta and maternal peripheral blood are reduced[25–27], and their inhibitory function is impaired due to increased pro-inflammatory Th17 cells[28,29]. This immune response suppression prevents exacerbation of inflammatory reactions, such as those observed in pre-eclampsia, leading to maternal endothelial dysfunction[30]. G-CSF exhibits anti-inflammatory properties both in vivo and in vitro[31]. G-CSF can induce Treg proliferation and differentiation, mobilizing them from bone marrow to placental tissue. Women with recurrent miscarriages treated with G-CSF have significantly increased Treg numbers in placental tissue compared to untreated women[24]. A recent study revealed that neutrophils may activate Tregs, promoting initial T-cell conversion to Tregs within placental tissue and the secretion of IL-10, IL-17, and VEGF[32]. Tregs induced by neutrophils exhibit proangiogenic activity in placental tissue and trophoblast cells. These findings also confirm that G-CSF may promote angiogenesis by activating neutrophils and inducing Tregs. A recent study by Gendie E. Lash et al. found G-CSF appears able to increase vascular smooth muscle cell (VSMC) disorganization and phenotypic switching in both an ex vivo vascular model and in vitro VSMC cultures. G-CSF may be an interesting potential therapeutic target for facilitating physiological vascular remodeling for the prevention of adverse obstetric outcomes[33].

The safety of G-CSF use during pregnancy has been partially validated. A recent study by Atasoy Karakas et al. found no increased risk of adverse perinatal outcomes or congenital anomalies in twin pregnancies following G-CSF usage in assisted reproductive technology treatments. This was compared to a 2.1% anomaly rate in the control group. Although dichorionic diamniotic (DCDA) twin pregnancies inherently possess a higher risk of mortality and congenital anomalies than singleton pregnancies, this risk was not explicitly tied to G-CSF use in the study[34]. Thus, while G-CSF appears safe in reproductive treatments, further research is required to elucidate any potential risks fully.

In the present study, we evaluated the clinical efficacy and safety of G-CSF in preventing PE in a high-risk population. We hope this will provide new insights into the role of G-CSF as a preventative therapy, specifically focusing on its impact on key biomarkers such as PIGF and the sFlt-1/PIGF ratio.

Materials and Methods

Treatment Methods

In pregnant women with a history of adverse pregnancy outcomes and high risk for PE in the current pregnancy, prophylactic G-CSF treatment was administered in addition to routine medicines (heparin, aspirin, calcium replacement or calcium supplements, folic acid). After early pregnancy screening indicated a high risk of preeclampsia, patients began oral administration of aspirin (150 mg/day) and calcium supplements (1.5–2 g/day) from 12–16 weeks of gestation, continuing until 36 weeks, or until the onset of labor, or the development of preeclampsia. In this study, most of the patients enrolled were those with recurrent miscarriage or repeated implantation failure, with 73.3% of the patients having concomitant immune-related diseases, including thrombophilia, obstetric antiphospholipid syndrome, etc. Heparin is the expert consensus-recommended medication for such patients[35]. The use of heparin was strictly in accordance with the recommendations in the Chinese expert consensus on diagnosis and management of recurrent spontaneous abortion (2022)[36]. Additionally, patients routinely supplemented with folic acid at a dose of 0.4 mg/day during pregnancy. All included patients had signed informed consent forms prior to treatment. The dose of G-CSF was 2–4 μg/kg/d based on patient tolerance[37], subcutaneously injected every 48 ± 6 h. All pregnant women received G-CSF treatment for at least one week, with a median treatment duration of 4 (1–8) weeks and a median total drug exposure of 1725 (375–4600) μg.

The study protocol was approved by the hospital's ethics committee (J2023-S052). The patients in the study were required to meet the following inclusion criteria: (1) According to the pragmatic guide for first-trimester screening and prevention of the International Federation of Gynecology and Obstetrics (FIGO)[7], pregnant women with any one of the following high-risk factors or any two of the following moderate-risk factors are eligible for inclusion in this study. High-risk factors include: History of pre-eclampsia in a previous pregnancy, especially early-onset and with adverse outcomes; type 1 or type 2 diabetes; chronic hypertension; multiple pregnancies; kidney disease; potential vascular complications with autoimmune diseases (antiphospholipid syndrome, systemic lupus erythematosus). Moderate-risk factors include: nulliparity; obesity (BMI > 30 kg/m^2); family history of pre-eclampsia in mother or sister; age ≥ 35 years; personal risk factors, such as a history of delivering low birth weight or SGA baby, previous adverse pregnancy outcome (e.g., stillbirth), pregnancy interval >10 years, in vitro fertilization (Table 1). (2) 12–16 weeks' gestation, with biomarkers indicating high risk for PE (serum PIGF<32 pg/mL[38,39], and/or sFlt-1/PIGF ≥ 38) during 5–15 weeks of pregnancy; (3) Signed informed consent. (4) Moreover, pregnant women should not have allergies to study drugs.

