

Antenatal Diagnostics and Treatment of Fetal Hemolytic Disease in Rhesus-Conflict Pregnancy

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Abstract In the article we provide results of antenatal diagnostic and fetal intravascular treatment of fetal hemolytic disease in rhesus-conflict pregnancy. The study involved repeatedly pregnant women with perinatal loss in the history and diagnosed with rhesus-immunization confirmed by laboratory and instrumental research methods. Measurement of peak systolic velocity in the middle cerebral artery was effective, descriptive practical diagnostic method for severe and mild forms of fetal hemolytic disease. Besides that, we revealed a reliable link of the parameters of peak systolic velocity with the severity of fetal hemolytic anemia according to cordocentesis results. Additionally to the aforesaid measurement cardiac-femoral index should be measured to increase sensitivity of ultra sound diagnostics for the detection of anemic form of fetal hemolytic disease. Thus, the only palliative treatment method for severe forms of fetal hemolytic disease is intravascular fetal transfusion of donor's washed erythrocytes which provides high rate of perinatal survival.

Keywords Rhesus-immunization, Cordocentesis, Velocity in the middle cerebral artery, Cardiac-femoral index, Fetal intravascular transfusion

1. Introduction

Maternal alloimmunization of erythrocytes is a rare pathology of pregnancy. Approximately 1-2 of one thousand women are immunized [1]. In spite of preventive measures taken, which are effective for more than 30 years already, the most often immunization is rhesus-immunization. Prevalence of rhesus-immunization in US is equal to six cases per 1000 alive born children and about 750 cases are annually registered in France [2]. Prevalence of rhesus-immunization is considered to be equal to 15–17% among European/North American population. Among the people with African and Indian origin that values drops till 3–8%. In Asia RhD negative can be observed only in 0.1–0.3% of the population [3].

According to the medical statistical data of the Ministry of Health within the last three years there is growth of morbidity rate of new-born hemolytic disease. In 2016 that pathology was registered in one thousand two hundred and thirty-eight (0.17%) new-born babies, in 2017 in one thousand six hundred and sixteen (0.23%), and in 2018 in two thousand forty-four children. Both percent value and absolute number tend for the growth of morbidity, in spite of

the performed immune prophylaxis of iso-immunization. In relation to weight category of new-born babies we noticed the following tendency: while in 2016-2017 higher morbidity rate was observed in children weighing 2500.0g and more, in 2018 higher prevalence of new-born hemolytic disease was observed among children whose weight varied from 1500 to 2499 gram. In the structure of perinatal morbidity the values also grow. So, in 2016 NHD (new-born hemolytic disease) occupied 1.6% of the total number of pathologies, in 2017 it was equal to 2.1%, while in 2018 it reached 2.6%.

The interest in the problem of fetal and new-born hemolytic disease in our country significantly increased within recent years not only due to the growth of morbidity rate, but also with the development and implementation of modern fetal correction methods for hemolytic disease, one of which is fetal intravascular hem transfusion.

Nowadays fetal intravascular transfusion is preferable treatment method for severe fetal anemia. From the technical point of view it can be performed starting from 18th week of pregnancy. Prior to the 18th week the procedure is hardly executable due to the size of umbilical vein [4]. That method was implemented into the practice in our Republic in 2019 on the basis of the Republican Perinatal Center.

The objective of our research was the assessment of the results of antenatal diagnostics and fetal intravascular treatment of fetal hemolytic disease in rhesus-conflict pregnancies.

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2. Research Data and Methods

The work was performed in the Unit of Pregnancy Pathologies of the Republican Perinatal Center of the Ministry of Health of Uzbekistan within 2019.

Totally 19 fetal intravascular blood transfusion operations were done. The study involved 16 repeatedly pregnant women aged from 24 to 38 years old with rhesus-negative blood and with rhesus-immunization. Average age was equal to 30.5 ± 0.2 years old. Three pregnant women (18.8%) were operated twice.

