

ANALYSIS OF NEWBORNS WITH ABO-IMMUNIZATION AGAINST THE BACKGROUND OF PLACENTAL DYSFUNCTION

Chorieva G.Z., Sadikova D.R., Sadullaeva U.A., Yangibayeva D.T.

Department of Obstetrics and Gynecology in Family Medicine, Tashkent Medical Academy, Tashkent

Abstract: 32 pregnant women with a diagnosis of placental dysfunction in pregnant women with ABO-immunization who received treatment with L-arginine and low molecular weight heparin during pregnancy were monitored. During pregnancy, the effectiveness of the therapeutic and preventive measures carried out was judged by the results of the BFPP, its final assessment, the condition of children at birth, and the course of the early neonatal period. Perinatal mortality in the group with placental dysfunction with ABO immunization, who received treatment, decreased by 21%, of which antenatal mortality - by 2.3 times, postnatal mortality – by 1.6 times.

Key words: ABO immunization, fetal biophysical profile, placental dysfunction, L-arginine, low molecular weight heparin.

Relevance: Hemolytic disease of the fetus and newborn, caused by isoserological incompatibility between mother and fetus for various erythrocyte antigens, remains a pressing problem of modern perinatology (12,13,15). Untimely diagnosis of hemolytic disease of the fetus and newborn and its inadequate therapy leads to disability of the child due to changes in immunological reactivity, as a result of which antenatal fetal death is possible (3,4,15).

In recent years, there has been a decrease in perinatal mortality in the world from hemolytic disease of the fetus and newborn: from 50 to 25% - due to exchange transfusions, from 16 to 13% - with the introduction of amniocentesis, from 25 to 16% - at early delivery, to 3% and less - after the beginning of invasive methods of diagnostics and treatment (intrauterine transfusions, cordocentesis). However, it is not possible to completely prevent morbidity and mortality of newborns with this pathology (6). Developing chronic hypoxic hypoxic conditions of the fetoplacental complex due to immunologic incompatibility lead to persistent secondary placental dysfunction syndrome (5,13).

In placental dysfunction (PD), pregnancy is practically with complications. According to the literature, the incidence of PD in habitual miscarriage ranges from 50 to 77%, in somatic pathology 24-45%.

In case of habitual non-pregnancy it ranges from 50 to 77%, in case of somatic pathology 24-45%, in gestosis it is 30.6% (4,14). The basis of pathogenesis in placental dysfunction is caused by uteroplacental blood flow disorders, and the clinical manifestations are directly caused by hypoxia and/or fetal growth retardation. The latter ranks fourth in the structure of perinatal morbidity and mortality, and signs of it are detected in 10% of live-born children (1,10,12). In blood incompatibility between mother and fetus according to the ABO system, placental maturation is more often disturbed. The placenta plays dynamic role in the processes of interaction of organisms - mother and fetus.

Increased rate of development of the placenta, the needs of the fetus are accompanied by special requirements for the metabolic processes underlying functional activity of the placenta. The study of metabolic processes in the placenta during physiologic pregnancy gives an idea of the ways of their coordination in the system of mother and fetus. ways of their coordination in the mother-placenta-fetus system (8,10). There is a constant increase in scientific works devoted to the role of proteolysis in the formation of metabolic and detoxifying functions of the placenta (7,11). The study of metabolic abnormalities in the placenta during

ABO immunization of pregnant women can serve as a model for studying the main mechanisms that constitute a disruption of adaptation-homeostatic reactions of maintenance of metabolism between the maternal and fetal organisms.

Under the influence of endogenous intoxication (EI) in the mother-placenta-fetus system, a "pathologic regulatory system" is formed "pathologic system of regulation", which contributes to the development of placental dysfunction, complications of pregnancy, labor and delivery, placental dysfunction, complications of pregnancy, labor, birth of low birth weight babies and determines a high frequency of HD in newborns (2,9).

The applied medicinal preparations contribute only to stabilization of the pathological process and maintenance of compensatory - adaptive mechanisms at the level that allows to ensure prolongation of pregnancy to a possible optimal term delivery, but it is not possible to completely rid the pregnant woman of placental dysfunction is not possible [1,8].

Search for new methods of correction of endogenous intoxication in pregnant women contributed to the inclusion of efferent methods in therapy, which contribute to the removal of toxic substances from the body of the pregnant woman and can significantly improve the state of organs and systems of natural detoxification, prolong pregnancy and produce more viable offspring.

