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EXPERIENCE IN THE TREATMENT OF IRON DEFICIENCY ANEMIA IN PREGNANT WOMEN AT RISK OF OBSTETRIC HEMORRHAGE

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Introduction. Iron deficiency anemia (IDA) complicates approximately 30–60 % of pregnancies worldwide. Maternal consequences of IDA include preterm birth, placental abruption, preeclampsia, and cesarean section.

The aim of the work is to evaluate the efficacy of parenteral therapy for moderate and severe iron deficiency anemia in pregnant women at high risk for obstetric hemorrhage.

Materials and methods. We conducted a prospective study to evaluate the effectiveness of treatment for moderate and severe IDA in 34 pregnant women at 28–30 weeks of gestation. A single dose of 500 mg of iron was administered 2–3 times in total. Control laboratory analyses were performed after 8, 14, and 21 days.

Results. Group I consisted of 12(35.3 %) women with severe anemia, while Group II included 22(64.7 %) pregnant women with moderate anemia. The obstetric history was complicated by uterine scars after cesarean section in 26(76.5 %) pregnant women; 16(72.7 %) had placenta previa, including 8(36.4 %) with placenta accreta. Following treatment with intravenous iron preparations, restoration of iron stores and an increase in hemoglobin levels began within 7–10 days, and by 3 weeks, hemoglobin, ferritin, and serum iron levels had reached values favorable for safe delivery. Among these women, hysterectomy was performed in only 5(14.7 %) cases, and blood transfusion was required in 3(8.8 %) cases.

Conclusions. Thus, effective interventions, including treatment of anemia before childbirth, made it possible to preserve reproductive function in 88 % of women at high obstetric risk. Treatment of anemia in pregnant women at high risk for massive obstetric hemorrhage with parenteral iron preparations effectively increased hemoglobin and ferritin levels 2–3 weeks after the last administration of the drug and may be recommended for use in practical obstetrics.

Keywords: iron deficiency anemia in pregnancy, complications, bleeding, mode of delivery, iron preparations.

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ДОСВІД ЛІКУВАННЯ ЗАЛІЗОДЕФІЦИТНОЇ АНЕМІЇ У ВАГІТНИХ ГРУПИ РИЗИКУ АКУШЕРСЬКИХ КРОВОТЕЧ

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Анемія є глобальною проблемою охорони здоров'я та ускладнює до 60 % вагітностей. Своєчасна діагностика та корекція мають велике значення для покращення перинатальних наслідків. У роботі досліджено ефективність парентеральної терапії залізодефіцитної анемії середнього та тяжкого ступенів у 34 вагітних (28–30 тиж. гестації). Усі пацієнтки з групи високого ризику щодо акушерської кровотечі з огляду на ускладнення вагітності (передлежання плаценти, placenta accreta) та обтяжений акушерський анамнез (рубці на матці після оперативних утручань). Внутрішньовенні препарати заліза ефективно підвищили рівень гемоглобіну, феритину через 2–3 тижні, що дозволяє рекомендувати метод для практичного акушерства. Адже завдяки ефективному лікуванню збережено репродуктивну функцію у 88 % жінок з групи високого акушерського ризику.

Ключові слова: залізодефіцитна анемія вагітних, ускладнення, кровотечі, метод розродження, препарати заліза.

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Стаття поширюється на умовах ліцензії

Introduction

Anemia is a global public health problem. The World Health Assembly endorsed a global nutrition target of a 50 % reduction in anemia among women of reproductive age by 2025 [1]. The World Health Organization (WHO) estimated the global burden of anemia-related deaths among women of reproductive age at approximately 16.800–28.000 deaths per year [2].

Iron deficiency anemia (IDA) complicates approximately 30–60 % of pregnancies worldwide. The proportion of pregnancy- and childbirth-related mortality attributable to iron deficiency anemia is unknown [3; 4].

