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Fetal hydrops and middle cerebral artery Doppler in prediction degree of fetal anemia and the best timing for therapy

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Summary

Purpose: To determine the role of fetal multiples of the median of middle cerebral artery peak systolic velocity (MoM MCA-PSV), in predicting the degree of fetal anemia for determination of the best timing for the second intrauterine intravascular transfusion (IUIVT) in hydropic fetuses with Rh alloimmunization. *Materials and Methods:* Prospective study of 30 monofetal pregnancies with maternal Rh D alloimmunization and hydrops fetalis, from 2005 to 2012 that underwent first and second IUIVT were assessed. *Results:* Thirty IUIVT were performed at 26.9 weeks (standard deviation, SD 4.3). Mean interval to the second procedure was 11.23 (SD 6.21) days and average hematocrit decline rate was 1.45%/day. The study did not demonstrated statistical significance between MCA-MoM-3 before the second IUIVT, and the mean decline rate in fetal hematocrit levels (expressed in percentage/day) $r = 0.220$; $p = 0.242$, and between MCA-MoM-3 and the time interval between both procedures (T) $r = -0.157$; $p = 0.408$. *Conclusion:* The measurements fetal MoM-MCA before every IUIVT cannot be useful as predictor for the best timing for the next IUIVT, but it can be useful in predicting severity of fetal anemia.

Key words: Hydrops fetalis; Intrauterine intravascular transfusion; Doppler.

Introduction

Hemolytic disease of the fetus and newborn (HDFN), is presently classified as an alloimmune hemolytic disorder. With severe RBC destruction, hepatic erythropoiesis, hepatic enlargement becomes extreme. Portal and umbilical hypertension develops. Placental perfusion is reduced and ascites appear. As it is well-known, that progressively greater distortion of hepatic cord by islets of erythropoesis occurs, hepatic circulation and hepatocyte function are reduced [1]. Hypoalbuminemia develops and produces generalized anasarca. Pleural and pericardial effusions appear. Death in utero usually occurs. Although the cause of hydrops fetalis still remains a theory, it fits the observed facts. It explains the varying degree of fetal anemia noted with Rh hydrops fetalis because of extent of hepatic hypertrophy, portal hypertension, and hepatocellular damage (not anemia) are the basic causes. Although anemia is usually severe, hydrops may occur with hemoglobin levels well above seven g/dl; conversely, an affected fetus may not be hydropic with hemoglobin levels well below five g/dl. Therefore, diagnosing fetal anemia in a non-invasive and accurate way is fundamental, as recent studies report [2-4]. Doppler assessment of the fetal middle cerebral artery (MCA) peak systolic velocity (PSV) has emerged as the best tool in predicting fetal anemia in at-risk pregnancies [5]. It is based on the principle that the anemic fetus preserves oxygen delivery to the brain by increasing cerebral flow of low viscosity blood. Mari *et al.* have proposed the cut off value for multiples of the median of middle cerebral artery peak systolic velocity (MoM MCA-PSV) of 1.29 for mild and one of 1.50 MoM for moderate, and finally MoM-MCA of 1.55 for severe anemia [6]. These cut-off values result in 100% sensitivity, based on a retrospective analysis of 111 fetuses. The sensitivity of increased MCA-PSV above 1.5 MoM in the prediction of moderate or severe anemia was 100% (95% CI 86-100), either in the presence or absence of hydrops.

In the past, amniocentesis to determine amniotic fluid bilirubin levels was the usual method for indirectly estimating the severity of fetal anemia [7]. Attempts should be made to avoid transplacental passage of needle because this can lead to fetomaternal hemorrhage and rise in maternal antibody titer. Intrauterine transfusion (IUT) is an effective treatment for severe fetal anemia. Perinatal loss occurs in about 1.6% of the procedures. Additional complications, described in the most studies include thrombosis v. umbilicalis (includes emergency cesarean section), infection, and rupture of the membranes [8]. Fetal medicine teams aim at optimizing the number of intrauterine intravascular transfusions (IUIVTs) and avoiding unnecessary procedures.

Scheier *et al.* showed that MCA-PSV is useful in the prediction of fetal anemia in the second transfusion, but less accurate for the third transfusion [3]. Possibly, this is due to hemodynamic changes induced by the presence of transfused

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adult cells in the fetal circulation. Recent study has reported an estimated fetal hematocrit (Hct) drop of 0.7-1% day [9]. This parameter depends on the presence of fetal hydrops, because of the association between fetal hydrops and higher fetal Hct decline.