Methods of research. We conducted a retrospective clinical and statistical analysis of 10740 delivery histories for the period 2005-2015 in the obstetric complex of the 2nd TMA clinic and found that 3222 women had O (I) Rh (+) blood group and the proportion of their delivery histories was 30%, while the proportion of ABO-immunization was 0,01%, the proportion of neonatal hemolytic disease development with ABO-immunization was 0,3%. We further analyzed 27 birth histories of ABO-immunized infants not treated during pregnancy for pre-existing ABO immunization and 22 newborn developmental histories.

The results of 95 pregnant women with ABO-immunization with gestational age from 16 to 38 weeks and 87 of their newborns in 2016-2019 were subjected to clinical and statistical analysis. Clinical observations in 65 patients were started from the gestational age at which the diagnosis of ABO-immunization was established. All pregnant women including the retrospective group were divided into 4 groups: Group 1 (comparison) - 27 pregnant women and 22 neonates with ABO-immunization who did not receive treatment during pregnancy (retrospective clinical and statistical analysis); Group 2 - 32 pregnant women with ABO-immunization who received conventional therapy with L-arginine (tivortine, aminar) 100.0 ml 1 time per day for 10 days, then 5 ml 4 times per day for 20 days; low molecular weight heparin (enoxaparin, calcium nadroparin) 1 time per day depending on body weight for 7 days and their 26 newborns. Conventional therapy was carried out from the time of diagnosis of ABO-immunization three times at gestational periods of 16-18; 24-26; 36-37 weeks; Group 3 - 33 pregnant women with ABO-immunization who received metabolic therapy with the drug Kokarnit. The drug was used starting from the 16th week of gestation at 2,0 ml daily intramuscularly for 10 days three times during the observation period and their 31 newborns. Group 4 (control) - 30 healthy pregnant women with O (I) group Rh positive blood and their 30 newborns without ABO-immunization.

The diagnosis of ABO-immunization was established on the basis of obstetric history, clinical manifestations, biochemical and immunohematological parameters, ultrasound, Cardiotocography and Dopplerometry results.

Markers of endogenous intoxication tyrosin peptidase, tryptophan peptidase (TZP, TRP) and MSM were determined according to the method of V.B. Gavrillov et al. (1999). The concentration of cytochrome C in serum was determined according to the method of N.A. Gvatua et al. (1990). The level of medium molecular weight substances (MMS) and cytochrome C in the placenta supernatant was investigated according to the method of M.Y. Malakhova (1999). The amount of MSM substances was expressed in mmol/g tissue. Oligopeptides were determined in diluted supernatant using the method of Lowry et al. (1991).

Immuno-hematologic studies were performed in 122 pregnant women. Blood group and Rh factor, natural and isoimmune agglutinins were determined. The level of antibodies was determined by enzyme-linked immunosorbent assay on a Human device (Austria), as well as by Coombs' test.

Fetometric indices were measured on an Aloka SSD-1700 apparatus (Japan). When studying the placenta, we used the classification of P. Grannum et al. (1979) according to the stages of maturation. Cardiotocographic examination (CTG) was performed in 122 pregnant women using an Agilent-50A (Philips, Germany) at a minimum of 30 weeks' gestation. Fetal biophysical profile (FBPP) was judged by respiratory movements, motor activity, fetal muscle tone, amniotic fluid volume, non-stress test (NST) according to F.A. Manning, (1980). Blood flow in uterine arteries, placental vessels, umbilical cord, fetal aorta, middle cerebral artery of the fetus was studied.

The obtained results were subjected to statistical processing using the Excell application program package. Comparison of parametric variants after preliminary assessment of the correctness of sample distribution was performed on the basis of Student's criterion (t) with calculation of error probability (p).

The results of retrospective analysis of the course of pregnancy, delivery, and postpartum period of 27 delivery histories, 22 histories of neonatal development, and the state of proteolysis and membrane processes in women with ABO-immunization who did not receive treatment during pregnancy for already existing ABO immunization are presented below.

Parity analysis showed that the number of first-pregnant women with ABO-immunization was 10 times higher than that of repeat-pregnant women, which coincides with the literature data on the frequent detection of ABO-immunization in first-pregnant women (E.K. Aylamazyan et al., 2007).