Table 2 showed a total of 60 eligible patients with an average age of 31.38 ± 5.10 years old, body mass index (BMI) of 22.82 ± 3.27 kg/m^2, the median number of previous adverse pregnancy outcomes of 1.5 times, and 12 cases (20.0%) of assisted repro-

Table 1. Risk Factors for Preeclampsia.

Risk	Rating Description
High risk factors (1 or more)	History of pre-eclampsia in a previous pregnancy, especially early-onset and with adverse outcomes; type 1 or type 2 diabetes; chronic hypertension; multiple pregnancies; kidney disease; potential vascular complications with autoimmune diseases (antiphospholipid syndrome, systemic lupus erythematosus).
Moderate risk factors (2 or more)	nulliparity; obesity (BMI > 30 kg/m^2); family history of pre-eclampsia in mother or sister; age ≥ 35 years; personal risk factors, such as a history of delivering low birth weight or SGA baby, previous adverse pregnancy outcome (e.g., stillbirth), pregnancy interval >10 years; in vitro fertilization

Table 2. A total of 60 eligible patients' characteristics.

General Demographic Characteristics	All (n = 60)
Maternal age	31.38 ± 5.10
BMI (kg/m^2)	22.82 ± 3.27
Number of adverse pregnancies	1.5 (1−5)
Current Pregnancy Outcome	
Singleton	59 (98.3%)
Twin	1 (1.7%)
Current Conception Method	
Natural	37 (61.7%)
Monitored ovulation induction	11 (18.3%)
IVF	12 (20.0%)
Risk Factors for Pre-eclampsia	
UTPI	
≥ 1.5	32 (53.3%)
≥ 1.5	28 (46.7%)
Presence of Autoimmune Disease or History of Autoimmune Disease	44 (73.3%)
Insulin resistance or impaired glucose tolerance	37 (61.7%)
History of chronic hypertension or hypertension	2 (3.3%)
Primiparity	45 (75.0%)
BMI ≥ 35 kg/m^2	1 (1.7%)
Age ≥ 40	5 (8.3%)
Serum biomarker levels at enrollment＞10 years	6 (10.0%)
Interpregnancy Interval	
PIGF < 32 pg/mL	4 (6.7%)
sFlt-1/PIGF ≥ 38	32 (53.3%)
PIGF < 32 pg/mL and sFlt-1/PIGF ≥ 38	24 (40.0%)

Note: BMI, Body Mass Index; IVF, vitro fertilization; UTPI, Uterine artery pulsatility index; sFlt-1, soluble fms-like tyrosine kinase-1; PIGF, placental growth factor.

ductive technology for the current pregnancy. All patients were at high risk for PE, with 44 cases (73.3%) having concomitant autoimmune diseases, 37 cases (61.7%) having insulin resistance or impaired glucose tolerance, and two patients (3.3%) having chronic hypertension. Four cases (6.7%) had abnormal PIGF at enrollment, 32 cases (53.3%) had abnormal sFlt-1/PIGF, and 24 patients (40.0%) had abnormalities in both.

Biochemical assays

PIGF and sFlt-1/PIGF levels were monitored every four weeks until they returned to normal. Patients were followed up until delivery, and pregnancy outcomes for the mothers and infants were collected. The primary study endpoint was the incidence of pre-eclampsia. Secondary study endpoints were pregnancy outcomes, changes in PIGF and sFlt-1/PIGF before and after treatment, and safety of G-CSF treatment.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 software. Quantitative data were analyzed using descriptive statistics, with normally distributed data presented as mean ± standard deviation and non-normally distributed data as median (maximum, minimum). Count data were presented as the number and percentage of each category. A paired t-test or paired Wilcoxon signed-rank test was used to compare serum biomarker levels before and after treatment. A P-value < 0.05 was considered statistically significant.

Results

Incidence rate of PE

The data in Table 3 indicates that among the 60 patients included in the study, the incidence rate of progression to PE was 1.8% (1/56, 95% CI: [0.05%, 9.56%]). Seven patients (12.5%) resulted in preterm birth, and 44 subjects (78.6%) underwent cesarean section. Fifty-seven newborns (one mother gave birth to twins) were followed up, with an average birth weight of 3022.28 ± 554.91 g, seven cases (12.8%) of low birth weight (< 2500 g), and one case (1.8%) of high birth weight (> 4000 g). No cases of asphyxia, perinatal death, or fetal growth restriction were observed. What needs illustration is that 4 patients were lost to follow-up and remain uncontactable to date, and one progressed to the pre-eclampsia stage among the 60 patients in our study.

