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Perinatal Outcomes in Pregnant Women with Anemia of Various Geneses

Victor E. Radzinsky, PhD, ScD[1]; Bakhtykei M. Gasanova, PhD[1]; Miroslava L. Polina, PhD[2*]; Natalya I. Douglas, PhD, ScD[3]; Irina S. Bulshiy, PGS[3]; Fatima I. Chotchayeva[4]; Tatyana V. Dedy, PhD[5]

[1]*RUDN University, Moscow, Russia*
[2]*Women's Health Medical Center, Moscow, Russia*
[3]*M. K. Ammosov North-Eastern Federal University, Yakutsk, Russia*
[4]*Republican Perinatal Center, Cherkessk, Russia*
[5]*Federal Medical-Biological Agency, Moscow, Russia*

Abstract

Modern methods for diagnosing disorders of iron metabolism (ferritin, C-reactive protein) in iron deficiency anemia (IDA) and anemia of chronic diseases (ACD) contribute to the identification of metabolic characteristics that negatively affect the mother-placenta-fetus system.

The biological response to hypoxia varies in anemia of different geneses: depletion of iron depot on the background of chronic infectious and inflammatory processes is accompanied by more obvious homeostasis disorders. Excessive activity of the peroxidase system (increase in prooxidant factors – malondialdehyde, catalase of blood serum and red blood cells, sulfhydryl groups) explains the large frequency of gestational complications and perinatal diseases in ACD women, such as morphofunctional immaturity, hypoxic-ischemic lesion of the central nervous system of newborns, and infectious and inflammatory diseases.

The degree of ante- and perinatal well-being in conditions of iron deficiency, accompanied by a violation of the molecular mechanisms of protein synthesis, depends on the activity of adaptive homeostatic mechanisms of the mother-placenta-fetus system. The strategy to reduce adverse perinatal outcomes includes identification of abnormal metabolism predictors with the expansion of the scope of examination in groups with high infectious risk, further monitoring of risk cases, and pathogenetic therapy. (**International Journal of Biomedicine. 2020;10(3):241-246.**)

Key Words: iron deficiency anemia • anemia of chronic diseases • outcomes • oxidative stress

Abbreviations

ACD, anemia of chronic diseases; **AOD**, antioxidant defense; **CRP**, C-reactive protein; **CP**, chronic pyelonephritis; **ESR**, erythrocyte sedimentation rate; **ID**, iron deficiency; **IDA**, iron deficiency anemia; **LPO**, lipid peroxidation; **MDA**, malondialdehyde; **MCV**, mean corpuscular volume; **MCHC**, mean corpuscular hemoglobin concentration; **MCH**, hemoglobin amount per RBC; **PI**; placental insufficiency; **PhP**, physiological pregnancy; **RBC**, red blood cell; **SI**, serum iron.

Introduction

Iron deficiency (ID) is a global public health problem affecting 10%–90% of pregnant women, from 5.4% in developed countries to more than 80% in developing ones.[1-3] The prevalence of anemia is heterogeneous in various regions of the Russian Federation. In the Republic of Sakha (Yakutia) (RS(Y)) in 2018, the frequency of anemia among diseases that preceded or occurred during pregnancy was higher than the all-Russian indicator (RS(Y)-42.3%; RF-35.6%). This discovery requires deep fundamental research on the nutritional characteristics and micronutrient-macronutrient status of pregnant women.

[*]***Corresponding author***: *Miroslava L. Polina, PhD. Women's Health Medical Center, Moscow, Russia, e-mail: polina.ml@mail.ru*

Despite the downward tendency of anemia in the Karachay-Cherkess Republic over the past decade, medical organizational approaches are advancing in order to improve the health of pregnant women and perinatal outcomes.

The development of anemia is associated with socio-economic conditions, protein deficiency in the diet, lack of essential vitamins and minerals (A, B_{12} and folic acid),, and chronic blood loss.[4] The biological role of iron in the body is multifaceted: oxygen transfer by red blood cells, providing redox processes, peroxidation reactions, synthesis of steroid and thyroid hormones, DNA, enzyme activity regulation.[5]

High frequency of gestational complications, fetal hypotrophy, asphyxia and pathological immaturity of newborns in anemia are considered to be the consequences of hemic and tissue hypoxia.

The potential mechanisms of the effect of ID on the body of the pregnant woman and the fetus differ depending on the genesis of the anemia, on the development of oxidative stress, and on disorders of the systemic response to inflammation and infection.