Analysis of the gynecological history showed that the aggravated gynecological history in ABO-immunization was aggravated by spontaneous miscarriage in 26% of cases, and in 14.8% - by undeveloped pregnancy, which can be considered both as a possible factor of immunization and as a complication of the course of pregnancy in ABO-immunization. Pregnant women with ABO immunization have a high incidence of threatened abortion - in 70.4% of cases, with almost equal frequency in both I (37.0%) and II (33.3%) halves of pregnancy, premature detachment of the normally located placenta as the most severe obstetric complication, at ABO-immunization was observed in almost half of the women in labor (48.1%), possibly associated with a high incidence of placental dysfunction (77.8%), developing against the background of intrauterine infection (IUI) (63%), premature rupture of the fetal bladder (44.4%). 63.0% of pregnant women with ABO-immunization had polyuria, which coincides with the literature data (Konoplannokov A.G., 2009; Mineeva N.V., 2010). Analysis of the course of labor revealed that 77.0% of women delivered on time and conservatively. Preterm labor was observed in 18% of cases, and delayed labor - in 4.5% of cases. When analyzing complications of labor and early postpartum period, atonic bleeding as well as uterine subinvolution were observed in 22.7% of cases. Thus, fetal growth retardation syndrome (FGS) was observed in 13.6% of women with ABO-immunization. More than 2/3 of the newborns were born in asphyxia (86.3%), and every second of them was born in severe asphyxia (31.7%). Perinatal mortality in the group of women with ABO-immunization, occurred in 54.4% of cases. These factors made it possible to assign pregnant women and women in labor with ABO-immunization to the risk group for the development of maternal and perinatal pathology.

Thus, retrospective analysis of the course of pregnancy, labor, postpartum period and the state of newborns in pregnant women with ABO-immunization who did not receive treatment during pregnancy showed a complicated course of gestation, labor and a high percentage of perinatal losses.

The course of this pregnancy in women of group 2 was complicated by: vomiting of pregnant women in 65.3%. Among the antenatal indicators that aggravate the sensitization of the maternal immune system, the most significant were: preterm delivery, which was observed

in 65.3%, with almost equal frequency in both early (34.6%) and late (30.7%) gestation, placental dysfunction in every second (50%), anemia in 96.1%, and intrauterine infection in 42.3% of cases. Term and vaginal delivery occurred 1.3 times more frequently than in the control group. Preterm labor was observed in 11.5% of cases. Labor was complicated in 23.1% of cases with prenatal rupture of fetal membranes, in 15.3% with premature detachment of the normally located placenta. Uterine subinvolution was observed in 15.3% of cases in the postpartum period. The obtained results showed that traditional therapy in pregnant women with ABO immunization had its positive effect on the course of pregnancy and the outcome of childbirth, but according to the main indicators the incidence of pathology remained higher than in the control group.

The effectiveness of the conducted therapeutic and preventive measures during pregnancy was judged by the results of fetal biophysical profile its final evaluation, the condition of children at birth, the course of their early neonatal period. Pathologic parameters of cardiotocography were insignificantly reduced, but 10 times higher than in the control group, normal parameters increased after treatment 1.5 times. The most pronounced deviations in 88.5% were observed on the side of fetal motor activity, which were 7.7% lower than before treatment.

Out of 26 pregnant women with ABO immunization who received traditional treatment, 17 (65.4%) had blood flow disorders in the mother-placenta-fetus system. Dopplerometric data revealed that after traditional treatment, uteroplacental-fetal blood flow disorders of uteroplacental-fetal flow decreased by 1.2 times due to a 1.7-fold decrease in utero-placental-fetal flow grade II disorders compared to the pre-treatment group.

Utero-placental-fetal flow disorders were leveled in 7.7% of pregnant women in the group that received traditional treatment.

Based on laboratory data immediately after birth, ABO-hemolytic disease was diagnosed in 92.3% of newborns of group 2 and in 100% of newborns of group 1.

Perinatal mortality in the group with ABO-immunization who received traditional treatment decreased 2.1-fold compared to Group 1 (15.7 and 33.3%, respectively). After traditional therapy, antenatal mortality decreased 2.3-fold, postnatal mortality decreased 1.6-fold, and intrapartum mortality was not observed in the group receiving traditional treatment.