Since 1987, Department for Gynecology and Obstetrics, Clinical Center of Serbia in Belgrade has been the national referral center for countries of the West Balkan, for the management, and intrauterine treatment of fetal anemia. The first IUIVT was performed on November 1987. In over 22 years, 498 IUIVTs were performed in 149 fetuses. After more than 20 years of experience, the present authors reported that incidence of HDFN due to red cell Rh alloimmunization in Serbia is 1.5-2%, according to recent dates from Serbian Ministry of Health.

The aim of the present study was to determine standardized MCA peak velocity MoM-MCA (MoM-MCA) as a predictor fetal Hct decrease between first and second IUIVT, which indicated the best time for the second IUIVT for fetal anemia in fetal hydrops due to red-cell alloimunization.

Materials and Methods

Thirty monofetal Rh D alloimmunized pregnancies, were prospectively studied at the Department of Gynecology and Obstetrics, Clinical Center of Serbia, from January 2006 to January 2012.

A computer database search was performed to identify all pregnancies with maternal Rh D alloimmunization and hydrops fetalis that underwent first and second intrauterine intravascular transfusions during the study period. All patients gave their written informed consent prior to their inclusion in the study. The research protocol was not required for approval by the relevant Institutional Review Board or Ethics Committee, because the were patients informed about fetal therapy (IUIVT), and since 1987, Department for Gynecology and Obstetrics, Clinical Center of Serbia in Belgrade has been the national referral center for countries of the West Balkan, for the management and intrauterine treatment of fetal anemia.

Ultrasound and Doppler examination were performed using ultrasound scanner with a 3.75-MHz curvilinear probe. Axial sections of brain, including thalami, and cavita septi pellucidi were obtained and the Circle of Willis was identified. All Doppler measurements were performed with the angle between the ultrasound beam and the direction of the blood flow, as close to 0° as possible, and never exceeding 30°. If the angle was > 0°, an angle correction was applied. MCA-PSV measurements were performed before IUIVT (24 hours) and the day after (12-24 hours).The highest point of the flow velocity waveform (peak systolic velocity) was measured with Mari *et al.*'s normograms in MoM established for various gestational ages used standardized MCA peak velocity (MoM-MCA) [6]. The maximum velocity was measured when a uniform Doppler signal of at least 60 seconds was obtained. MoM-MCA was measured in the resting state.

Irradiated, washed and cytomegalovirus, HBs, HCV, and HIV antibodies-negative packed donor red cells with an Hct of 80-90% were used for IUIVT. The volume of blood transfused was calculated based on increase fetal Hct during IUIVT and weeks of gestation when procedure was performed. The volume of blood was calculated using the formula described by Plećaš *et al.*, at each procedure was calculated to achieve a post-transfusion fetal hematocrit level equivalent to 40-50%.[10] Under aseptic conditions, a 20- or 22-gauge spinal needle was inserted into the umbilical vein at the insertion site of the placenta, under continuous ultrasound guidance. Assessment of the hematolological parameters was immediately performed. Fetal blood type and the direct antiglobulin test were performed afterwards. The needle was rinsed with saline before each post-transfusion sample, to avoid a false high post-transfusion Hct.

V = volume of transfused blood; GA = gestational age;

$$\text{Volume (ml)} = 169.43 - 13.29\ (\text{GA}) + 0.274\ (\text{GA}^2) - 4.17\ (\text{Hct increase}) + 0.209\ (\text{GA} \times \text{Hct increase}),\ r^2 = 0.85$$

Standardized fetal hematocrit (z-Ht) was defined as the number of the standard deviations (SDs) from the normal mean for gestational age. The fetal IUIVT was immediately carried out when fetal Hct was 20-25% or the cut off value for MoM MCA of 1.29 for moderate anemia or the cut off value for MoM-MCA of 1.50 for severe anemia. Measured values for MoM-MCA in hydropic fetuses in the present study were between 1.29-1.85.

