

THE PHARMA INNOVATION

The Ways of Improving Treatment of Anemia in Pregnant Women

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In this article the examination data of 124 pregnant women with anemia in the third trimester of pregnancy is presented, 30 pregnant women - with physiological course of pregnancy. It was noticed that, in pregnant women with iron deficiency anemia with an adequate level of sEPO (serum erythropoietin) after treatment with iron supplements a positive effect was achieved. In pregnant women with an inadequate level of sEPO who received only iron supplements, positive changes were not noticed. It is shown that, in pregnant women with an inadequate levels sEPO who along with iron supplements were receiving rEPO (recombinant erythropoietin) a positive dynamics was observed after treatment. Clinical effect in pregnant women who were receiving iron supplements along with rEPO appeared more rapidly and was more pronounced than in patients treated with conventional therapy. We have marked the positive effects of the proposed treatment on gestation course.

Keyword: Anemia Treatment in Pregnant Women, Recombinant Erythropoietin, Iron.

INTRODUCTION: Anemia challenges the course of pregnancy, childbirth, and postnatal period, adversely affects the intrauterine condition of a fetus and a newborn [1,4].

However, despite urgency and importance of anemia problem in pregnant women and its threatening effects on a fetus, general traditional methods of anemia treatment, including the use of iron supplements and vitamins, are used in obstetric practice up to now. Practice shows lack of effectiveness of this therapy, and conduction of blood transfusions in pregnant women is harmful [2, 3].

Therefore, research and introduction of new effective treatment methods of this disease is

essential for maintaining of health and reproductive function of women, reduction of perinatal loss.

On the basis of studied literature [5,8,10] and received own results, the use of rEPO medicine for treatment of gestational anemia in combination with iron supplements we considered etiologically and pathogenetically reasoned, which will enable to accelerate the process of erythropoiesis and therefore, more likely to achieve positive effect of treatment and influence the course of the postnatal period. When we had added rEPO medicine to a complex scheme of anemia treatment in pregnant, we persuaded not only the goal to combine the principle of substitution therapy with iron

supplements and the principle of hematopoiesis stimulation with erythropoietin and to accelerate the achievement of the effect, due to the fact that erythropoietin accelerates the growth, proliferation and differentiation of early progenitor cells of erythropoiesis, accelerates the synthesis of haemoglobin in erythrocyte [3,7,9]. The latter one is especially necessary for patients before the birth, when it is important to achieve faster results for the prevention of postnatal complications.

THE AIM OF RESEARCH:

To improve anemia treatment effectiveness in pregnant women on the basis of evaluation of erythropoietin production adequacy and development of differentiated treatment approaches.

MATERIAL AND METHODS.

124 pregnant women with anemia of moderate and severe stages during the third trimester of gestation were under supervision, they were treated at the departments of Obstetric Pathology and Extragenital Pathology of the Regional Perinatal Center in Ivano-Frankivsk. All pregnant women with anemia were divided into two groups: the first group of pregnant - with moderate anemia (63 persons), pregnant women of the second group - with severe anemia (61 persons). 30 pregnant women constituted a control group - with physiological course of pregnancy. During the study of socio-demographic characteristics of surveyed pregnant women was found that the average age of women with anemia of moderate severity was $23,6 \pm 0,7$, with severe anemia - $27,3 \pm 0,7$, in a control group - $24,7 \pm 0,7$.

Determination of general blood analysis was performed on hematology analyzer BC - 3000 plus / VS - 2800, automatic (BC - 3000 plus / BC - 2800 Auto Hematology Analyzer.) made by "Mindray", China.

Reticulocyte production index was calculated (RPI) in cases of severe anemia, which allowed to determine the type of erythropoiesis. The value of

this index was calculated according to the formula:

$$RPI = \text{Ret}\% \times \text{Hct}\% / 45 \times 1,85,$$

where

RPI - index of reticulocytes production,

Ret% - content of reticulocytes in %,

Hct% - the value of hematocrit with normal blood parameters in %,

1,85 - time of reticulocytes maturation.