Modern methods of diagnosing anemia contribute to the identification of its types, in relation to metabolic characteristics affecting angiogenesis, placentation and antenatal development of the fetus; however, opinions are ambiguous.[5]

Reducing gestational complications and perinatal morbidity is not possible in the absence of clear criteria for differentiating IDA and ACD, for which therapy with iron-containing drugs has been proved inefficient.[6]

Differentiation of the genesis of anemia from an early date is crucial in order to prevent negative pregnancy outcomes and preserve the cognitive potential of the fetus. The key role in the selection of treatment tactics is determined by ID type (absolute or functional), with impaired distribution on the background of chronic inflammatory diseases (intestines, liver, kidneys), and obesity.

Risks associated with ID hypodiagnostics on the background of a systemic inflammatory reaction, in connection to pregnancy outcomes, are underestimated.

The accompanying inflammatory process in the body distorts the iron metabolic pattern: functional deficiency with its unchanged total content occurs due to sequestration in the reticuloendothelial system.

ACD (ICD D63.8) appears to be the pathogenetic response of the body to a long-term infectious, inflammatory or autoimmune process, with impaired erythroid proliferation predecessors.[6] "Infect anemia" of pregnant women is a special case of ACD (4% of all anemia), resistant to iron treatment.[5]

The diagnostic value of hematological and biochemical parameters for various anemia geneses is debatable.

A common criterion for anemia in the first trimester of pregnancy was found to be a hemoglobin level less than 110 g/l.[4] Risk of adverse outcomes for mother, fetus and newborn appears, according to a meta-analysis, at a hemoglobin level of less than 110-100 g/l in the first two trimesters of pregnancy,[7] according to other sources – in the presence of severe anemia.[8]

The diagnostic value of the parameters of the general blood test (MCV [the average RBC size], MCH, color index) as isolated IDA markers is disputed,[9] in contrast to the greater sensitivity of MCHC.[10]

The gold standard for IDA is a decrease in ferritin less than 30 mcg/l, regardless of hemoglobin and SI concentrations[4] Additionally noted is erythrocytes hypochromia, a decrease in the average hemoglobin content in an erythrocyte, SI less than 15 ng/ml, a tendency to leukopenia, and an increase in the ESR.[11]

The combination of ID and a chronic inflammatory process complicates the assessment of iron metabolism.[6] Pregnant women with ACD are distinguished by ferritin variability from normal to elevated indices as protein of acute inflammation phase.[12] The informative value of CRP content in the diagnosis of ID among pregnant women with autoimmune and inflammatory diseases is superior to transferrin and its soluble receptor, hepcidin.[13]

Preclinical diagnosis of PI among pregnant women with anemia is considered possible on the basis of the assessment of individual parameters of homeostasis in its various types,[5,14] especially in groups with high infectious risk.

The LPO activation in PhP is explained by the need for the accumulation of "strategic" iron resources.[15] Oxidative stress during pregnancy is caused by increased metabolism; lack of a number of factors (catalase, glutathione peroxidase and glutathione transferase) requires inhibiting the synthesis of hydroperoxides.[15]

The consistency of the mechanisms for suppressing excess hydroperoxides affects the prognosis of consequences of anemia for the embryo/fetus and placental-fetal interaction.

The specificity of LPO-activity/AOD-processes in various types of anemia has been poorly studied.[16-18]

Ideas of anemia types among pregnant women allow us to address the pathogenetic therapy of the diseases. Prescribing iron preparations resulted in a decrease in anemia by 70%, ID – by 57% until the time of childbirth.[19] On the contrary, the consequences of unreasonable ferrotherapy in normal or elevated levels of ferritin include competitive binding of iron by microbial and tumor cells, development of oxidative stress due to an excess of free radicals, endothelial dysfunction, and gestational diabetes mellitus.[20,21]

The effect of metabolic disorders in IDA and ACD on perinatal outcomes and the real prognostic value of peroxidation markers remain unclear.[12,22]

The general objective of the current study was to evaluate the effect of homeostasis features of iron metabolism and oxidative status among pregnant women with anemia of various geneses on perinatal outcomes.

Materials and Methods

The study cohort included pregnant women with IDA (n=286) and ACD ("infect anemia") (n=184). Healthy pregnant women made up the control group (n=34). Written informed consent was obtained from all participants.