The rate of fetal Hct fall after the first IUIVT was calculated by dividing the difference between the post-transfusion (post-2 Hct) and the pre-transfusion Hct (pre- Hct-3) at the second IUIVT and interval in days between both transfusions.

$$\text{Hct decline (\%/day)} = \text{post-transfusion (post-Hct-2)} - \text{pre-transfusion (pre-Hct-3)/ time interval between IUIVT-1 and IUIVT-2}$$

Exclusion criteria of the present study were pregnancies submitted to only one IUIVT and cases in which post-transfusion or pre-transfusion blood samples were not obtained, multifetal pregnancies, intrauterine fetal demise, suspected fetal congenital malformations, and fetal anemia due to other antibodies (C, Kell).

Results are described as mean, standard deviation, and relative frequencies. Hct mean decline rates were compared between medical procedures with paired *t*-test. Pearson's correlation test was used to determine variables that correlate significantly with rate of fetal Hct decline. Statistical analysis included: gestational age at each procedure, standardized MCA peak systolic velocity just before and up to 24 hours after the IUIVT, fetal Hct levels before and after the first transfusion, and volume of blood transfused. Continuous variables were presented as mean (SD as 95% confidence interval, CI) assessed for normality.

Results

During the study period, 30 singleton pregnancies underwent first and second IUIVTs to treat hydrops fetalis due to anemia because of Rh alloimmune disease. All women had previous history and 19 (63.4%) had a moderate titer (1:64) and 11 (36.6%) had a high titer (1:128), and with anti-D antibodies.

First IUIVT was performed at a mean gestation 26.97 (SD 4.32), and mean volume of blood transfused was 41.1 ml (SD18.3). The mean pre-transfusion Hct-1 was 23.2% (SD 8.7%), the mean post-transfusion Hct-2 was 42% (SD 8.1%). The mean pre-transfusion Hct-3 before second IUIVT was 26.5% (SD 7%) The mean standardized pre-transfusion MCA MoM-1 was 1. 57 (SD 0.21), the mean standardized post-transfusion MCA MoM-2 was 1.17 (SD

Table 1. — *First and second IUIVT.*

	Intrauterine intravascular transfusion	
	First /Me ± SD [d] /	Second/Me ± SD [d] /
Gestational age (weeks)	26.97 ± 4.33	28.63 ± 4.56
Middle cerebral artery		
PSV (cm/sec) [a]	55.70 ± 18.45	61.47 ± 17.33
MoM [c]	1.57 ± 0.21	1.55 ± 0.16
Hct (%)[b]		
Before	23.2 ± 8.7	26.5 ± 7.0
After	42 ± 8.1	43 ± 7.1

IUIVT, intrauterine intravascular transfusion; PSV [a], peak systolic velocity; Hct [b], hematocrit; MoM [c], multiples of the median; SD [d], standard deviation. Values are expressed as mean ± standard deviation.

0.24), and the mean standardized MCA MoM-3 before the second IUIVT was 1.55 (SD 0.16). Mean interval to the second procedure was 11.23 (SD 6.21) days and average hematocrit decline rate 1.45% /day. Table 1 summarizes data at first and second transfusions.

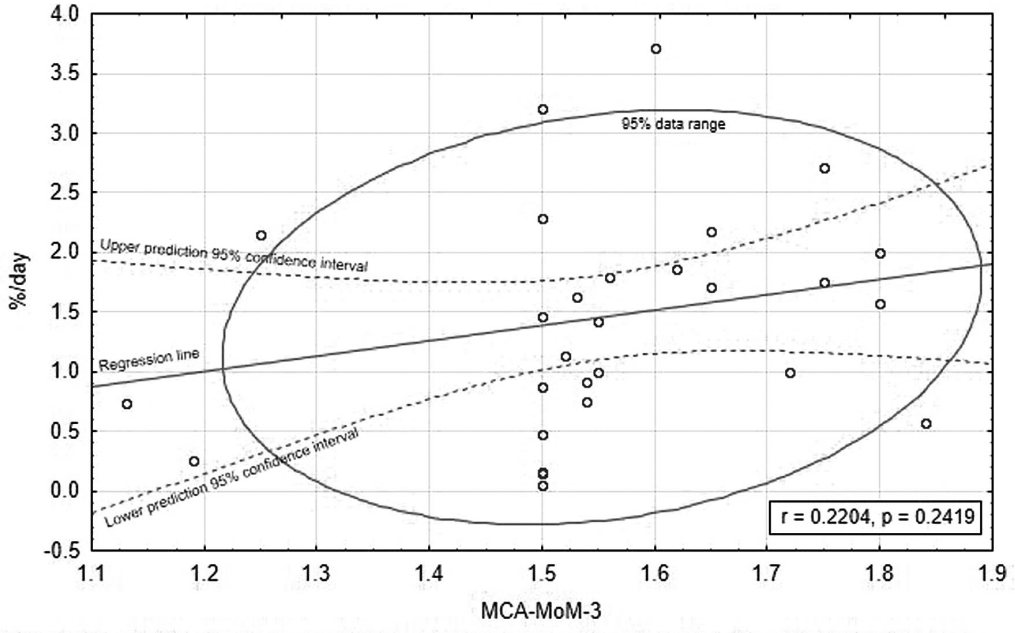
There was as expected, statistically significant difference between fetal pre-transfusion Hct-1 before the first IUIVT and post-transfusion Hct after the first IUIVT Hct-2 $p < 0.001$, 95% CI for difference was (−0.225 and −0.149), and also between Hct-2 and pre-transfusion Hct-3 before the second IUIVT; $p \leq 0.001$; 95% CI for difference was (0.128 and 0.180). PSV-MCA decreased immediately after transfusion in 27 but did not change in three cases. This study also showed that MCA MoM-1 before the first IUIVT exhibited inverse statistically significant correlate with pret-transfusion Hct-1 $r = -0.633$; $p = 0.000$ and MCA-MoM-2 with post-transfusion Hct-2 $r = -0.583$; $p = 0.001$.