It is known that isolated iron deficiency (iron deficiency without anemia, referred to as latent iron deficiency) and IDA in pregnant women increase maternal morbidity and mortality. Maternal consequences of IDA include impaired thyroid function, preterm birth (OR 1.54; 95 % CI, 1.36–1.76), placental abruption, preeclampsia, eclampsia, and cesarean section (OR 1.30; 95 % CI, 1.13–1.49) [5]. Maternal IDA is associated with an increased risk of postpartum depression, reduced quality of life, severe postpartum hemorrhage, maternal shock, more frequent admission of mothers to intensive care units, hysterectomy, antenatal and postpartum maternal sepsis, the need for blood transfusion (OR 5.48; 95 % CI, 4.57–6.58), poor wound healing, heart failure, and even maternal death (OR 2.36; 95 % CI, 1.60) [6–10].

During pregnancy, plasma volume increases by approximately 40–50 %, whereas red blood cell mass increases by only 15–25 %. This expected physiological change is reflected in a decrease in hemoglobin and hematocrit levels. Fetal growth and placental requirements result in a threefold increase in iron requirements during the second and third trimesters [9–11]. Despite physiological amenorrhea during pregnancy and increased iron absorption, most pregnant women cannot maintain adequate stores of this micronutrient without additional supplementation, particularly during the second and third trimesters.

During pregnancy, IDA is associated with adverse effects on fetal nervous system development, including an increased risk of autism spectrum disorders, intellectual disability, attention-deficit/hyperactivity disorder, and other persistent psychosocial dysfunctions in offspring [12–14]. To meet the increasing need for iron for fetal development and during lactation, an additional amount of exogenous iron is required. Overall, approximately 1000 mg of iron is lost during pregnancy and lactation. As a result, pregnant women should consume 27 mg of iron daily. During lactation, a daily intake of 10 mg of iron is required [10–13].

Severe iron deficiency is defined as a serum ferritin level below 20–30 ng/mL, while mild or moderate iron deficiency is defined as a level below 70–100 ng/mL. Ferritin levels are used as a reserve marker for identification. Ferritin is a soluble iron depot required for normal erythrocyte formation. One ferritin molecule can bind up to 4500 iron atoms in the form of a hydroxide and phosphate complex. At the same time, it protects the body from the toxic effects of iron by storing it in the oxidized trivalent state, which is unable to catalyze free radical production. Ferritin is present in small amounts in the blood serum, where it enters as a result of active secretion and cell destruction, and its concentration allows assessment of iron stores in the body [14; 15].

Oral iron is poorly tolerated by pregnant women, and there is increasing evidence supporting the greater efficacy and reduced adverse effects of intravenous iron preparations. Parenteral administration of iron preparations has been safe and effective in numerous studies involving pregnant women.

Recently, new type II and type III iron complexes have been developed that can be used for rapid replenishment of iron stores. Parenteral administration of iron preparations continues to be underutilized due to concerns regarding the acceptability of previous intravenous iron preparations, despite the growing body of evidence supporting the safety of newer preparations in pregnant women [14].

The FER-ASAP study included pregnant women with IDA, and the results demonstrated the superiority of intravenous iron preparations over oral preparations in terms of hemoglobin concentration, which was maintained for more than 6 weeks. Thus, hemoglobin levels increased in women with mild, moderate, and severe IDA and in women with iron deficiency alone 2–3 weeks after infusion ($p < 0.01$ for all). No serious adverse effects were reported; minor transient adverse reactions (including local skin irritation, nausea, and headache) were recorded in only 11 % of women. No adverse effects on the fetus or newborn were observed [15].

Compared with oral iron preparations, parenteral administration demonstrates a significant reduction in the severity of IDA during pregnancy and the postpartum period, provides a more rapid increase in hemoglobin concentration, safely corrects iron deficiency in pregnant women, and does not cause hemoconcentration. Such an approach is more likely to prevent adverse maternal outcomes and minimize the development of adverse reactions. In addition, numerous clinical trials have shown that parenteral administration of iron preparations is safe during the second and third trimesters of pregnancy [16–19]. At the same time, the need for such correction is increasing substantially because, according to current studies, prolonged exposure to an armed conflict zone has led to an increase in the incidence of extragenital pathology and bleeding in pregnant women due to severe psychological and social stress [20]. Parenteral iron therapy has made a significant contribution to the treatment of IDA in pregnant women.

Aim of the study – to evaluate the effectiveness of parenteral therapy for moderate and severe iron deficiency anemia in pregnant women at high risk of obstetric hemorrhage.