The traditional therapy had an effect on the decrease of antibody titer, except for the titer of isoimmune antibodies 1:2-1:4, where, on the contrary, the titer increased 2.4 times. The titer of natural antibodies decreased 2-fold after treatment. The highest percentage of children born with hemolytic disease was observed at titers 1:8-1:16 - in 37,5%. 14 (58.3%) of sick children had a mild course, and moderate and severe courses were observed in equal numbers in 5 children in 20.8% each.

Thus, the conducted analysis allows us to conclude that a certain antibody titer is not a reliable criterion of ABO-hemolytic disease, but it should be taken into account as a risk factor for the development of immunopathology. The titer of immune antibodies 1:8-1:16 is critical in the occurrence of ABO-immunization and severe form of neonatal hemolytic disease.

The conducted studies showed that in women with ABO immunization after traditional therapy there was a distinct dynamics of decrease in all investigated indicators of proteolysis. Thus, in maternal blood serum the level of TZP and MSM exceeded the control data by 1.2 times. In the blood serum of pregnant women with ABO-immunization, the content of Cytochrome C increased unreliably (1.1-fold) at the same time ($P < 0.01$). The content of MSM in urine obtained from pregnant women with ABO-immunization exceeded the control data by 1.4 times.

In cord blood, the content of TZP and TRP was elevated by 45.5 and 33.7% ($P < 0.001$ and $P < 0.01$), respectively, MSM254 and MSM280 by 52.0 and 30.3%, respectively, and Cytochrome C by 36.1% compared with controls.

It should be emphasized that the observed unidirectional dynamics of TZP, TRP, MSM254, MSM280 and cytochrome C increase in maternal blood and urine, as well as in cord

blood serum, to a large extent indicates a common mechanism of endogenous intoxication development, membrane pathology in the processes of immunological incompatibility of maternal and fetal blood, which probably determines the high frequency of hemolytic disease formation in newborns from mothers with ABO immunization.

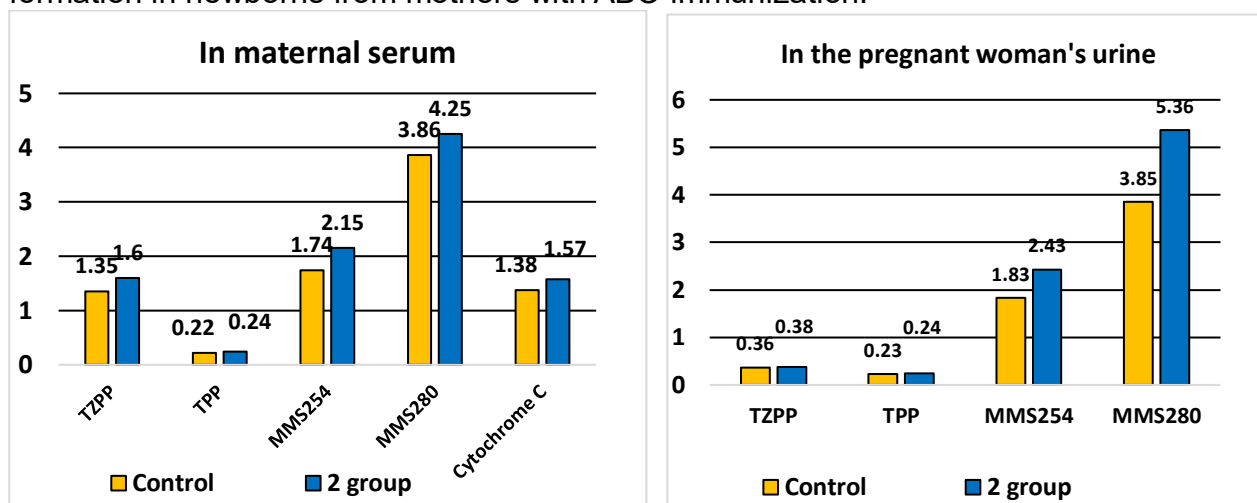


Figure 1. Proteolysis indices and cytochrome C level in serum and urine of pregnant women, %.

Thus, in the maternal serum and in the cord blood of newborns with ABO-immunization after traditional treatment the content of oligopeptides (OP) was reduced by an average of 13% compared to the control, while the content of cytochrome C was increased by 12%.

The analysis of the oligopeptide component of the pool of MSM substances in the central and peripheral parts of the placentas of the examined groups of women revealed differences in the content of OPs.