Gestation term for all women was from 23 to 33 weeks of pregnancy. Average statistical gestation term was 29.3 ± 0.03 weeks.

Intrauterine intravascular transfusion induces more complications when it is performed prior to 20 weeks or after 32 weeks of pregnancy [5,6].

Inclusion criteria to the group were: informed voluntary consent of a patient to participate in fetal intravascular blood transfusion; fetal hemoglobin level below 90.0g/L, packed cell volume below 30% according to cordocentesis data, single pregnancy, gestation term prior to 33 weeks, absence of data about immune prophylaxis after previous pregnancies, and reproductive loss in history.

Exclusion criteria were: fetal hemoglobin level above 90.0g/L, packed cell volume above 30% according to cordocentesis data, first pregnancy, multiple pregnancy, mature pregnancy, severe somatic pathology, and woman's refusal to participate.

All pregnant women in the clinic had ultra sound diagnostics with Doppler metering using modern ultra sound apparatus «VOLUSON-E9» expert class. While ultra sound showed fetometric data and cardiac-femoral index, Doppler metering was used to assess not only uterine-placental-fetal blood flow, but also to determine peak velocity in fetal middle cerebral artery. In the Unit of Pregnancy Pathology before operation all women had standard prophylactic of fetal RDS with Dexamethasone 24 mg (6mg intramuscular twice a day for 2 days).

All pregnant women had trans-abdominal cordocentesis in compliance with one-needle method. The basic indication for the performance of cordocentesis was rise of peak systolic velocity of blood flow above gestation norm, i.e. above 1.5 Mom in 100% cases. Invasive procedure was performed using "free hand" method. In other words, ultra sound specialist performed navigation using convex sensor, while obstetrician gynecologist performed puncture. None of pregnant women required anesthesia at the time of cordocentesis.

In 13 cases puncture was done extra placental, i.e. a free umbilical loop was found to perform puncture of umbilical vein. In 6 cases trans-placental umbilical puncture was performed, as placenta was located along the anterior wall. We used «Spinocan» puncture needle B-Braun-22G, 88 mm long. Before the procedure a standard processing of the surgery area was done. One milliliter blood sample was

taken from umbilical vein. After that express definition of fetal hemoglobin amount, packed cell volume, blood group, and rhesus factor was performed within 30 minutes in the laboratory of the Perinatal Center. Besides that, we determined amount of total and indirect bilirubin in fetal blood. In case of detection of severe fetal hemolytic anemia the second stage of treatment was started, i.e. fetal intravascular transfusion.

For that purpose to immobilization of the fetus Arduan (Pipekuronium) solution 0.1mg was injected into umbilical vein. After that B-braun perfusor extension proximal lead 150.0 cm long and 1.5*2.7mm in diameter was attached to the puncture needle, while the second distal end of the perfusor was adjusted with a sterile 10.0ml syringe filled with erythrocyte mass. Transfusion was done five times with washed erythrocyte mass, which was prepared at the same day in the Republican Center of blood transfusion. Amount of washed erythrocyte mass was estimated according to the gestation term, supposed fetal mass, and values of fetal hemoglobin and packed cell volume. The volume of transfusion was from 45.0 mL to 95.0 mL (average 55.8mL). The speed of washed erythrocytes excretion was equal to 2.0 mL per minute with perfusor. In the process of the operation all pregnant women had fetal heartbeat monitoring using ultra sound, and definition of resistance index (RI) in fetal umbilical vein by means of Doppler metering. Average duration of the procedure was from 40 to 90 minutes dependently of the amount of infused erythrocyte mass. After the operation all pregnant women were prescribed single intravenous injection of antibiotic for prophylaxis. Average term of a pregnant woman staying in clinic was 2-3 days.

Statistical analysis of the obtained results was performed with the help of Microsoft Office, Excel 2010 standard software.