Inclusion criteria: single-child progressive pregnancy, the presence of anemia before planning pregnancy, the informed consent of a woman to use biological material for scientific purposes.

Research methods included the assessment of a general blood test (RBCs, hemoglobin, platelets, white blood cells,

lymphocytes, monocytes, ESR, MCV, MCH, SI, CRP, ferritin (ELISA-ferritin test system (St. Petersburg)), total protein, and pro- and antioxidant factors (catalase of blood serum and RBCs, sulfhydryl groups, ceruloplasmin, and MDA in blood serum).

In IDA, anemia treatment included 100-300 mg ferrous iron per day, in ACD – identification and treatment of subclinical infectious and inflammatory diseases, and urogenital infections (antibiotic therapy, antioxidants, total tocopherols, polyunsaturated fatty acids, and probiotics). The general recommendation for pregnant women with anemia is folate supplementation (400-800 mcg per day), vitamins, minerals, and diet (protein, oligopeptides).

Statistical analysis was performed using the Statistica 10 software package (Stat-Soft Inc., USA). The normality of distribution of continuous variables was tested by the Shapiro-Wilk test. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean (M) and standard error of the mean (SEM) for continuous variables. Student's unpaired t-test was used to compare average values for data with normal distribution. Group comparisons with respect to categorical variables are performed using chi-square tests with Yates correction or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P \leq 0.05$ was considered statistically significant.

Results and Discussion

The average age of participants with ACD was 26.8±3.2 years, IDA – 27.3±4.1years, without significant intergroup differences. Data on past illnesses of participants with IDA and ACD are presented in Table 1.

Table 1.

Chronic diseases of pregnant women with anemia of various geneses

Diseases	IDA (n=286)	ACD (n=184)	*P*-value
Sinusitis	16 (5.6)	27 (14.7)	0.002
Rhinitis. nasopharyngitis and pharyngitis	33 (11.5)	66(35.9)	0.0005
Respiratory diseases	21 (7.3)	45 (24.4)	0.0005
Kidney diseases	41 (14.3)	67 (36.4)	0.0005
Inflammatory diseases of the female pelvic organs	78 (27.4)	99 (53.8)	0.0005

A number of chronic diseases (sinusitis (*P*=0.002), upper (*P*=0.0005) and lower (*P*=0.0005) respiratory tract diseases, CP (*P*=0.0005)) identified pregnant women with ACD as a group with a high infectious risk.

Inflammatory diseases of the female pelvic organs were characteristic of almost half of the women with ACD and only a quarter with IDA (*P*=0.0005).

Pregnancy in ACD women was more often complicated by gestational pyelonephritis (*P*=0.0009), CP exacerbation (*P*=0.0005), and acute respiratory infections (*P*=0.0005), compared with IDA women (Table 2).

Table 2.

Pregnancy complications in anemia of various geneses

Pregnancy complications and diseases	IDA	ACD	*P*-value
Gestational pyelonephritis	24 (8.4)	38 (20.6)	0.0009
Exacerbation of CP	11 (3.8)	43 (23.4)	0.0005
Sonographic signs of fetal infection	18 (6.3)	39 (21.2)	0.0005
Acute respiratory viral infections	21 (7.3)	34 (18.5)	0.001

Sonographic signs of fetal infection were noted three times more often in ACD (*P*=0.001).

A study of the hematological parameters of pregnant women showed a greater decrease in MCV and MCH in the ACD group in contrast to the average hemoglobin values (Table 3).

Table 3.

Hematological parameters of pregnant women with anemia of various geneses

Parameters	IDA (1)	ACD (2)	Control group (3)	*P*-value
*Erythrocytes,10^{12}/l	3.37±0.05	3.44±0.04	3.9±0.05	P_{1-3}=0.03 P_{2-3}=0.005
Hemoglobin, g/l	95.4±6.4	106.8±5.4	136.6±5.3	P_{1-3}=0.002 P_{2-3}=0.03
*Platelets, 10^9/l	248.5±11.6	218.5±9.6	248.5±11.6	P>0.05
MCV, fl	83.5±1.2	92.5±1.1	98.5±1.4	P_{1-2}=0.005 P_{1-3}=0.03 P_{2-3}=0.02
MCH, pg	28.4±0.5	31.3±0.52	33.3±0.4	P_{1-2}=0.04 P_{1-3}=0.03 P_{2-3}=0.001
*Leukocytes,10^9/l	5.6±0.8	6.2±1.1	5.2±0.8	P>0.05

**- The content of leukocytes and platelets in groups with anemia did not significantly differ from that in healthy pregnant women.*

The results of hematological and biochemical parameters of pregnant women with anemia of various geneses are presented in Table 4.