Pearson's test demonstrated that the mean decline rate in fetal Hct levels between first and second IUIVT (expressed in percentage/day) showed insignificant correlation with post-transfusion Hct-2 $r = -0.116$; $p = 0.543$ and pre-transfusion Hct-3 $r = -0.207$; $p = 0.273$. There were also insignificant correlations between the mean decline rate in fetal Hct levels and measurements MCA-MoM-2 $r = 0.081$; $p = 0.670$ after the first IUIVT and also between the mean decline rate in fetal Hct levels and MCA-MoM-3 before second IUIVT $r = 0.220$; $p = 0.242$ (Figure 1).

The study documented insignificant negative correlation between mean decline rate in fetal Hct levels and the interval between both procedures (T) $r = -0.154$, $p = 0.433$, and also between the interval between both procedures (expressed in days) (T) and measurement MCA MoM-3 before the second IUIVT $r = -0.157$; $p = 0.408$ (Figure 2). There were also negative insignificant correlations between mean decline rate in fetal Hct levels between first and second IUIVT and the volume of blood to be transfused $r = -0.370$; $p = 0.05$

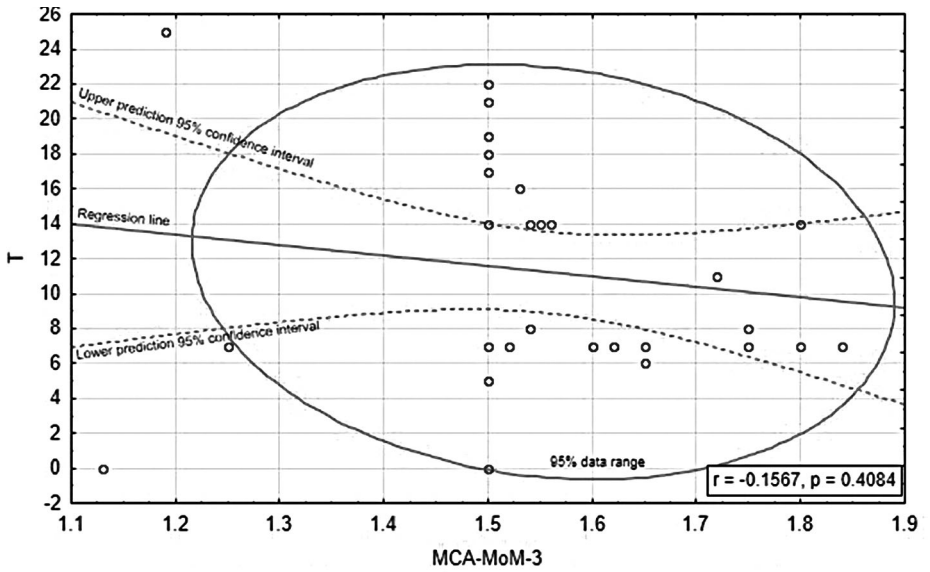
Discussion

IUIVT for severe fetal anemia are performed between 19 to 34 weeks of gestation in the present Department (Table 1). As previous study showed, before 18 weeks, fetal transfusions are rarely successful due to limited visualization and small size of the relevant anatomic structures [11]. As



MCA-MoM-3: multiples of the median of middle cerebral artery peak systolic velocity before the second IUIVT (intrauterine intravascular transfusion)
%/day: the mean decline rate in fetal hematocrit levels (expressed in percentage/day)

Figure 1. — The study demonstrated statistically insignificant correlation between MCA-MoM-3 and the mean decline rate in fetal Hct levels expressed in percentage/day.