3. Results of the Study and Discussion

According to the parity pregnant women were as follows: three women had 2nd pregnancy, 6 women (37.5%) had 3 deliveries, it was 4th delivery in three women (18.8%), 5th delivery for three women (18.8%), and 6th delivery for one woman (Figure 1).

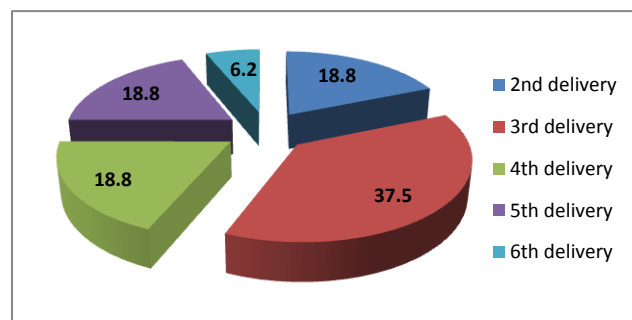


Figure 1. Distribution of the examined pregnant women according to parity

According to reproductive loss histories all women had perinatal loss of fetus due to immune dropsy. Seven women (43.8%) had stillborns, other seven (43.8%) had early neonatal death of children; all these women had replacement blood transfusion (RBT) after birth. Two women (12.5%) lost their children in infancy. Other two women (12.5%) had invalid children with cerebral palsy at home. Non-developing pregnancy was registered in one woman (6.25%), extra uterine pregnancy was observed also in one woman (6.25%). Three (18.8%) had spontaneous miscarriages at early term, while other two (12.5%) had artificial abortions in history.

According to the level of incomplete recourse antibodies in pregnant women we revealed that the range of growth was from 1:16 to 1:512. One woman had a titer equal to 1:16, three had 1:32, while five women (31.2%) had a titer of antibodies equal to 1:64. High titer 1:128 was registered in four women (25.0%), 1:256 in one, and other two women (12.5%) had as high titer as 1:512.

Ten women (62.5%) during the whole gestation period and until the next impregnation received rhesus immune sensitizing in the form of multiple plasmapheresis.

Three pregnant women (18.8%) had genotyping of fetal rhesus based on mother's blood sample at early term of pregnancy, when in all cases fetal rhesus was found to be positive.

Some authors [7] showed perfect efficiency of that non-invasive screening method in 416 Rh-negative maternal serums taken in the first trimester of pregnancy with 100% sensitivity and 95.2% specificity. In 2.2% of the cases fetal genotyping was indefinite, which could be due to a large proportion of African women in the group.

Peak systolic velocity of blood flow in fetal middle cerebral artery in the whole group before fetal hem transfusion was average 72.85 ± 1.79 cm/sec, and that was significantly more than 1.5 MoM.

We applied measurement of cardiac-femoral index (ratio of the greatest diameter of heart during diastole to the length of fetal femur) as an additional marker of fetal hemolytic anemia. All 16 patients had a stable dynamic increase of CFI (0.62-0.72; 0.67 ± 0.01). Thus, sensitivity of that marker was equal to 100%.

Table 1. Hematological and biochemical parameters of fetal venous blood before intrauterine blood transfusion

Parameter	Mild anemia (n-2)	Severe anemia (n-14)
Hemoglobin g/L	102.5 100-105	72.3 39-90
Packed cell volume, %	34.5 33-36	26.4 15-36
Total bilirubin mmol/L	13.4 11.8-15	61.7 20.5-110
Indirect bilirubin, mmol/L	13.4 11.8-15	45.7 15.5-74

In two cases (12.5%) we revealed mild fetal hemolytic anemia. Distribution of hematologic parameters in venous blood according to cordocentesis results in compliance with the severity of fetal anemia is presented in the table herein.

In case of severe fetal anemia hemoglobin concentration and packed cell volume were reliably lower than in case of mild anemia. The amount of total and indirect bilirubin in fetal venous blood was not reliably higher both in case of mild and severe anemia.

As a result of correlation analysis we determined a direct link between peak systolic velocity in MCA and severity of fetal hemolytic anemia according to cordocentesis data ($r=+0.856$; $p<0.01$).

