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Use of alternative methods in the treatment of anemia in pregnant women – prospective observational study

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ABSTRACT

Objectives: Anemia in pregnant women is a common condition, diagnosed when the concentration of hemoglobin falls below 11 g/dL. Taking into consideration the accounts of nephrologists about good results of treatment of secondary anemia using erythropoietin in patients with renal failure, we tried to use EPO to cure anemia in pregnant women.

The aim of the study was to evaluate the results of EPO treatment on pregnant women diagnosed with iron deficiency anemia, as well as possible side effects.

Material and methods: The study consisted of 25 patients:

Group I — treated with iron supplement administered parenterally — Ferrum Lek every two days intramuscularly.

Group II — treated with recombinant human erythropoietin — 1000 j intravenously every three days, with oral iron supplements.

Results: After a week of treatment the positive response was higher in the second group (92.3% in II, vs 33.3% in I, $p < 0.005$).

The average increase of hemoglobin and RBC was significantly higher in II group.

An increase in hemoglobin did not correlate with the age of women ($r = 0.07$) or with the duration of pregnancy ($r = 0.08$). However, a negative correlation was found between basic hemoglobin level and its increase after treatment ($r = 0.602$).

Conclusions: EPO administered with the oral dose of iron in pregnant women with anemia caused by iron deficiency shows higher effectiveness than the use of iron preparations parenterally.

The usage of EPO during pregnancy is not related to any dangerous side effects for the mother or fetus.

Key words: pregnancy; anemia; erythropoetin

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INTRODUCTION

Anemia in pregnant women is a commonly diagnosed condition, especially in the 2nd and 3rd trimesters. It is estimated that in Poland, 30–41% of women suffer from it, in the United States, up to 25%, and in Europe, less than 10%. It is most commonly found in women from environments with low social and economic status [1]. According to the WHO (World Health Organization), 11 g% (6.82 mmol/L) of hemoglobin in the blood is considered to be the lower limit of the normal, independent of the advancement of pregnancy.

A small degree of anemia is a natural physiological phenomenon during pregnancy. It is caused by the increased volume of plasma in proportion to the increase in the volume of the morphotic blood elements (anemia due to "dilution"). Pathological anemia is diagnosed when the concentration of hemoglobin falls below 11 g/dL (according to the WHO). We distinguish three types of anemia: mild (10.9–10 g/dL), moderate (9.9–7 g/dL) and severe (< 7 g/dL) [2]. The most common cause of anemia in pregnant women is iron deficiency, less commonly folic acid or vitamin B12 deficiency [1]. It is also often diagnosed in multiple pregnancies, in those infected with the HIV (human immunodeficiency virus), and in women suffering from chronic renal failure.

Anemia caused by iron deficiency constitutes approximately 80% of all cases of anemia [1].

The consequences of anemia during pregnancy include, among other things, the following: placental function

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disorder and related complications (intrauterine growth restriction, premature birth, intrauterine fetal demise), abnormal uterine activity during birth or post-partum atony related to the metabolic process disorders of the uterine muscle. There is also an increased risk of perinatal infections that result from changes in the immune system. Severe circulatory decompensation and DIC (disseminated intravascular coagulation) may also occur due to the lack of erythrocyte reserve in case of increased bleeding during birth. Children born to anemic mothers are often premature, and even if they are born on predicted due dates, they usually have a lower birth weight, adaptation process disorders and deficiency anemia [3].

Due to the most commonly occurring anemia pathogenesis during pregnancy, first-line treatment is the iron supplementation in the form of an oral preparation or parenterally in case of suspected problems with iron assimilation from the gastrointestinal tract [3].

Endogenic EPO (*erythropoietin*) is a glycoprotein with a 34 kDa mass composed of 166 amino acids. Its principal source are Leydig cells in kidneys (80–90%) and Ito cells in the liver (10–20%). Its small amounts are also produced in the liver, lungs, testicles, uterus, spleen, lymphocytes, megakaryocytes of the brain, and cornea. During fetal life, its primary source is the fetus' liver and placenta [3]. EPO coding gene is located on chromosome 7, whereas the factor regulating its production is the concentration of oxygen in the blood flowing through the kidneys.

