Early Prognosic Criteria of Placental Insufficiency Development in Pregnant Women with Iron Deficiency Anemia

DOI: 10.17691/stm2016.8.4.15
Received November 11, 2015

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The aim of the investigation was to detect early prognostic criteria of placental insufficiency development in pregnant women with iron deficiency anemia (IDA).

Materials and Methods. 143 pregnant women have been examined: 107 patients with IDA (main group) and 36 women with a physiological course of pregnancy (control group). The main group, in its turn, was divided into two subgroups: group 1 (n=28) included women with IDA found before 12 weeks of gestation, group 2 (n=79) comprised pregnant women with IDA diagnosed at 20–24 weeks. When laboratory signs of IDA were initially revealed, all patients of the main group were determined the degree of oxidative modification of blood serum proteins by the level of carbonyl derivatives based on the reaction of oxidized amino acid protein residues with 2,4-dinitrophenylhydrazine with formation of aldehyde- and ketone-dinitrophenylhydrazones (ADNPH, KDNPH). The level of the given proteins was investigated in the blood serum of the pregnant women in the control group at the same time.

Results. It has been established, that changes in ADNPH and KDNPH levels in spontaneous oxidation is an early prognostic criterion of forming placental disorders in pregnant women with IDA, detected in I and II trimester of pregnancy. A mathematical model of placental insufficiency development in pregnant women with IDA has been worked out, which enables one to form a group of risk.

Key words: iron deficiency anemia of pregnant women; placental insufficiency; oxidative protein modification; prognostication; placental insufficiency of pregnant women with IDA.

Iron deficiency anemia (IDA) is the most common extragenital pathology in pregnancy [1, 2]. According to the WHO data (2011), 38% of pregnant women (32.4 million females) at the age of 15–49 years suffer from IDA [3]. The incidence of this pathology among pregnant women in Russia amounts to 32% [3]. IDA in pregnancy is caused by insufficient supply of iron, necessary for hemopoiesis, to satisfy the increased demand of maternal and fetal organisms [4].

In 12% of women IDA develops prior to pregnancy [5], in 22–28% of cases it is diagnosed in the first trimester of gestation, and in the second trimester IDA incidence increases to 42% [6, 7]. Iron deficiency condition during pregnancy may result in some complications: miscarriage, preeclampsia, premature detachment of normally located placenta, primary and secondary placental insufficiency [3, 8, 9]. During delivery, IDA leads to abnormalities of labor, bleeding, obstetrical traumas on the part of mother and fetus, which worsens perinatal outcomes. If prevalence of anemia exceeds 40%, experts of WHO define the problem as not solely a medical one, but involving national interests.

Up to 60% of perinatal pathology is formed in the antenatal period, and its main cause is placental insufficiency [10, 11]. In IDA placental insufficiency develops in 18–24% of cases [9]. In some investigations a combination of IDA and placental insufficiency is noted in 40.6% of observations [12].

A wide prevalence of IDA among pregnant women, the occurrence of iron deficiency manifestation at the early stages of gestation and a high percentage of placental insufficiency intercurrently with this extragenital pathology inspires the search of early prognostic criteria of forming placental disorders in pregnant women with IDA.

The aim of the investigation was to detect early prognostic criteria of placental insufficiency development in pregnant women with iron deficiency anemia.

Materials and Methods. The work has been carried

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out in Nizhny Novgorod during 2010–2015 in the Women's Consulting Center of City Clinical Hospital No.40, functioning as a Regional Perinatal Center, jointly with the Department of Biology of Nizhny Novgorod State Medical Academy.

107 pregnant women with IDA (main group) and 36 women with a physiological course of pregnancy (control group) have been examined. The main group, in its turn, was divided into two subgroups: group 1 (n=28) included women with IDA found before 12 weeks of gestation; group 2 (n=79) comprised pregnant women with IDA diagnosed at 20–24 weeks.

The study complies with the Declaration of Helsinki (the Declaration was passed in Helsinki, Finland, June, 1964, and revised in October, 2000, Edinburg, Scotland) and was performed following approval by the Ethic Committee of Nizhny Novgorod State Medical Academy. Written informed consent was obtained from every patient.

An algorithm of women examination was in compliance with order No.572н "On approval of the Procedure of rendering medical aid in "obstetrics and gynecology" (excluding the use of auxiliary reproductive technologies)" of the Ministry of Health of the Russian Federation, November 12, 2012.

All patients with IDA had a mild degree of the disease and received antianemic therapy (Sorbifer, containing ferrous iron, perorally, in the daily dosage of 200–300 mg by a continuous course, fasting, 1 h before meals; once a normal level of hemoglobin is reached according to the results of clinical blood test, therapy is continued with the same medication for a long time in the dosage of 100 mg before going to bed every other day to saturate an iron depot in the organism of a pregnant woman).

Criteria of establishing a diagnosis of mild IDA:

reduction of hemoglobin level in the clinical blood count: in the first trimester to less than 110 g/L, in the second trimester to less than 105 g/L; erythrocytes less than $3.9 \cdot 10^{12}$/L; hematocrit less than 37%; average erythrocyte volume below 80; average concentration of hemoglobin in erythrocyte below 300;

serum ferritin level below 30 mg/dl.

Criteria of excluding from the groups:

IDA of average and severe degree;

malignant neoplasms;

bacterial and viral infections;

inflammatory diseases in acute phase;

hereditary pathology in mother and fetus;

abnormal development of the reproductive system in mother;

habitual poisoning (smoking, alcohol, drugs);

multiple pregnancy;

preeclampsia;

abnormal placentation.