Materials and Methods

A prospective study was conducted to evaluate the effectiveness of treatment of moderate and severe IDA in 34 pregnant women at 28–30 weeks of gestation using parenteral iron preparations. The control group included 50 women at 28–32 weeks of gestation without signs of anemia at the time of enrollment and throughout the entire observation period. Group I consisted of 12 women with severe anemia, and Group II included 22 pregnant women with moderate anemia. The diagnosis of iron deficiency was established and confirmed by appropriate laboratory tests (determination of plasma ferritin levels, serum iron, hemoglobin, hematocrit, and erythrocyte count). The treatment protocol included

intravenous administration of iron (ferric carboxymaltose) at a dose of 500 mg at intervals of 5–7 days: patients in Group I received three intravenous administrations of the drug, while patients in Group II received two infusions. Control laboratory tests were performed 8 days and 2 and 3 weeks after the initiation of treatment.

Given the small size of the study groups, quantitative variables (hemoglobin, ferritin, serum iron levels, etc.) were presented as the median (Me), and between-group differences were assessed using the Mann–Whitney U test. Categorical variables were presented as relative values and their errors (P ± p, %), and were compared using Pearson's χ^2 test or Fisher's exact test.

All studies were conducted in accordance with the principles of the World Medical Association Code of Ethics (Declaration of Helsinki). The Declaration of Helsinki of the World Medical Association (WMA) is a fundamental international document establishing ethical principles for medical research involving human subjects, including work with biological materials and personal data. Adopted in 1964, it serves as a major guideline for bioethics, protecting the rights, safety, and dignity of patients.

Research results and their discussion

According to the data from our study, pregnant women with severe anemia had inadequate nutrition and lived in difficult social conditions in 83.3 % of cases. More than 80 % of all pregnant women with anemia were multiparous women, and one in four of them had a history of more than 5 deliveries. An interval of less than 2 years between deliveries was reported in 30 % of the women examined. Among extragenital pathology, kidney diseases were present in 40 % of pregnant women.

The obstetric history was complicated by uterine scars after cesarean section in 26(76.5 %) pregnant women, of whom 14(63.6 %) had undergone more than 3 cesarean sections. Placenta previa was present in 16(72.7 %) women, of whom 8(36.4 %) had placenta accreta. The above-mentioned group of pregnant women with placentation abnormalities and anemia has the highest risk of pathological bleeding during operative delivery. Treatment of anemia before delivery is an important measure for preventing adverse maternal outcomes.

The clinical and anamnestic characteristics, features of pregnancy course in the study patients, and possible factors contributing to the development of anemia are presented in Table 1.

Analysis of the obtained data demonstrated that patients in Groups I and II had a significantly higher level of somatic and obstetric complications compared with the control group ($p < 0.05$).

The laboratory examination data at admission, presented in Table 2, indicate that pregnant women with anemia had decreased levels of hemoglobin, erythrocytes, color index, serum iron, and ferritin. In pregnant women with severe IDA, the ferritin level was substantially decreased to 12.8 ng/mL, and serum iron was 15.6 μmol/L. Thus, before the initiation of treatment, pregnant women in Groups I and II demonstrated a statistically significant decrease in the main hematological parameters compared with the control group ($p < 0.05$).

Analysis of the course of pregnancy (Fig. 1) established that pale skin and mucous membranes were observed in 100 % of women with severe anemia, general weakness in 92 %, and drowsiness and decreased appetite in 66 %. The threat of preterm birth was observed in half of the pregnant women in Group I and in 32 % of patients in Group II.