The target spot of the erythropoietin activity is the hematopoietic system located in the bone marrow, and its principal function is to regulate erythrocyte production. EPO has an effect on the target cells through a receptor (EPO-R) that belongs to the first family of cytokine receptors. The combination of EPO and EPO-R activates tyrosine kinase JAK-2, which leads to the activation of genes Bcl-2 and Bcl-XL through the cytoplasmic transcription factor STAT5. Those genes stop apoptosis of precursor cells of the erythrocytic system and stimulate their maturation to the stadium of the mature erythrocyte [4, 5]. An increased number of mature erythrocytes appears as a result of that. Hypoxia causes an increased production of EPO and an increased number of red blood cells, which, in the reverse mechanism, causes the decrease of synthesis of this cytokine and the decrease of its concentration in blood. Taking into consideration the accounts of nephrologists about very good results of treatment of secondary anemia using erythropoietin in patients with renal failure, research concerning the use of that substance in pregnant women has been conducted since the end of the 20th century [6].

The production of human recombinant erythropoietin (rHuEpo) through genetic engineering has allowed for its practical use in the treatment of anemia. There have also been publications regarding its use in pregnant women. Not all the aspects of EPO's activity are known though, and some mentions of the potential threats related to its application found in literature require research. It should be remembered that there is a limited number of academic papers considering this topic and as a result the population of this study is also limited.

Aim of the study

The objective of the conducted research was the assessment of treatment results in pregnant women with diagnosed anemia caused by iron deficiency with the use of EPO, as well as possible side effects. Literature provides data regarding the use of EPO together with Fe preparations in the treatment of postpartum anemia.

We have to remember that biological EPO activity reaches beyond hematological changes. Many studies have demonstrated that cytokine has autocrine and paracrine effect on other tissues showing neuroprotective, anti-inflammatory, and antioxidant activity; it stimulates nitric oxide and intensifies angiogenesis [4, 5].

Currently, apart from the interest of the effect of EPO on hematopoiesis, more and more attention in being brought to its potential effect on the fetus and the role it plays in the development of pregnancy. It was demonstrated that the concentration of cytokine in blood of pregnant women changes and reaches maximum values around the middle of pregnancy, which is probably related to the physiological blood hemodilution. Due to the size of the particle, EPO does not penetrate the placenta, which was also proved in the conditions of experimental perfusion of a fragment of placenta in an in vitro test [7, 8].

Fetus produces EPO primarily in the liver. Its third source during pregnancy is the placenta. Due to the existing separate co-parameters for the mother and the fetus and the fact that what stimulates its production is hypoxia, the concentration of EPO is treated by many authors as a sensitive marker of fetal asphyxia [4, 9].

Literature points out the increase in the EPO concentration in the plasma of the mother during preeclampsia, and, according to Hershkovitz et al., the reason for that is the diminished flow through placenta, its hypoxia and related to it increased production of EPO by the trophoblast's cells [10]. Although mother's EPO has no effect on the fetus, its potential effect on the placenta is unknown, particularly since Resh et al. found in an in vitro study a vasoconstrictive effect of EPO on the umbilical cells, especially the umbilical vein. However, other scientists concentrate on the development of an early pregnancy and stress the positive of EPO on the angiogenesis of the trophoblast's cells. Considerable differences have been found in the concentration of cytokine in plasm in

pregnant women and the expression of EPO-R receptors on the trophoblast in cases of regular and pathological pregnancies [9, 11].

MATERIAL AND METHODS

The study group included 25 patients with gestational age between 18 and 35 weeks, treated for treatment-resistant anemia with the use of oral iron preparations. The study was conducted with pregnant women from the Pregnant Pathology Department, Medical University of Lodz, in 2006–2012. Every patient was informed about possible ways of treatment and gave informed consent to iron and EPO therapy. The size of the group depended on the number of patients with the above mentioned diagnosis hospitalized in the ward during that period of time. The patients were divided into two groups:

Group I — patients treated with iron preparations administered parenterally (Ferrum Lek 1 amp every other day, intramuscular). Women with the initial level of hemoglobin equal or over 9.2 g%, but not higher than 10.9 g%, were placed in this group.

Group II — patients treated with human recombinant erythropoietin (rHuEpo) of 1000 u. intravenously, every three days (initial hemoglobin level of HB < 9.2 g%). In this group, iron supplementation with oral preparations was also used.