All these pregnant women had preterm deliveries. Out of these 16 women fourteen (87.5%) had alive born babies. In the majority of cases (13 women, 81.2%) pregnancy finished by planned Caesar's section, while the rest three women (18.8%) had natural preterm deliveries.

World Health Organization recommends delayed ligation of umbilical cord within the first minute after birth, advantages of which were demonstrated both in mature and preterm children in the hemoglobin amount at birth, demand in transfusion and other therapeutic methods for treatment of new-born babies with retardation of both physical and mental development [8-9]. All preterm new-born babies at the moment of birth had delayed ligation of umbilical cord, which was not counter-indicated.

After birth five new-born babies (31.2%) had edematous form of hemolytic disease, while eleven (68.8%) children had anemic-icteric form of new-born hemolytic disease (figure 2).

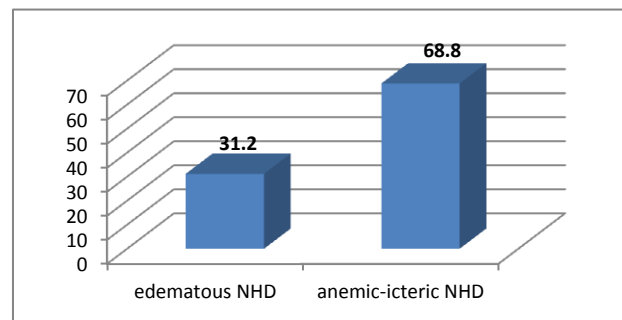


Figure 2. Prevalence of NHD dependently on the form of the disease

Fourteen new-born children after birth had replacement blood transfusion. According to perinatal indicators there were two antenatal fetal deaths and two early neonatal deaths of new-born babies.

Only four new-born babies (25.0%) were born in asphyxia, with Apgar score 1-6 (3.5 ± 0.01 points) and underwent resuscitation. Other children's score according to Apgar scale was equal to 7 and more (8.6 ± 0.01).

According to Van Kamp I.L. et al (2005), who performed retrospective analysis of 740 intrauterine, intravascular transfusions and revealed total proportion of complications equal to 9.0% during pregnancy. In it 3.0% were

complications during the intervention, 5.9% were emergency Caesar's section (2.4% Caesar's sections at the moment of the procedure), 2.7% intrauterine fetal death, and 2.0% new-born babies deaths due to blood transfusion.

In these cases, taking into account absence of experience, analysis of the structure and importance of the complications appearing during intrauterine hem transfusions revealed the following: complications developed in 25.0%. In the structure of intra operative complications we could observe fetal bradycardia in one case (6.25%), formation of umbilical hematoma also in one case (6.25%).

Amongst post operative complications observed in pregnant women involved into our study in two cases (12.5%) within the first week after intrauterine intervention the women had preterm deliveries; there was one case (6.25%) of antenatal fetal death within initial 12 hours after transfusion due to thrombosis of umbilical veins.

4. Conclusions

1. Doppler measurement of the peak systolic velocity in the middle cerebral artery is effective, descriptive, and practical diagnostic method in cases of severe forms of fetal hemolytic disease.
2. We revealed a reliable direct correlation between the value of peak systolic velocity in the MCA and severity of fetal hemolytic anemia according to cordocentesis data.
3. Cardiac femoral index should be determined additionally to the measurement of the peak systolic velocity in MCA to increase sensitivity of ultra sound diagnostics in the detection of anemic type of fetal hemolytic disease.
4. The only palliative treatment method for severe forms of fetal hemolytic disease is intravascular intrauterine transfusion of washed erythrocytes, which provides high rate of perinatal survival.
5. For the achievement of good perinatal outcomes immunized women of our Republic should be observed dynamically during pregnancy in perinatal centers equipped with modern ultra sound apparatus and with specialists providing modern therapeutic-diagnostic standard management of patients like that.

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