A set, made by the firm "Filist - Diagnostics" (Ukraine), was used to determine iron concentration, iron binding capacity of blood serum and the percentage of transferrin saturation.

Determination of erythropoietin level in human blood serum was performed by an immunoenzyme technique with a test set "Vector-Best", Russia. Indices of sEPO level in pregnant women with moderate and severe anemia were significantly heterogeneous. For a detailed analysis of the level of sEPO production we used the method for assessing the adequacy of EPO proposed by Barosi G. [6] in pregnant women with anemia by studying the correlation of sEPO and hematocrit. Nomographic method of laboratory results interpretation through computer processing was used. The results were presented in the form of scatter chart constructed with the help of Microsoft Excell XP. We received distribution of the sEPO values depending on hematocrit indices. The level of sEPO was considered an adequate when the resultant point was within the confidence interval. When this point was situated below the confidence interval limit – it indicated about an inadequate production of sEPO.

Statistical analysis of data was performed with the use of a standard program STATISTICA 7.0. Likelihood assessment of average numbers differences was performed using paired Student t-test. Indices were considered credible at $p < 0.05$.

RESULTS:

Iron substituting therapy (200 mg /day for elemental iron) was prescribed to all pregnant women with moderate and severe anemia for two-three weeks. After a course of iron substituting therapy with iron supplements we found that not in all pregnant women with anemia positive effect of the therapy was achieved. Thus, in 98 (79,0±3,7%) pregnant observed positive effects of the proposed treatment, in 22 (17,7±3,4%) of pregnant women the effect of treatment was not noticed, $p<0.05$, and in 4 (3,2±1,6%) of pregnant women a negative dynamics of haemoglobin level took place after the therapy, $p<0.05$.

When comparing the indices of sEPO level in pregnant women with anemia with the indices of sEPO level in pregnant women with physiological course of pregnancy we have found that a sufficient level of sEPO occurred in 33(26,6± 3,9%) of pregnant women with anemia. An inadequate sEPO level was diagnosed in 3 (2,4±1,4%) pregnant women with anemia. In 88 (70,9±4,1%) pregnant women with anemia the indices of sEPO level were significantly higher in comparison with a control group.

Therefore, the analysis of the literature and of our research has served as a reason for sEPO and hematocrit correlation study. In regard with this fact, we have studied the adequacy of EPO production for anemia during pregnancy, using the method of Barosi G. [6].

The research has found that in 98 (79,0±3,7%) of pregnant women an adequate level of sEPO to anemia degree took place, in 26 pregnant women (21,0±3,7%) an inadequate level of sEPO to anemia degree was diagnosed. Concerning this fact, on the basis of sEPO levels analysis and detection of an inadequate EPO production phenomenon, pregnant women from two groups were divided into the following subgroups:

- A. Pregnant women with an adequate level of sEPO, n=98,
- B. Pregnant women with an inadequate level of sEPO, n=26.

As a result of an inadequate EPO production detection in pregnant women with moderate and severe anemia, on this basis we have proposed to include to treatment complex of anemia in pregnant women recombinant erythropoietin for the first time.

Standard iron substituting therapy (200 mg/day for elemental iron) was appointed to all pregnant women with an adequate level of sEPO, standard iron substituting therapy was appointed to 10 pregnant women with an inadequate level of sEPO, standard iron substituting therapy in combination with rEPO in a course dose of 450 IU / kg were appointed to 16 pregnant women with an inadequate level of sEPO. Analysis of clinical effect of treatment showed that in pregnant women with anemia with an adequate level of sEPO who took iron supplements only, complaints that were noticed before treatment, were preserved for a longer time, and only after completion of therapy 59 (60,2±4,9%) of 98 pregnant women experienced a reduction of general weakness and fatigue, sleep and appetite came to norm. The reduction of anemic hypoxia signs was noted in 13 (81,3±9,8%) of 16 pregnant women with the use of iron supplements and rEPO. Thus, the reduction of general weakness, fatigue after treatment was noted in 11 (68,8±11,6%) pregnant women; the increase of physical activity was observed in 9 (56,3±12,4%); headache, dizziness stopped bothering 12 (75,0±10,8%) pregnant women. Only in one pregnant woman changes in the complaints were not found. The dynamics of the peripheral blood indices in pregnant women with iron deficiency anemia, with an inadequate level of sEPO after the treatment are presented in Table 1.