Table 1

Course of pregnancy in the examined women

Course of pregnancy	Group I (n = 12)		Group II (n = 22)		Control (n = 50)	
	Abs. No.	P ± p, %	Abs. No.	P ± p, %	Abs. No.	P ± p, %
Primigravidas	0	0.0 ± 0.0	4	18.2 ± 8.2	21	42.0 ± 7.0
Multiparous women	10	83.3 ± 10.8*	18	81.8 ± 8.2*	5	10.0 ± 4.2
>3 deliveries	1	8.3 ± 8.0	8	36.4 ± 10.3	3	6.0 ± 3.4
>4 deliveries	6	50.0 ± 14.4*	6	27.3 ± 9.5*	2	4.0 ± 2.8
>5 deliveries	3	25.0 ± 12.5*	4	18.2 ± 8.2*	0	0.0 ± 0.0
Inadequate nutrition	10	83.3 ± 10.8*	8	36.4 ± 10.3*	2	4.0 ± 2.8
Kidney diseases	5	41.7 ± 14.2*	9	40.9 ± 10.5*	4	8.0 ± 3.8
Cardiovascular diseases	2	16.7 ± 10.8	4	18.2 ± 8.2	2	4.0 ± 2.8
Gestational diabetes mellitus	2	16.7 ± 10.8	2	9.1 ± 6.1	3	6.0 ± 3.4
Threatened pregnancy termination with bleeding	2	16.7 ± 10.8	8	36.4 ± 10.3	6	12.0 ± 4.6
Placenta previa	6	50.0 ± 14.4*	10	45.5 ± 10.6*	2	4.0 ± 2.8
Placenta accreta	4	33.3 ± 13.6*	4	18.2 ± 8.2*	0	0.0 ± 0.0
Uterine scar after cesarean section	9	75.0 ± 12.5*	17	77.3 ± 8.9*	7	14.0 ± 4.9
1 cesarean section	1	8.3 ± 8.0	4	18.2 ± 8.2	6	12.0 ± 4.6
2 cesarean sections	2	16.7 ± 10.8*	5	22.7 ± 8.9*	1	2.0 ± 2.0
3 cesarean sections	4	33.3 ± 13.6*	6	27.3 ± 9.5*	0	0.0 ± 0.0
4 cesarean sections	2	16.7 ± 10.8	2	9.1 ± 6.1	0	0.0 ± 0.0
Cervical suture	0	0.0 ± 0.0	2	9.1 ± 6.1	2	4.0 ± 2.8

Note. **Abs. No.** – absolute number of cases; **P** – relative value (%); **p** – error of the relative value (%); * – statistically significant difference compared with the control group ($p < 0.05$).

Table 2

Laboratory examination data of pregnant women before treatment

Laboratory parameters	Group I (n = 12)	Group II (n = 22)	Control group (n = 50)
Hemoglobin, g/L	65.8 ± 1.4	78.5 ± 1.1	118.5 ± 1.2
Erythrocytes, 10^{12}/L	2.28 ± 0.08	2.98 ± 0.06	3.95 ± 0.05
Hematocrit, %	32.0 ± 0.8	36.0 ± 0.6	37.8 ± 0.4
Color index	0.70 ± 0.02	0.80 ± 0.01	0.92 ± 0.01
Platelets, 10^9/L	185.0 ± 5.2	210.0 ± 4.1	225.0 ± 4.8
Reticulocytes, %	0.50 ± 0.04	0.90 ± 0.03	1.10 ± 0.05
Leukocytes, 10^9/L	10.6 ± 0.4	12.5 ± 0.5	8.2 ± 0.3
Ferritin, ng/mL	12.8 ± 0.9	28.5 ± 1.2	45.2 ± 1.9
Serum iron, µmol/L	15.6 ± 0.8	32.8 ± 1.4	18.6 ± 0.7

Note. Data are presented as M ± m (arithmetic mean ± standard error of the mean); the difference between the parameters in Groups I and II and the control group is statistically significant for all parameters ($p < 0.05$).

Fetal growth restriction was diagnosed in 84 % of women in Group I and 65 % of women in Group II. Therefore, maternal anemia contributed to impaired fetoplacental blood flow and the development of this complication. Moderate preeclampsia was present in half of all women with IDA examined. Thus, IDA in pregnant women had an adverse effect on the course of pregnancy and fetal condition.

The following treatment with parenteral iron preparations (ferric carboxymaltose) at a dose of 500 mg was administered: pregnant women in Group I received the drug three times at intervals of 5–7 days, while pregnant women in Group II received it twice. After the first administration of the drug, 50 % of pregnant women reported an improvement in their general condition, a decrease in fatigue, and improvement in appetite and mood.