Table 3. Pregnancy Outcomes for Mothers.

Maternal Clinical Outcomes	All (n = 56)
Severe pre-eclampsia	1 (1.8%)
Abdominal effusion	1 (1.8%)
Acute kidney injury	1 (1.8%)
Preterm delivery	7 (12.5%)
Mode of Delivery	
Vaginal delivery	12 (21.4%)
Cesarean section	44 (78.6%)

Note: Four patients were lost to follow up.

Changes of serum biomarker levels in PIGF and sFlt-1/PIGF ratio

The data in Table 4 showed that serum PIGF levels significantly increased by 316.2% (35.2 ± 14.5 vs. 146.5 ± 91.4, $P < 0.001$), and serum sFlt-1/PIGF levels significantly decreased by 70.0% (59.3 ± 20.5 vs. 17.8 ± 10.6, $P < 0.001$) after treatment (Table 5).

Table 4. Pregnancy Outcomes for Neonates.

Neonatal Clinical Outcomes	All (n = 57)
Birth Weight (g)	3022.28 ± 554.91
Weight <2500 g	7 (12.3%)
2500 g ≤ weight ≤ 4000 g	49 (85.9%)
Weight >4000 g	1 (1.8%)
Sex of Neonate	
Male	34 (59.6%)
Female	23 (40.4%)
Neonatal asphyxia	0 (0.0%)
Perinatal death	0 (0.0%)
Fetal growth restriction	0 (0.0%)

Note: among the 56 patients who could be followed up, one gave birth to a pair of twins.

Table 5. Serum biomarker levels of pregnant women before and after treatment.

Serum Biomarkers	PIGF (n = 60)	sFlt-1/PIGF (n = 60)
Before treatment	35.2 ± 14.5	59.3 ± 20.5
After treatment	146.5 ± 91.4	17.8 ± 10.6
P-value	< 0.001	< 0.001
Before treatment abnormality	25 (41.7%)	56 (93%)
After treatment abnormality	1 (7.0%)	2 (3.3%)
P-value	< 0.001	< 0.001

Note: PIGF and sFlt-1/PIGF levels were monitored every 4 weeks; PIGF, placental growth factor; sFlt-1: soluble fms-like tyrosine kinase-1.

Adverse reactions to G-CSF

The main adverse events during G-CSF treatment were dizziness (20.0%), fatigue (15.0%), muscle pain (10.0%), nausea (5.0%), and headache (5.0%), as described in Table 6. Patients received heparin, aspirin, calcium replacement or supplements, and folic acid during G-CSF treatment. All patients tolerated the treatment well without requiring any additional special interventions. Some adverse events were related to the physiological status of pregnant women, and no grade 3 or higher adverse events were observed.

Table 6. Adverse events during treatment.

Adverse Event Category	All (n = 60)
Neurological Adverse Events	
Dizziness	12 (20.0%)
Headache	3 (5.0%)
Systemic Disease and Site Reactions	
Fatigue	9 (15.0%)
Fever	1 (1.7%)
Musculoskeletal and Connective Tissue Adverse Events	
Muscle pain	6 (10.0%)
Limb pain	2 (3.3%)
Gastrointestinal Disease	
Nausea	3 (5.0%)

Note: Adverse reactions occurring during hospitalization at any level will be reported and recorded.

Discussion

In cases of high risk for PE, low-dose aspirin can reduce the incidence of PE and related adverse pregnancy outcomes (premature birth, fetal growth restriction) by 10–20%. In addition to low-dose aspirin, the INOVASIA Study explored the efficacy of prevention using a combination of low-dose aspirin, calcium, and pravastatin[30]. We included G-CSF as an intervention to prevent preeclampsia in the present study. This intervention may have played a positive role in preventing the progression of preeclampsia, enabling us to maintain a low incidence of preeclampsia even among patients with relatively higher risk. Moreover, patients at high risk of PE and with insufficient PIGF expression at 12 weeks of pregnancy are likely to experience a decrease in PIGF and adverse pregnancy outcomes if not intervened[40]. Thus, the preventive medication regimens for high-risk pre-eclampsia, consisting of G-CSF combined with heparin, aspirin, calcium substitutes or calcium supplements, and folic acid, demonstrated a high efficacy rate in this study.

The International Federation of Gynecology and Obstetrics (FIGO) recommends early pregnancy screening and prevention guidelines for pre-eclampsia, and it is believed that an sFlt-1/PIGF ratio ≥ 38 indicates that pregnant women may develop PE within four weeks after examination[41]. Early intervention with G-CSF may change the pregnancy outcomes for pregnant women with a high risk of PE. Previous studies have shown that G-CSF expression is downregulated in pre-eclamptic pregnant women compared to those with normal blood pressure. The downregulation of G-CSF may be related to insufficient trophoblast invasion and impaired angiogenesis in pre-eclamptic women[42,43].