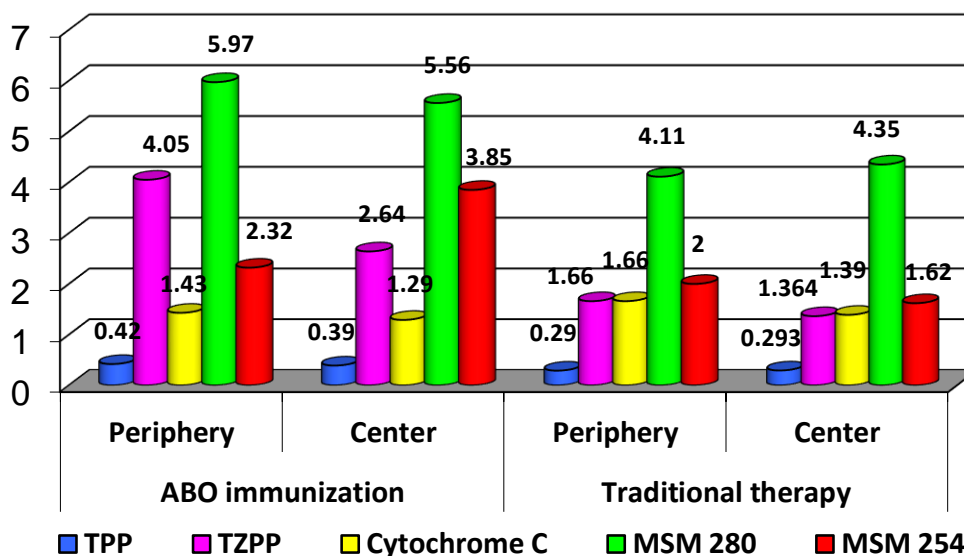


Figure 2. Proteolysis indices and Cytochrome C level in different parts of the placenta, mg/tissue.

Thus, in the placenta of the mother with ABO-immunization after conventional treatment, the content of TPP in the center and periphery compared with the group before treatment was reduced by 2 and 2, 4-fold ($P < 0.05$), TPP by 25.0 and 32.0% ($P < 0.05$), MCM254 by 2.4 and 1.7-fold ($P < 0.05$ and $P < 0.05$), MCM280 by 22.0 and 14.0% ($P < 0.05$ and $P < 0.05$), and Cytochrome C content was increased by 1.1 and 1.2-fold ($P < 0.05$).

The conducted studies showed that in women with ABO-immunization after traditional therapy there was a distinct dynamics of decrease in all studied indicators of proteolysis.