The reason for that group selection was the profile of the patient hospitalized in the pathological pregnancy ward. Light and moderate anemias are the most common types of disorders found in pregnant women. It seemed reasonable to use these two groups of patients to carry out the tests.

In both groups, patients received orally 5 mg of folic acid daily.

All important information, as a standard medical interview, had been collected from the patients before the implementation of the treatment. No patient had symptoms of eating disorders or used a restrictive or vegetarian diet. None of them were under treatment for hypertension or chronic infections, either. Before the examination, each patient had a blood test, iron concentration in plasma test, and a total and latent iron binding capacity tests, in order to corroborate the diagnosis of deficiency anemia. A follow-up test of the erythrocytic system was performed again in the eighth day of the treatment.

Afterwards, the differences in the values of particular parameters in relation to the test results from before the treatment were assessed. Those differences were marked as Д. Treatment effectiveness was compared taking into account the concentration of hemoglobin and the numerical value of erythrocytes. The general condition of the pregnant women and the well-being of the fetuses were supervised with the use of cardiotocographic data and fetal motor activity.

Statistical analysis

The statistical analysis was performed with the use of a computer program named Statistica 12. In order to assess the normality of distribution, Shapiro-Wilk test was used, whereas equality of variances was tested using Brown – Forsythe test. The comparisons between the groups were conducted using t-Student, Mann – Whitney U, and chi2 tests. $P < 0.05$ was adopted as the level of statistical significance

RESULTS

Results obtained in the compared groups can be observed in the table below.

The evaluated factors were: pregnant women's age, body weight, weight gain during pregnancy (Tab. 1).

The parameters of the erythrocytic system, platelets, and leucocytes were assessed, and the results can be found in Table 2.

In accordance with the assumed method of the patients' placement in groups, the average hemoglobin concentration was lower in Group II in comparison to Group I ($p = 0.0011$). However, when taking into account the average number of erythrocytes in patients of both groups before treatment, no significant statistical difference was observed ($p = 0.1628$).

Table 3 presents the obtained differences of the formerly assessed parameters 7 days into the treatment, illustrated as Д.

One week into the treatment, 33.3% of the tested patients from Group I and 92.3% of those from Group II ($p < 0.005$) responded to the treatment positively.

Table 1. Groups characteristics

	Group 1 — Ferrum N = 12		Group 2 — EPO N = 13		P
	Average	Standard deviation	Average	Standard deviation	
Gestational age [w]	28.6	6.47	29.5	4.6	0.8939
Body weight before pregnancy [kg]	66.7	4.83	66.2	10.94	0.7330
Weight gain [kg]	9.7	4.22	9.46	3.59	0.8878
Pregnant women's age	30.1	5.53	28.8	6.63	0.1425

Table 2. Parameter values in peripheral blood

	Group 1 — Ferrum N = 12		Group 2 — EPO N- = 13		P
	Average	Standard deviation	Average	Standard deviation	
WBC [thous.]	9.73	3.16	10.05	2.39	0.7927
Erythrocytes [mln]	3.58	0.65	3.15	0.41	0.1628
Hb [g/dL]	9.83	1.15	8.52	0.62	0.0011
PLT [thous.]	233.1	55.05	269.2	97.14	0.3143

Table 3. Differences of evaluated parameters

	Group 1 — Ferrum N = 12		Group 2 — EPO N- = 13		P
	Average	Standard deviation	Average	Standard deviation	
Д WBC [thous.]	1.45	1.94	0.61	2.68	0.3671
Д Erytrocyty [mln]	0.2	0.52	0.22	0.29	0.0235
Д Hb [g/dL]	0.2	0.61	0.69	0.59	0.0436
Д PLT [thous.]	26.73	40.27	3.76	95.66	0.7098

Comparing the results obtained after the treatment, it was demonstrated that the patients from Group II, who were treated with EPO, had a significantly higher average hemoglobin and erythrocytes growth than the pregnant women in Group I, who were treated exclusively with an iron preparation.

Besides, it was found that the growth of hemoglobin concentration after the treatment was not related to the age of the woman (Pearson coefficient value r = 0.07) or the gestational period (r = 0.08). A negative correlation was noticed though between the initial hemoglobin concentration before the treatment and its growth after the research was concluded (r = 0.602).

Only one patient from Group II demonstrated a short-term temporary increase of blood pressure to the value of 150/94 mm Hg. No pathological reactions in the pregnant women's bodies to the administered erythropoietin or any threat to the fetus in any pregnant women were observed.

