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Influence of maternal hemoconcentration on fetal development.

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ABSTRACT

This paper deals with the modern views on the rheological properties of blood in pregnant women and their effect on placental blood flow, fetal growth and development. Physiological role of hemodilution was determined during the second trimester of pregnancy. We have presented our own data on gestation process and perinatal outcomes in women with elevated blood concentration indices. It was found that the most typical complication in such cases is a fetal growth retardation, being detected in 40% of cases. It has been shown that the pathophysiological mechanism of this condition is based on the increased viscosity of blood in the small vessels and on disorders of microcirculatory blood flow. The rationality of the therapy aimed at improving the rheological properties of blood has been proved. In particular, pregnant women with high hemoglobin indices in the second trimester are recommended to take Dipyridamole.

Keywords: pregnancy, hemodilution, blood viscosity, microcirculation, fetal growth retardation

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INTRODUCTION

The most important task of modern obstetrics is the prevention and treatment of serious complications of pregnancy, having a direct effect on perinatal outcomes for both the mother and her fetus. Among these complications a prominent place belongs to the placental insufficiency (PI) and the syndrome of fetal growth retardation (FGRS). FGRS is known to be the most common cause of low birth weight, its frequency varies from 3-10% in developed countries, up to 15-20% in developing countries. The effect of FGRS and low weight on stillbirths and infant mortality can be found in 66-69% of cases [1, 2]. The reasons for FGRS are numerous. They can include maternal age, parity, excessive and low body weight during pregnancy, gestational hypertension, extragenital pathology, etc. For all the variety of factors associated with fetal growth retardation, the pathogenetic mechanisms of this complication are largely universal. Their implementation is performed largely due to the structural features of placenta and the hemodynamic characteristics of female blood, which is the sole supplier of energy and plastic resources to the fetus [3-5].

It is known that the physical properties of the blood play a key role in the implementation of its rheological capabilities. Maintenance of the placental blood flow requires a high turnover in the microcirculatory component. It is important to remind that the blood is not a non-Newtonian fluid and its viscosity is a variable that depends on the diameter of the vessel and ranges within 1.7 - 22.9 mPa.s [6]. The smaller the diameter of the vessel is, the higher the viscosity of the blood flowing therein is. This proportion is described by Caisson model, and the viscosity index mostly depends on the concentration of formed elements, that is, on hematocrit and, indirectly, on the level of hemoglobin. Good blood flow in intervillous space can be achieved only by reducing the concentration of red blood cells. This is what the process of physiological hemodilution is aimed at, which is based on the increase in the circulating plasma volume. It is most noticeable in the second trimester of pregnancy. During this period, the second wave of trophoblast invasion ends and the further gestation development is largely programmed [3, 7-9].

Physiological frames of the concentration characteristics of blood in pregnant women still remain a subject of debate. The lower limit of the normal hemoglobin range in the second trimester is 105-110 g/L [1-10]. The upper limits are not defined at all, and this applies to both the pregnancy in general, and its individual stages. At the same time, it is quite obvious that the lack of hemodilution may be a marker of the coming trouble based on the increased blood viscosity and impaired microcirculation [11-13]. There is evidence that the risk of perinatal mortality is 2.6 times higher in women with higher levels of hemoglobin. As a result of the analysis of 295,651 birth outcomes, a high level of hemoglobin was defined as an independent risk factor for adverse perinatal outcomes [14-15].

MATERIALS AND METHODS

We decided to determine the upper concentration limit of blood parameters in women in the medium gestation term. the average index of hemoglobin was evaluated in a sample of 280 pregnant women suffering from anemia being on terms of 16-24 weeks. It was established that the average hemoglobin level was 118.4 g/l (± 95% CI: 116.7-120.0 g/l), and the first standard deviation was recorded at 126.6 g/l. A suddenly large percentage of women was discovered, who had hemoglobin level exceeding this value - 18.5% (52 patients). We conducted observation over their pregnancy (group I), and compared with women with hemoglobin levels of 110-126.5 g/l (50 randomly selected women, group II).