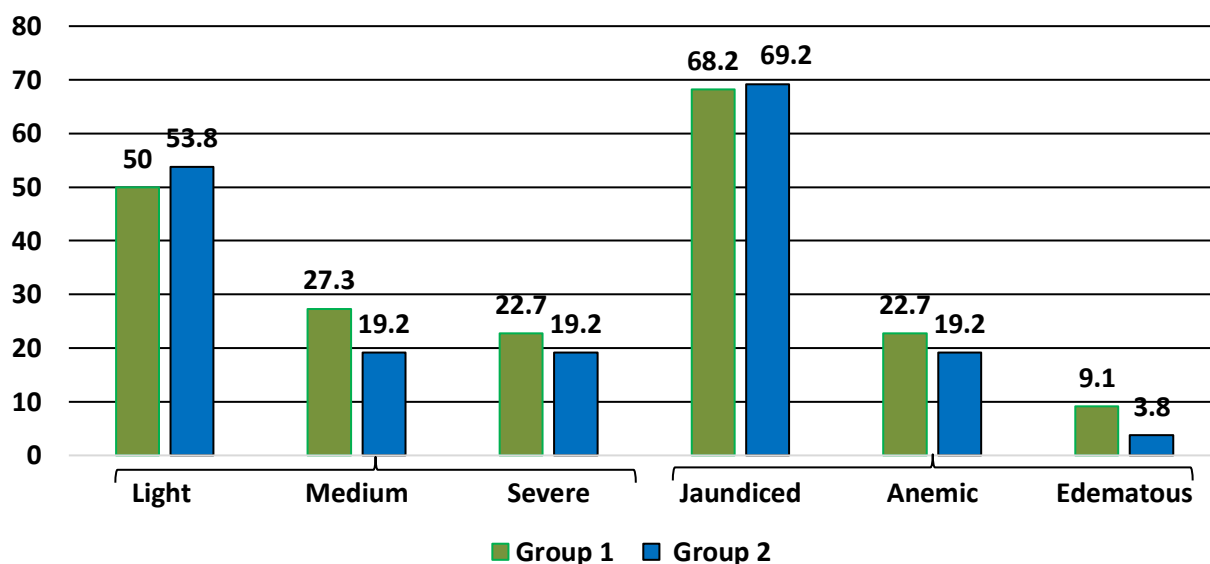


Fig. 3. Severity and forms of neonatal hemolytic disease, %.

In group 2, 7.7% of newborns were born healthy, the birth of children with ABO-hemolytic disease was observed 10% less often, with a moderately severe form was less in 1.3 times, the severe form - in 10%.

From the above data, we can conclude that traditional therapy has a certain positive effect: slightly increases the final score (BFPP) reduces the frequency of birth of children with hemolytic disease, asphyxia, promotes earlier breastfeeding. However, such treatment does not lead to improvement of all indicators to values close to control, which necessitates the search for new, pathogenetically based methods of prevention and treatment.

The results of therapeutic and prophylactic measures with the inclusion of a drug with antihypoxic and metabolic properties Kokarnit in ABO-immunized pregnant women are presented below.

Group 3 consisted of 31 pregnant women with ABO-immunization aged 19 to 37 years. When prescribing the metabolic drug Kokarnit in pregnant women with ABO-immunization, a pronounced positive dynamics of the course and outcome of labor was observed. Thus, placental dysfunction on the background of endogenous intoxication was diagnosed in group 3 by 31% less often than in the group of pregnant women with traditional treatment.

Also, the effectiveness of the conducted treatment during pregnancy was judged by the results of fetal biophysical profile, its final evaluation, the condition of children at birth, the course of the early neonatal period. CTG indicating fetal hypoxia was observed in 12.9%, which is 5.2 times less frequent than before treatment.

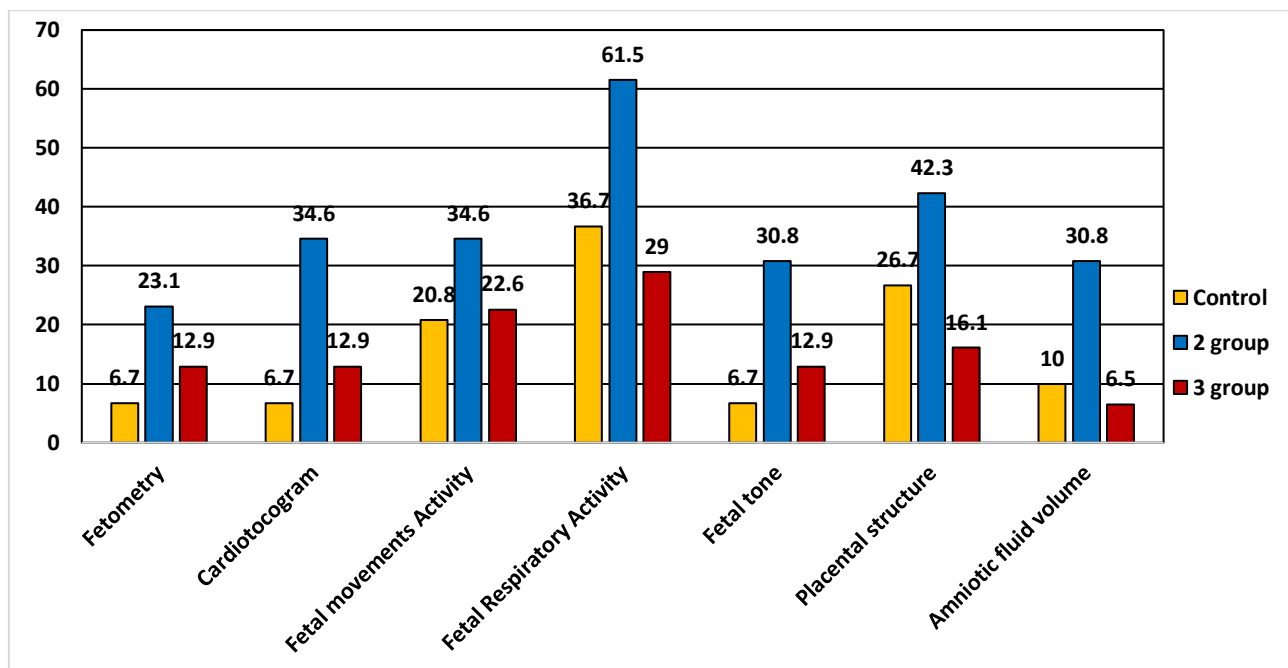


Figure 4. Pathologic features of the fetal biophysical profile in different treatment approaches