Our retrospective study found that for pregnant women identified as high-risk through both risk factor screening and biomarker testing in early pregnancy, the addition of Granulocyte Colony-Stimulating Factor (G-CSF) to the treatment regimen of aspirin and calcium supplements can further reduce the incidence of preeclampsia. Moreover, this combined treatment approach effectively corrects the imbalance of PlGF and sFlt-1 levels. In our study, the incidence of preeclampsia was as low as 1.8%. In contrast, previous studies involving similar high-risk populations have reported that the incidence of preeclampsia can reach up to 35% with treatment using aspirin and calcium supplements alone, with a further imbalance in the ratio of placental growth factor (PlGF) to soluble fms-like tyrosine kinase-1 (sFlt-1). Even with the addition of pravastatin to the treatment regimen, the incidence of preeclampsia remained as high as 17.5%.

The administration of G-CSF in pregnant individuals has been established as a safe, efficacious, and well-tolerated therapeutic option. Extensive research dating back to 1998 underscores its capacity to bolster neonatal resilience and elevate Absolute Neutrophil Count (ANC) among women with profound neutropenia[44], without any adverse consequences on healthy newborns[45,46]. A 2010 report further underscores the substantial elevation in pregnancy rates among women with severe chronic neutropenia following long-term G-CSF therapy[47]. Notably, even in exceptional scenarios such as peripheral blood stem cell and bone marrow transplantation, G-CSF can be administered without eliciting detrimental effects on the fetus[48]. The dosage of G-CSF must be meticulously titrated based on individual patient's physiological responses, with a recommended safe dosage range of 2–4 μg/kg/day[49].

It is imperative to acknowledge the inherent limitations of our study. Firstly, being a retrospective investigation, we compared and analyzed the clinical outcomes of high-risk preeclampsia (PE) patients who received G-CSF in addition to conventional treatment [Aspirin (150 mg/d) and calcium supplements (1.5–2 g/d) were administered orally from 12–16 weeks of gestation until 36 weeks of gestation or delivery or diagnosis of preeclampsia.] within a relatively short period and with limited resources. We found that G-CSF may have reduced the risk of PE occurrence to some extent. However, compared with rigorously designed and well-documented randomized controlled trials, our study conclusions lack persuasiveness. Secondly, owing to constraints in follow-up capabilities, we were unable to obtain pregnancy follow-up data for four patients despite our diligent efforts to contact the relevant parties. Consequently, our study necessitates further validation via large-scale randomized controlled trials. The proposed mechanisms of action and treatment protocols involving G-CSF in this study are grounded in prior research conducted among pregnant women with recurrent miscarriages. For pregnant women at heightened risk of pre-eclampsia, the role of G-CSF in regulating trophoblast cell activity and modulating pregnancy-related immune responses warrants deeper investigation. Additionally, optimal dosing schedules, frequencies, and durations of treatment require exhaustive exploration.

Conclusions

In conclusion, this study explored the clinical efficacy and safety of the prophylactic use of G-CSF in pregnant women at high risk for preeclampsia. The short-term safety of G-CSF in these women was found to be tolerable within a dose range of 2–4 μg/kg/day. Furthermore, G-CSF was effective in preventing the development of preeclampsia in 91.7% of high-risk pregnant women, as observed in 60 clinical cases, by positively correcting the imbalance of PIGF and sFlt-1 levels.

Abbreviation

ANC, Absolute Neutrophil Count; BMI, Body Mass Index; CI, Confidence Interval; DCDA, Dichorionic Diamniotic; FIGO, International Federation of Gynecology and Obstetrics; G-CSF, Granulocyte Colony-Stimulating Factor; hCG, human Chorionic Gonadotropin; IL, Interleukin; IVF, In Vitro Fertilization; PE, Preeclampsia; PlGF, Placental Growth Factor; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, Small for Gestational Age; SPSS, Statistical Package for the Social Sciences; Th17, T helper 17 cells; Treg, Regulatory T cells; UTPI, Uterine Artery Pulsatility Index; VEGF, Vascular Endothelial Growth Factor; VSMC, Vascular Smooth Muscle Cell.

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Conflicts of interest

The authors affirm that they do not have any known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First People's Hospital of Guiyang City, with the approval number (J2023-S052). All procedures performed in studies involving human participants were under the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients signed a written informed consent form before treatment.

Authors' contribution

XFW wrote the article and collected/organized data. ALW reviewed the article, managed patients, and collected data. ZHS reviewed the article and contributed to the research design. All authors reviewed the article.

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