RESULTS

Comparison of the basic anamnestic characteristics revealed that at the same average age the number of nulliparous women in group I was higher (63%), while in the control group the proportion of patients with first and repetitive delivery was 48% and 52% (p=0,04), respectively. The dynamics of Hb index at different periods of pregnancy showed that a minor feature of women in group I was decline in this index from the first to second trimester with a further stabilization at middle level 129.3 g/l (± 95% CI 126.7-131.9 g/l). At the same time, 20% of the patients had very high indices - 140-149 g/l. The control group showed another dynamics. In particular, despite Hb values close to those in the group I at the beginning of pregnancy, it significantly decreased by week 20-21 (up to 113.2 g/l, ± 95% CI -116.1-120.2 g/l). 22% of women had

symptoms of anemia appeared during this period. However, by delivery, Hb increased again and was 118.5 g/l (± 95% CI 117.2-119.7 g/l).

The occurrence of ultrasound markers of the beginning feto-placental insufficiency in women of group I was already observed during second trimester, week 18-22. At this time, symptoms such as a change in thickness and degree of maturity of the placenta occurred in 27% of patients and by week 32-36 in 37%. Signs of intrauterine fetal suffering in the third trimester were recorded in 27% of cases. In group II, ultrasonic placental abnormalities were detected only in the third trimester, in a small percentage of cases, accompanied by symptoms of chronic fetal hypoxia (about 4%, the differences are significant with group I, x^2 = 10.13, p=0.0015). Implementation of placental insufficiency in FGRS (according to ultrasound findings) in women of group I occurred, as a rule, in the last third of pregnancy, sometimes prior to 30-week period. Fetal development retardation was recorded in 42% of women with high levels of Hb. In control group, FGRS was found in only 4% of patients (x^2 = 19.32, p = 0.00). The availability of hemoconcentration increased the chances of FGRS development by more than 16 times (OR=16.25±0.77, ±95% CI, 3.55 - 74.2).

In most cases, prenatal diagnosis was confirmed after birth. Delivery in both groups occurred on symmetrical terms. At the same time, the average weight of newborns of women with haemoconcentration was 3,057 g (± 95% CI: 2927.9-3186.2 g), and in the control group - 3,480 g (± 95% CI: 3362.1-3614.6 g, t = 4,79, p = 0.001). The number of children with a confirmed diagnosis of FGRS in group I reached 43% and repeated the results of antenatal diagnosis. Hypoxia at birth was observed in 52% of newborns; in every third case, it was moderate or severe. 17% of cases required the second stage of treatment. In group II, children with low birth weight were only 6%. The progress of early neonatal period, as a rule, was of physiological nature.

Assuming that the main cause of the worst perinatal outcome was an impairment of rheological properties of blood, associated with its increased concentration, we conducted a study of blood viscosity in the range of high and low shear rates. This simulated the situation in the large and the smallest vessels. We used a rotary microviscometer MVR-1 "Rosinka" with shear speeds from 25 to 250 s^{-1}. In women of main group, the whole blood viscosity at a shear rate of 25 s^{-1} amounted to 10.46 ± 4.55 cP, at a shear rate of 150 s^{-1} - 3.08 ± 0.78 cP, and at 250 s^{-1} - 1.85 ± 0.21 cP. In the control group, the viscosity index was respectively equal to 5.21 ± 4.75 cP, 2.16 ± 0.27 cP, and 1.54 ± 0.09 cP. The greatest parameters difference was achieved at low shear rates - women of group I blood had 2-times higher viscosity (t = 4.80, p = 0.005). Consequently, its turnover in small vessels and intervillous space was significantly impaired. Therefore, we have confirmed this hypothesis.