Normal fetal respiratory movements were 2.7 times more frequent in this group than in the pre-treatment group. Normal fetal muscle tone was significantly more frequent (2.3 times) than before treatment (87.1%). A normal amount of amniotic fluid was observed in 77.4% of cases, which was 35.5% higher than before treatment.

Dopplerometric data showed that after treatment with Kokarnit, the impairment of premature detachment of the normally located placenta decreased by 32.3%. The average Apgar score was 9.0 points.

There were no cases of late miscarriage, premature labor, discoordination of labor activity, complications of the postpartum period in the group receiving metabolic therapy.

When assessing the condition of newborns on the Apgar scale, it was found that after the inclusion of antihypoxant Kokarnit in the therapy group, the frequency of neonatal asphyxia decreased by 3.2 times.

Thus, the number of children with a mild course of hemolytic disease, born from women who received metabolic therapy, compared to the 2nd group, increased 1.6 times, while with a moderately severe course this indicator decreased 3.3 times, and the severe form of the disease and death of newborns from hemolytic disease was not observed (Fig. 5).

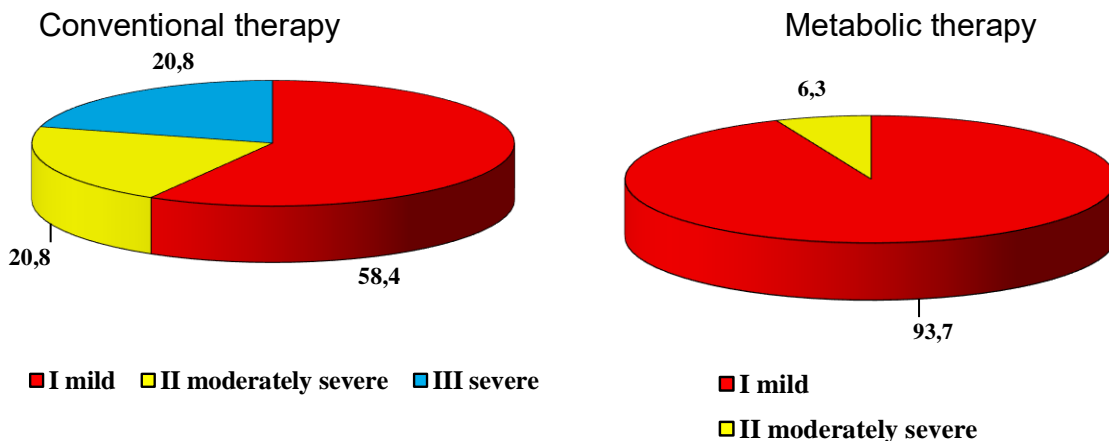


Figure 5. Severity of hemolytic disease depending on the treatment.

In all newborns hemolytic disease ended with recovery, the period of hospital stay averaged 5.4 ± 0.23 days, which is 2 days less than in group 2.

Analysis of the obtained results showed that the content of EI markers in the mother's blood serum in comparison with the data of the comparison group after three-course prescription of Kokarnit preparation decreased -TRP in 1.2, Cytochrome C - in 1.7 times, in maternal urine - TZP - 2 times, MSM280 - 1.2 times, in the peripheral part of the placenta - TZP and MSM254 - 1.2 times, TPP - 1.3 times, and increase in the level of Cytochrome C - by 12%, in the central part of the placenta decrease - TRP and MSM254 - 1.2 times and increase in Cytochrome C - by 10%.

Positive metabolic changes in the organism of mother and fetus after administration of antihypoxant Kokarnit lead to a decrease in the placenta tissue of toxic products of proteolysis and an increase in the level of Cytochrome C in the central part of the placenta.