Table 4.

The results of studies of iron metabolism and pro-inflammatory markers among women with anemia of various geneses

Hematological parameters	IDA	ACD	*P*-value
Ferritin reduction, mcg/l	286 (100.0)	0	-
Normal ferritin level, mcg/l	0	34 (18.5)	-
Increased ferritin level, mcg/l	0	150 (81.5)	-
C-reactive protein, mg/l	0	184 (100.0)	-
Lymphocytosis	28 (9.8)	54 (29.3)	0.0005
Monocytosis	23 (8.0)	42 (22.8)	0.0005
ESR increase, mm/h	13 (4.5)	27 (14.7)	0.0009
Serum iron, mcmol/l	7.8±2.6	12.4±4.2	0.001
Total protein, g/l	74.6±4.2	69.4±5.3	0.03

Unreasonable reliance on hemoglobin and SI exclusively in IDA diagnosis confirms the low ferritin with MCV and MCH in comparison with "infect anemia." [23] True ID with a decrease in MCV (<80%) and ferritin(<12 ng/ml), as well as SI (<40 mcg/dl), was also confirmed by other authors.[24]

The depletion of iron reserves during ACD was accompanied by a range of ferritin from normal (18.5%) to elevated (81.5%), due to the redistribution of abnormal microbiome of various loci of the body on the background of chronic inflammatory processes.

Iron sequestration in macrophages and hepatocytes reflects the protective mechanism, which reduces competition for a biological resource between pathogens and the body of a pregnant woman.

The normal level of ferritin is explained by the physiological increase in acute phase proteins.[6] The standard of ACD is a pro-inflammatory shift of the leukocyte formula in some cases (lymphocytosis, monocytosis and increased ESR), and CRP due to tissue alteration. An inflammatory reaction with CRP>6ng/ml in 52.2% of women with anemia versus 28.8% in its absence was noted by Mburu et al.[25]

Reactive changes in erythropoiesis and iron metabolism during inflammation, infection, or autoimmune disease[26] indicate a difference in the pathogenetic mechanisms of iron deficiency in IDA and ACD.

A significant protein deficiency, along with low hemoglobin in the presence of normal and high ferritin content, means a violation of the activity of the iron transport chain, its release from macrophages and delivery to tissues.[6,20]

SI content was found to be reduced in IDA and corresponded to reference values in the group with ACD (P=0.001).

The analysis of the activity of free radical oxidation processes indicated an increased production of a number of free radical molecules in ACD (Table 5).

Table 5.

Pro- and antioxidant factors in samples of pregnant women with anemia of various geneses

Parameters	IDA (1)	ACD (2)	Control group (3)	P-value
Malonic dialdehyde, mcmol/l	1.3±0.1	1.7±0.1	1.2±0.4	P_{1-3}=0.005 P_{2-3}=0.01
Erythrocyte catalase activity, mkat/l	74.9±1.4	87.4±2.7	74.7±0.9	P_{1-3}=0.001 P_{2-3}=0.02
Serum catalase activity, mkat/l	14.8±1.5	29.6±2.4	15.7±0.5	P_{1-3}=0.001 P_{2-3}=0.005
Ceruloplasmin, mg/l	369.8±12.5	406.3±14.1	366.9±13.5	P>0.05
SH-groups, mmol/l	13.3±0.4	17.2±1.3	12.4±0.4	P_{1-3}=0.005 P_{2-3}=0.01

The decrease in compensatory abilities of the body on the background of excessive production of prooxidant factors (MDA, SH-groups, catalase of blood serum and RBCs) among pregnant women with ACD corresponds to the state of endointoxication associated with obstetric complications.[27]

The prevalence of free radical reactions should be regarded as homeostasis failure caused by functional defectiveness of iron antioxidant enzymes.

The concentration of one of the main antioxidants of ceruloplasmin, glycoprotein of the alpha-2-globulin blood fraction did not significantly increase, confirming the limited immune reserves in the group with "infect anemia." Such observations allow us to note that the imbalance of pro- and antioxidant factors with the development of oxidative stress during ACD is accompanied by depletion of the erythroid germ.

The reduction of the number of factors providing protection from the damaging effects of hydroperoxides was accompanied by an increase in redox cell potential.