Laboratory examinations were performed after 8 days and after 2 and 3 weeks. The results of the laboratory examinations (Fig. 2) indicate that restoration of iron stores and an increase in hemoglobin levels begin within 7–10 days after the initiation of treatment, and after 2–3 weeks, hemoglobin, ferritin, and serum iron levels reach normal values, contributing to safe delivery.

All examined pregnant women were at high risk of pathological obstetric hemorrhage due to existing obstetric pathology (placenta previa and placenta accreta), a complicated obstetric history (uterine scar after multiple surgical interventions), and anemia. Vaginal deliveries proceeded physiologically without complications. Cesarean section was performed in 26(76.5 %) pregnant women due to uterine scar, placenta previa, and placenta accreta. For the purpose of surgical hemostasis and to reduce blood loss, temporary balloon occlusion of the aorta was performed in 4(11.7 %) women, which reduced blood loss. Hysterectomy was performed in only 5(14.7 %) women due to placenta accreta, and hemotransfusion was performed in 3(8.8 %) cases. The course of labor in patients in Groups I and II was characterized by a higher frequency of preterm delivery at 35–36 weeks of gestation (66.7 ± 13.6 % and 63.6 ± 10.3 %, respectively), unlike the control group, in which all women (100.0 %) delivered at 37–38 weeks of gestation. Table 3 presents the gestational age and mode of delivery.