In the course of the investigation, intensity of the processes of free radical oxidation of blood plasma proteins by the level of carbonyl derivatives to identify placental insufficiency markers has been estimated. Reactions of oxidized amino acid protein residues with 2,4-dinitrophenylhydrazine with formation of aldehyde- and ketone-dinitrophenylhydrazones (ADNPH, KDNPH) have been studied (R.L. Levine, 1990; Y.Y. Dubinina et al., 1995). The levels of the obtained compounds were registered using Genesis-10UV spectrophotometer (Thermo Scientific, USA) at 270 and 363 nm wavelengths, expressed in the units of optical density related to 1 g of protein, using the coefficient of molar extinction $22 \cdot 10^3$ $M^{-1}cm^{-1}$. To determine total protein concentration, a kit of reagents produced by Vital Diagnostic Co. (Russia) was used.

The incidence of forming placental insufficiency in the main group of pregnant women was studied retrospectively based on the data of US fetometry, placentometry and Doppler ultrasonography of the vessels of the uterus-placenta-fetus complex using MEDISON MYSONO U6-RUS ultrasound device (Samsung Medison, South Korea), morphological examination of placentas according to a standard methodology, described by A.P. Milovanov (1999), the association of ADNPH with KDNPH in the blood serum of the women of this group was also established.

By means of logistic regression analysis (A.-K. Nilsdotter et al., 2003; L. Gossec et al., 2005; E.V. Zhilina, 2010) a mathematical model of placental insufficiency development in pregnant women with IDA was obtained.

The results of the investigation were processed using a licensed Statistica 8.0 program.

Results and Discussion. All pregnant women were residents of the same region of Nizhny Novgorod; the age and social status of the women in the main and control groups, as well as in the subgroups of the main group did not differ significantly ($p>0.05$).

Pregnant women of subgroup 1 (12; 42.9%) were noted to have significantly more frequent menstrual bleedings in the history compared to the control group ($p<0.05$), that explains the preexisting character of IDA in these women. The incidence of chronic gastroduodenitis in these females (10; 35.7%) statistically significantly exceeded that in the control group (1; 5.6%), that correlated with the literature data on the role of gastrointestinal pathology in the IDA genesis [13, 14]. Subgroup 2 did not differ significantly from the control group by the quantity of pregnant women with the given pathology ($p>0.05$).

Working together with the Department of Biology of Nizhny Novgorod State Medical Academy, we investigated the intensity of the processes of free radical oxidation of blood plasma proteins by the level of carbonyl derivatives and defined two most essential factors, influencing the probability of placental insufficiency development in pregnant women with IDA — products of oxidative protein destruction in spontaneous oxidation: ADNPHsp and KDNPHsp [15].

On the basis of the data obtained, a mathematical

model of calculating the risk of placental insufficiency (Rpi) occurrence in women with IDA has been worked out:

$$Rpi=\exp[(-4.156+(0.432)\cdot ADNPHsp+(-0.038)\cdot KDNPHsp)]/1+\exp[(-4.156+(0.432)\cdot ADNPHsp+(-0.038)\cdot KDNPHsp)].$$

It was estimated that placental insufficiency is likely to develop at Rpi≥0.54. The variables, used in the logistic regression equation, had the characteristics presented in Table 1.

Chances of complication of gestation period by placental insufficiency in pregnant women with IDA have been assessed (Table 2). When values of i-variable increase by 1, the chance of placental insufficiency development increases by the number of times equal to the odds ratio.

Besides, the value interval for each of the variable includes a true value with a probability of 95%, and statistical significance of parameters is expressed in the p-level value [15].

The regression model obtained was verified by plotting a ROC-curve. The value of AUC index appeared to be equal to 0.96, indicating a high quality of the received result [15].

It was estimated that diagnostic sensitivity of the obtained test was 93%, diagnostic specificity 80%, and diagnostic efficacy 87%.

Mean value of Rpi in the control group, in accordance with the mathematical model developed by us, amounted to 0.052±0.052, which statistically significantly differed from the values in subgroups 1 (Rpi=0.821±0.096) and 2 of the main group (Rpi=0.688±0.155) ($p<0.05$).

Thus, the developed mathematical model by Rpi values in pregnant women with IDA allows for formation of groups at risk for placental insufficiency with high diagnostic sensitivity and efficacy.

Table 1

Characteristic of variables in the logistic regression equation

Variables (n=107)	bi	p-level
ADNPHsp	0.432	0.0087
KDNPHsp	–0.038	0.0069

Here: bi values express natural logarithms of odds ratio (assessment) of placental insufficiency development for each of the parameter. Values of p-level indicate the level of statistical significance for each of bi [15].

Table 2

Assessment of chances of placental insufficiency development

Variables	Odds ratio	95% confidence interval	p-level
ADNPHsp	1.54	1.12; 2.11	0.0087
KDNPHsp	0.96	0.81; 1.42	0.0069

Conclusion. Changes in the levels of aldehyde- and ketone-dinitrophenylhydrazones in spontaneous oxidation is an early prognostic criterion of forming placental disorders in pregnant women with IDA detected in the first and second trimester of pregnancy.

Study Funding and Conflicts of Interest. The work was not supported by any source. The authors declare no conflicts of interest related to this study.

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