In pregnant women with an inadequate level of sEPO, a result of iron supplements treatment only, did not achieve a positive effect (Table 1). Thus, the indices of haemoglobin and hematocrit, erythrocyte count preserved the initial data. In this group there was increase of reticulocytes in the peripheral blood from 0,8±0,1% to 1,1±0,1%, $p<0.05$.

Table 1: The dynamics of the peripheral blood indices in pregnant women with iron deficiency anemia with an inadequate level of sEPO after the treatment

Indicator	Pregnant women with an inadequate level of sEPO(iron), n=10						Pregnant women with an inadequate level of sEPO(iron+ rEPO), n=16					
	Before treatment			After treatment			Before treatment			After treatment		
	M	±σ	±m	M	±σ	±m	M	±σ	±m	M	±σ	±m
Level of haemoglobin (g/l)	78,8	9,4	2,9	81,5	5,9	1,9	64,6	7,2	1,8	91,9*°	9,5	2,4
Red blood cell count (x10 ¹²)	3,0	0,6	0,2	3,0	0,5	0,2	2,7	0,4	0,1	3,3*	0,4	0,1
Color index (%)	0,8	0,1	0,04	0,8	0,1	0,03	0,7	0,1	0,03	0,9*	0,1	0,03
Hematocrit (%)	23,3	2,8	0,9	24,1	4,8	1,5	21,6	4,0	1,0	27,1*	4,0	1,0
Number of reticulocytes (%)	0,8	0,3	0,1	1,1*	0,4	0,1	0,6	0,3	0,1	5,4*°	1,6	0,4
Reticulocyte index	0,2	0,1	0,02	0,3*	0,2	0,1	0,2	0,1	0,02	1,8*°	0,6	0,2

Note:

* - valid difference in data in each group before treatment and after the treatment, p<0.05;

° - valid difference in data between the groups after the treatment, p <0.05.

In pregnant women with an inadequate level of sEPO, who received rEPO along with iron supplements a positive trend was observed after treatment. Thus, analyzing the indices of haemogram we can see that haemoglobin level was rising from 64,6±1,8 g/l to 91,9±2,4 g /l, p<0.05, red blood cells count also significantly increased from 2,7±0, 1 x 10¹² to 3,3±0,1 x10¹², p<0.05. Similarly, hematocrit level has increased in this group from 21,6 ±1,0% to 27,1±1,0%, p<0.05. It should be noted that at an inadequate level of sEPO a regenerative ability of red blood shoot was quite large: the level of reticulocytes has increased from 0,6±0,1% to 5,4±0,4%, p<0.05. The increase of reticulocytes number is an indicator of erythropoietin activity of bone marrow, and changes in the hypochromic red blood cells count indicate the absorption of iron by erythrocytes [3,11,12].

The dynamics of erythrocytes and iron metabolism indices in pregnant women with iron deficiency anemia, with an inadequate level of sEPO after the treatment are presented in Table 2. In pregnant women with an inadequate level of sEPO on the background of a conducted treatment

with iron supplements an increase of the average volume of red blood cells from 78,6±4,5 fl to 93,0±4,1 fl, p<0.05 was marked. An improvement of iron metabolism indices was not observed in this group (Table 2).