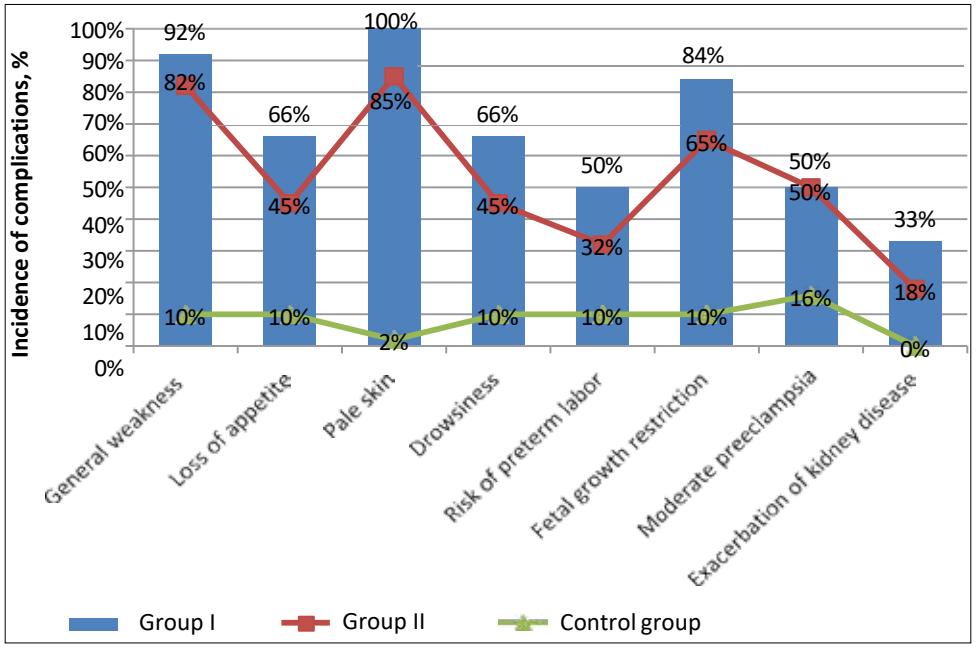


Fig. 1. Complications of pregnancy in the examined women

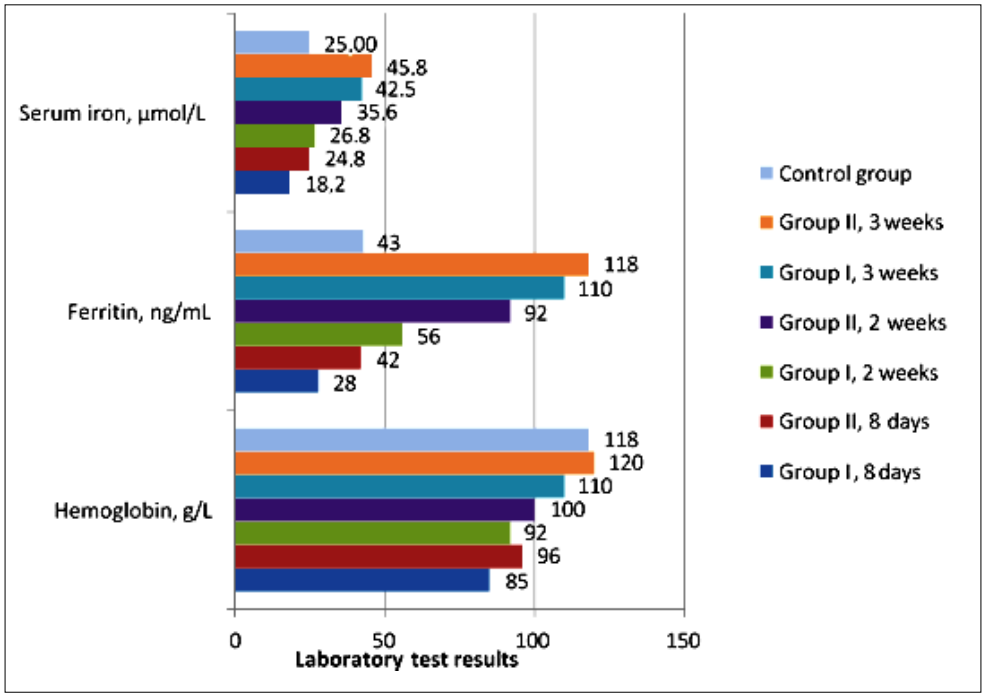


Fig. 2. Laboratory examination data of pregnant women after treatment

Table 3

Gestational age and mode of delivery in pregnant women of the study groups

Gestational age and mode of delivery	Group I (n = 12)		Group II (n = 22)		Control group (n = 50)	
	Abs. No.	P ± p, %	Abs. No.	P ± p, %	Abs. No.	P ± p, %
Delivery at 37–38 weeks of gestation	3	25.0 ± 12.5*	8	36.4 ± 10.3*	50	100.0 ± 0.0
35–36 weeks of gestation	8	66.7 ± 13.6*	14	63.6 ± 10.3*	0	0.0 ± 0.0
34 weeks of gestation	1	8.3 ± 8.0	0	0.0 ± 0.0	0	0.0 ± 0.0
Vaginal delivery	3	25.0 ± 12.5*	5	22.7 ± 8.9*	48	96.0 ± 2.8
Cesarean section	9	75.0 ± 12.5*	17	77.3 ± 8.9*	2	4.0 ± 2.8
Devasculari-zation of uterine vessels	5	41.7 ± 14.2*	6	27.3 ± 9.5*	0	0.0 ± 0.0
Temporary balloon occlusion of the aorta	3	25.0 ± 12.5*	1	4.5 ± 4.4	0	0.0 ± 0.0
Hysterectomy	3	25.0 ± 12.5*	2	9.1 ± 6.1	0	0.0 ± 0.0
Pathological blood loss	2	16.7 ± 10.8*	1	4.5 ± 4.4	0	0.0 ± 0.0
Hemotrans-fusion	2	16.7 ± 10.8*	1	4.5 ± 4.4	0	0.0 ± 0.0

Note. Abs. No. – absolute number of cases; P – relative value (%); p – error of the relative value (%); * – statistically significant difference compared with the control group ($p < 0.05$).

Thus, due to effective interventions (treatment of anemia before delivery), it was possible to preserve reproductive function in 88 % of women in the high obstetric risk group.

Conclusions

At late stages of pregnancy, when operative delivery is planned, the time before delivery is a limiting factor; therefore, the administration of parenteral iron preparations is a more appropriate option for rapid and effective correction of anemia, especially for those with severe IDA. The results of laboratory examinations indicate that restoration of iron stores and an increase in hemoglobin levels begin within 7–10 days after the initiation of treatment, and after 2–3 weeks, hemoglobin, ferritin, and serum iron levels reach normal values, contributing to safe delivery. Treatment of anemia in pregnant women at high risk of massive obstetric hemorrhage with parenteral iron preparations effectively increased hemoglobin and ferritin levels and contributed to a reduction in blood loss during delivery, as well as a reduction in the frequency of hysterectomy and hemotransfusion, which may be recommended for practical obstetrics.

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