The research draws attention to the important and often forgotten pregnancy pathology which is anemia. The presented study has numerous limitations, caused mainly by the number of patients participating in it, but it shows promising data for research in the future. It is worth mentioning that future studies should include patients with severe anemia.

DISCUSSION

Due to the high prevalence and the consequences it has for both the mother and the fetus, anemia caused by iron deficiency constitutes a significant problem in modern perinatology. The traditional treatment method involves leveling the quantity of iron in the body through its supplementation administered orally. In case of suspected problems with iron assimilation in the gastrointestinal tract, it should be administered parenterally.

The normalization of existing iron deficiency from before pregnancy requires time and it also depends on a patient's acceptance and her cooperation with medications and diet. If the treatment results are ineffective, a blood transfusion can be an alternative, which, however, can cause numerous undesirable post-transfusion complications, both immediate and remote. Moreover, for a large group of women, treatment with blood derivatives is unacceptable for religious reasons. This is why the use of EPO with pregnant women has become a promising method of therapy in the treatment of anemia.

The results of the performed study were assessed one week into the treatment. The positive effect was reached in 92.3% of women treated with iron + EPO, but only in 33.3% of those who received only iron. Positive results were also obtained by Breymann et al. [12], who stress that treatment with both iron only and iron plus EPO are effective; however, pregnant women who were given the combination of both reached the desired level of hemoglobin, i.e. 11 g/dL, sooner. Similar good results are presented by Krafft et al. [13], who simultaneously point out the need to search for the causes why some patients did not show any improvement after being treated with the same iron preparations, despite being diagnosed with deficiency anemia. Many authors report positive effects of using EPO in the treatment of anemia in pregnant women. Sifakis et al. [14] report a quick positive reaction to the treatment in 73% of the pregnant

women, observing an increase of the Hb (haemoglobin) concentration by 3 g/dL in the first two weeks.

From among the patients treated with EPO, one had an excessive increase of blood pressure, which could have been an example of undesirable side effects.

As noted by Fisher, the administration of EPO may carry the risk of adverse side effects, especially hypertension and prothrombotic action [11]. Patomechanism of this disorder consists in the retention of Ca ions in the intercellular space and decrease of the reactivity to the vasodilatory effect of nitric oxide. According to Fisher, EPO may stimulate increased production of endothelin and changes in the production of prostacyclin and may foster the production of renin and angiotensin [15]. In existing literature, however, there are no data on serious complications in mothers during the EPO treatment. In our study, we have observed only once an increase of blood pressure in the pregnant women- one patient demonstrated a short-term temporary increase of blood pressure to the value of 150/94 mm Hg. Single reports found in literature concern cases of some significant increase of blood pressure after the administration of EPO; however, they occurred to women with prior chronic renal disease [11].

Literature provides data regarding the use of EPO together with Fe preparations in the treatment of postpartum anemia. Wagstrom et al. compared the results of treatment of pregnant women given iron only and those given iron + EPO. They did not observe any significant differences and both methods proved effective [11]. On the other hand, Meyer found in pregnant women treated with EPO less severe symptoms of baby blues in comparison to the patients treated exclusively with Fe [16].

The research draws attention to important and often forgotten pregnancy pathology, which is anemia. Presented study has numerous limitations, caused mainly by the number of patients participating, but shows promising data for research in the future. It is worth mentioning that future studies should include patients with severe anemia.

Erythropoietin is a cytokine not entirely explored in the context of its application in pregnant women. Its basic use as a substance assisting erythropoiesis in the treatment of patients with anemia is rather well explored and often practised with a good result. On the basis of the available literature and our own research, it should be regarded as a valuable form of therapy. Positive effects of EPO as a medication normalizing hemoglobin and erythrocyte levels concern a great majority of the treated patients and so far no severe negative effects have been found. Further research regarding the significance of erythropoietin should be conducted as it seems that there are considerably higher possibilities of the application of this cytokine in therapy than currently used.

CONCLUSIONS

Erythropoietin administered together with the oral dose of iron in pregnant women with anemia caused by iron deficiency shows higher effectiveness than the therapy with the use of iron preparations administered parenterally.

The treatment with the use of erythropoietin during pregnancy is not related to any dangerous side effects for the mother or the fetus.

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