In pregnant women with an inadequate level of sEPO on the background of a conducted treatment with iron supplements and rEPO the dynamics among the indices of iron metabolism was observed: increased serum iron level from 6,3±0,9 mcmol/l to 8,4±0,9 mcmol/l, p<0.05. On the background of a conducted therapy transferrin saturation percent increased from 6,1±1,0% to 13,3±1,6%, p<0.05. Total iron binding capacity and latent iron binding capacity decreased from 107,5±4,6 mcmol/l to 65,6±2,7 mcmol/l, p<0.05, and from 101,3±4,9 mcmol/l to 57,2±3,0 mcmol/l, p<0.05, respectively. Among the main parameters of erythrocytes a significant increase in the average content of haemoglobin, p<0.05, and in the average concentration of haemoglobin, p<0.05, was observed in pregnant women with an inadequate level of sEPO on the background of iron supplements and rEPO use.

Table 2: The dynamics of erythrocyte and iron metabolism indices in pregnant women with iron deficiency anemia with an inadequate level of sEPO after the treatment.

Indices	Pregnant women with an inadequate level of sEPO (iron), n=10						Pregnant women with an inadequate level of sEPO (iron+rEPO), n=16					
	Before treatment			After treatment			Before treatment			After treatment		
	M	±σ	±m	M	±σ	±m	M	±σ	±m	M	±σ	±m
MCV, fl	78,6	14,1	4,5	93,0 *	13,0	4,1	80,2	17,1	4,3	83,8	11,2	2,8
MCH, pg	26,6	4,7	1,5	27,4	4,2	1,3	24,1	4,2	1,0	28,7*	4,6	1,2
MCHC, g/dl	34,0	3,7	1,2	29,7*	4,7	1,5	30,3	2,6	0,7	34,4*	5,1	1,3
Fe, mcmmole/l	7,8	3,4	1,1	9,3	3,5	1,1	6,3	3,7	0,9	8,4*	3,6	0,9
TIBC, mcmmole/l	95,8	15,4	4,9	86,0	11,7	3,7	107,5	18,4	4,6	65,6 [°]	11,0	2,7
LIBC, mcmmole/l	88,0	17,6	5,6	76,7	14,3	4,5	101,3	19,8	4,9	57,2*	12,1	3,0
TSAT with ferrum, %	8,6	4,7	1,5	11,4	5,6	1,8	6,1	4,2	1,0	13,3 [°]	6,3	1,6

Note:

* - valid difference in data in each group before treatment and after the treatment, p<0.05;

p<0.05;

° - valid difference in data between the groups after the treatment, p<0.05.

DISCUSSION:

Positive effect was achieved during the treatment of pregnant women with moderate and severe anemia with an inadequate level of sEPO, which were receiving rEPO along with iron supplements. Clinical effect in pregnant women receiving rEPO drugs along with iron supplements was more prominent and appeared faster than in patients treated with a conventional therapy.

The realization of hemic reserve of body oxygenation is provided due to the increase of erythropoiesis, increase of erythrocyte count, haemoglobin concentration, and hematocrit indices in pregnant women with anemia who were treated with iron supplements and erythropoietin. Stimulation of erythropoiesis,

increase of red blood cells count occurs as a result of erythropoietin as well [8,9].

Thus, the results of a conducted research prove a significant clinical efficiency and pronounced hemostimulating effect of the use of rEPO for anemia during pregnancy. rEPO stimulates erythropoiesis and improves red blood count, reduces the severity of anemia. This, in turn, helps significantly reduce the number of blood transfusions.

CONCLUSIONS:

1. Iron deficiency anemia in pregnant refers to clinical syndromes in which an inadequate production of EPO is observed. This is proved by enhancement of clinical, hematological parameters, as well as by changes in serum parameters of iron metabolism in the group of patients who were taking rEPO.

2. Adequate treatment of anemia in pregnant women in consideration of true adequacy of EPO improves the clinical course of the disease, hematological parameters, has a positive effect on the course of pregnancy and intrauterine fetal condition.

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