The value of hematological and biochemical studies for the preclinical diagnosis of PN among pregnant women with anemia was 100% for ACD and 63.6% IDA.

The morphological basis of PI in anemia of various geneses proves to be angiopathy of the uterine vessels, revealed in studies of the placental bed.[5,28] The lack of complete transformation of the spiral arteries, then the utero-placental, with the abnormal development of the villous tree, affects the functional activity of the utero-fetal-placental complex of pregnant women with anemia. Universal metabolic reactions with ID among pregnant women with anemia of various geneses show that its participation is limited in the physiological reactions of the body and the other plastic resources necessary for fetal growth.[29]

In groups with anemia, urgent birthgiving was 82.3%, premature – 17.6%, and caesarean section – 12.8%.

Newborns from mothers with ACD differed slightly in body weight – 2970±280 g/l versus 2850±140 g/l in the IDA group (P=0.07). Obviously, non-replenished ID, even with high compensatory resources of the placenta, leads to a deterioration of placental angiogenesis, fetal ischemia and growth restriction, and newborns of low weight.[30] The number of newborns in the groups of women with anemia who needed to be transferred to the intensive care unit (ICU) was 16.2%; in the ACD group it was almost three times higher (24.4% and 8.7%) than in the IDA group: however, without statistically significant differences. The number of children requiring nursing was slightly higher in the ACD group than in the IDA group (24.4% versus 11.5%; χ^2=4.3, P=0.04).

Anthropometry of newborns from mothers with anemia was inferior to the parameters of healthy ones, without affecting their viability, with a greater need for intensive care in the ACD group.[29] In groups with anemia, 8.5% of newborns had a small gestational period at birth, 23.6% had hypotrophy (Table 6).

Table 6.

Perinatal morbidity in groups of women with anemia of various geneses

Newborns' diseases	IDA	ACD	P-value
Hypotrophy	59 (20.6)	49 (26.6)	0.2
Infectious and inflammatory diseases	14 (4.9)	27 (14.7)	0.001
Morphofunctional immaturity	47 (16.4)	63 (34.2)	0.0005
Hypoxic-ischemic brain damage	51 (17.8)	58 (31.5)	0.002
Premature newborns	18 (6.3)	20 (10.9)	0.1

The decrease in compensatory resources of pregnant women with "infect anemia" explained a three-fold increase in the frequency of infectious and inflammatory diseases (omphalitis, conjunctivitis, dacryocystitis, vesiculopustulosis) (P=0.001). Signs of morphofunctional immaturity were detected in almost half of newborns in the ACD group, and half as often in the IDA group (P=0.0005).

Hypoxic-ischemic damage to the central nervous system of newborns was noted more often in the group with "infect anemia" – almost one and a half times. High perinatal morbidity among women with anemia is caused by chronic hypoxia, which reflects morphofunctional failure of the placenta.[27,31] Obviously, unfavorable antenatal conditions for fetal development among pregnant women with anemia are determined by the underdevelopment of terminal placental villi [29] and their dystrophic changes.

The degree of dysregulation of the processes of cell growth and metabolism in the fetoplacental system differs depending on the genesis of anemia. Plastic deficiency is the starting point of the violation of the molecular mechanisms of protein biosynthesis in the placenta of pregnant women with anemia, being more vivid in "infect anemia." The "crisis" of placental angiogenesis in ACD determines the worst perinatal outcomes, due to damaging effects with the development of molecular-cellular "stress" in the mother-placenta-fetus system from the early stages of embryogenesis. Increased production of LPO markers corresponds to a violation of redox processes and biochemical reactions in the mitochondrial respiratory chain.[32]

Assessment of metabolism among pregnant women with anemia will make it possible to diagnose the degree of compensation for circulatory hypoxic disorders in the mother-placenta-fetus system.

Improving treatment and diagnostic approaches to pregnant women with anemia involves expanding the scope of examination (CRP, pro- and antioxidant defense factors) in groups with high infectious risk in order to identify markers of latent and subclinical infectious and inflammatory diseases. Significant adaptive homeostatic changes (oxidative stress on the background of an inflammatory response) among ACD women confirm the possibility of predicting adverse perinatal outcomes.

Early pathogenetic therapy will limit the degree of metabolic disorders among pregnant women with anemia, compensating for the consequences of abnormal placentation, and, therefore of perinatal morbidity.

Competing Interests

The authors declare that they have no competing interests.

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