Visualization of the impaired fluid properties of blood is possible via biomicroscopy of vessels of the eyeball conjunctiva. Possibility of extrapolating local data to the systemic circulation was proved in the course of experimental and clinical studies [16]. Biomicroscopy was conducted using a slit lamp ЩЛ-2Б. Quantitative assessment of conjunctival microcirculation was performed according to the system criteria by L.T. Malaia et al. (1977) with the calculation of the partial and total conjunctival index (CoI) in points. We considered vascular abnormalities (changes in the arterioles and venules diameter ratios, number of functioning capillaries, mobilization degree of arteriolo-venular shunts), and extra- and intravascular pathology (hemorrhage, perivascular edema, sludge phenomenon and microthrombosis). It was found that the vascular CoI in the main group was 8.71 points (± 95% CI 7.55 - 9.88), and in the control group - 0.75 points (± 95% CI 0.46 - 1.04, t = 10.64, p = 0.001). The difference in microcirculation indices was formed due to pronounced vascular changes in pregnant women with hemoconcentration. Against the background of degenerative damages to the vascular wall representing a non-uniform caliber and tortuosity, the arterial vasoconstriction was observed. The number of arteriolo-venular anastomoses increased, resulting in cavitation of the capillary network - reduction in the number of functioning capillaries. As a result, blood flow in vascular conjunctival pool slowed down. Intravascular pathological component was also well represented in the main group, mainly due to the sludge-phenomenon in the venules and capillaries. Partial CoI was 1.29 points (± 95% CI 1.08 - 1.5). No intravascular changes were revealed in the control group.

No differences in the extravascular index was found between the groups. As a result, the total conjunctival index in group I was 10.14 points (± 95% CI 8.91 - 11.37) and in the control group - only 0.75 points (± 95% CI 0.46 - 1.04. t = 11.85, p = 0.00). Biomicroscopic findings showed that the increased blood viscosity in pregnant women with hemoconcentration is directly implementated in the form of severe systemic

microcirculation disturbances. Apparently, this leads to a drop in uteroplacental blood flow and creates conditions for FGRS development.

SUMMARY

Thus, a moderate hemoconcentration in the second trimester of pregnancy represents a significant problem. Despite the fact that this is a fairly common situation, it often falls out of view of experts. A lack of medical suspicion and misunderstanding of the negative effects in terms of hemoconcentration, coinciding with the second wave of trophoblast invasion, may lead to adverse perinatal outcomes. Currently, there is no way to reduce the concentration of blood parameters in pregnant women. However, it is possible to improve both its rheology and flow properties, and thus ensure effective microhemodynamics. In this context, the capabilities of Dipyridamole, a well-studied drug, which has firmly come into common obstetrical practice, attract the attention. The pharmacological basis of Dipyridamole action is the inhibition of adenosine capture by platelets, red blood cells and endothelial cells. This correlates with an increase in the local concentration of adenosine. The latter, by affecting platelet A2-receptors, stimulates the adenylyl cyclases and promotes the increase in the concentration of 3,5-cyclic adenosine monophosphate. This mechanism determines the inhibition of platelet aggregation, and supports local vasodilating influence of Dipyridamole. In addition, the vasodilating effect is associated with the ability of the drug to potentiate the endothelial cell stimulating synthesis of nitric oxide. Angiogenic activity is determined by the stimulation of the formation of collateral arteries and capillaries. The ability of Dipyridamole to inhibit the activity of renin in blood plasma and reduce the concentration of aldosterone, inhibiting thereby the functionality of the renin-angiotensin-aldosterone system, has a positive effect on patients with hypertension. Today, the Dipyridamole effects on prevention of vascular complications, such as pregnancy preeclampsia, have been proven. WHO recommends its use along with acetylsalicylic acid for the said purposes. It is known that, in combination with low molecular weight heparin, Dipyridamole reduces the frequency of antenatal losses, premature birth and low fetal weight in women at high risk of placental insufficiency [17-20].

CONCLUSION

Subject to our data, there is no doubt about the prescription of Dipyridamole in therapeutic doses (100-150 mg daily) for patients in the second trimester with hemoglobin level greater than 126 g/l. Improvement of the utero-placental blood flow due to the pharmacological effects of the drug can prevent FGRS and become an effective fetal protection under impaired microcirculation and compromised blood rheology.

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