Conclusion: Thus, the results show that in the group of pregnant women receiving Kokarnit, there was a decrease in the incidence of neonatal asphyxia, in particular its severe forms, did not develop a severe form of hemolytic disease, more often causing postnatal mortality, metabolic therapy allowed to reduce the frequency of early delivery in hemolytic disease and adverse perinatal outcomes and has a pronounced therapeutic effect on the state of the fetus with hemolytic disease, developing in conditions of placental dysfunction, leads to an increase in the number of mild forms of hemolytic disease.

References

1. Александрович А.С., Пальцева А.И., Алексинский В.С. Особенности морфологии плаценты у беременных с фетоплацентарной недостаточностью//Современные проблемы гигиены, радиационной и экологической медицины. Гродненский государственный медицинский университет (Гродно) №9. 2019. С.3-15.
2. Анташян Г. Г. Энтеросорбенты в лечении и профилактике гемолитической болезни плода и новорожденного // Медицинская наука и образование Урала. - № 4. - 2009. - С. 4-7.
3. Аряев М.Л., Васильченко Л.В., Мерикова Н.Л., Шевченко И.М. Клинико-биохимическое обоснование использования энтеросорбции у новорожденных с гемолитической болезнью // Перинатология и педиатрия 2(62)/2015. С. 86-89.
4. Барановская Ю.П. Клинико-иммунологические факторы формирования плацентарной недостаточности. 14.01.01-Акушерство и гинекология: Автореф. дис. канд. мед. наук - М., 2013. -23 с.
5. Гужвина Е.Н., Мамиев О.Б., Ильенко Л.И. Новые подходы к диагностике и коррекции плацентарной недостаточности // Российский вестник перинатологии и педиатрии. - №6. 2012 - С. 11-16.
6. Керимова Э.А. и др. Динамика показателей врожденного и адаптивного иммунитета у плодов с гемолитической болезнью, обусловленной резус-конфликтом, перенесших однократное внутриутробное внутрисосудистое переливание крови // Российский вестник акушера-гинеколога 1, 2018. 15-18с.
7. Липатов И.С., Тезиков Ю.В. Прогнозирование и диагностика плацентарной недостаточности на основе маркеров эндотелиальной дисфункции, децидуализации, апоптоза и клеточной пролиферации // Саратовский научно-медицинский журнал. 2011. Том 7, № 1. С. 52-59.
8. Неровня А.М., Киселев А.И. Морфогистологические особенности плацент при беременности, осложненной гестозом, и состоянии здоровья новорожденных // Охрана материнства и детства.- 2012. №2 20.
9. Хардилов А.В., Петров С.В., Клишкин А.С., Лядвин А.Ю. Влияние эндогенной интоксикации при различных вариантах неосложненного пиелонефрита беременных на состояние маточно-плацентарно-плодового кровотока. // Акушерство и гинекология. - 2016.- №10.- С. 48-51.

10. Chorjeva Gulchekhra. Some Links of the Pathogenesis of endogenous Intoxication in the Mother's Organism with ABO Immunization. Am J Biomed Sci & Res. 2019-5(5). AJBSR.MS.ID.000945. DOI:10.34297/AJBSR.2019.05.000945.
11. Черных С.В. и др. Синдром эндогенной интоксикации в акушерстве. Механизмы повреждающего действия бактериального эндотоксина // Медико-социальные проблемы семьи. Том 22, №2, 2017. 133-141с.
12. Bennardello F., Coluzzi S., Curciarello G., Todros T., Villa S.; Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) and Italian Society of Gynaecology and Obstetrics (SIGO) working group. Recommendations for the prevention and treatment of haemolytic disease of the foetus and newborn. Blood Transfus. 2015. 13(1):109-34. doi: 10.2450/2014.0119-14.
13. Chorjeva G., Sadikova D., Yuldasheva D., Sadullaeva U. A Retrospective Analysis of the Course of Pregnancy, Childbirth, the Postpartum Period and the Condition of Newborns in pregnant Women with ABO Immunization // Global journal of Medical Research: E -Gynecology and Obstetrics. Volume 20 Issue 2 Version 1.0 Year 2020 P.41-49
14. Daniela G. ABO blood group incompatibility and infertility: still an open debate// American Society for Reproductive Medicine. Vol. 107 no. 3. 2017
15. Qureshi H. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn// Transfusion Medicine. 2014. British Blood Transfusion Society. P. 8-20.