MCA-MoM-3: multiples of the median of middle cerebral artery peak systolic velocity before the second IUIVT (intrauterine intravascular transfusion)
T: the time interval between the first and second IUIVT.

Figure 2. — The study demonstrated statistically insignificant correlation between MCA-MoM-3 and the time interval between both procedures (T).

Plećaš *et al.* have reported after 34 weeks, the procedure is generally considered riskier than late preterm delivery and neonatal treatment of severe anemia [10].

As Moise previously reported, and that the present study expected, demonstrated statistically significant difference among all of three variables Hct-1, Hct-2, and Hct-3 [7]. It may reflect the severity of the anemia. The present study also confirms high sensitivity of fetal pre-transfusion Hct-1 (100%) and Hct-3 (94.45%) as predictor's of severity of fetal anemia. However, it is well-known, that sensitivities are lower in prospective series than in retrospective series from which cut-off values have been derived (in the present study zHct ≤ −5 SDs). However, the study shows inverse insignificant correlation between the mean fetal Hct decrease and post-transfusion fetal Hct-2 and also between the mean of fetal Hct decrease and pre-transfusion Hct-3.This parameter must be interpreted also as a significant indicator of Rh(D) alloimmunization severity. As Egberts *et al.* reported significant correlation of mean decline rate and time interval between both procedures indicates that the study was not conclusive [12]. In fact, it has been shown that transfused adult red cells destruction in non-linear fashion, possibly reflecting mechanical effects of hemoconcentration, and biochemical effects of a fetal circulation on transfused adult red cells and membranes. Besides this, adult red cells are supposed to have a reduced lifespan in more severely anemic fetuses. Sumacher *et al.* and Egberts *et al.* have hypothesized that more fetal red cells disappear during the first days after the transfusions [13, 14].

Recent study shows an estimated fetal Hct drop of 0.7-1% day. In the present study, the authors noticed an average decline rate of 1.45 %/ Hct per day [9]. Scheier *et al.* reported that MCA PSV exhibits a significant correlation with fetal hemoglobin concentration before the first and before the second IUIVT [3]. However, the present study confirmed statistical significant correlations between MCA MoM-1 and fetal Hct-1 before the first IUIVT and also between MCA MoM-2 and fetal Hct-2 after the first IUIVT. It can be useful to time subsequent transfusions. As Nishie *et al.* reported on the evaluation of fetal myocardial performance, it may help establish the best moment for fetal treatment before myocardial function is affected [15]. Radunović *et al.* previously reported that volume of blood to be transfused could increase fetal Hct and viscosity [16]. The fetal cardiac failure would eventually occur [17]. Nishie *et al.* showed that MCA Doppler prediction performance is slightly lower in subsequent transfusions compared with first time transfusions, as the present study demonstrated [15]. The present authors found a sensitivity of pre-transfusion MCA-MoM-1 for severe anemia before the first IUIVT which was 100% and the sensitivity of pre-transfusion MCA-MoM-3 before the second IUIVT which was 88.89%, in the prediction of severe fetal anemia (cut-off value for severity anemia MCA MoM ≥ 1.5). The present study documented that MCA Doppler can be useful in prediction severity of fetal anemia before the first as before the second IUIVT. The sensitivities are always lower in prospective than in retrospective series.

Fetal hematocrit was not the only parameter that changes during IUIVT. After IUIVT, a relatively large fetal blood volume is injected into fetal vascular space, the fetal blood volume remains at the same level for 24 hours.It is known

that through loss of plasma from fetal circulation, after packed red cell transfusion, the fetal blood volume increases by only half of the transfused volume As Loboto *et al.* reported in cases of severe fetal anemia, the amount of blood that can be transfused is limited by fetal tolerance to volume overload [9]. The present study documented that the mean decline rate in fetal Hct levels between first and second IUIVT and the volume of blood to be transfused insignificantly correlated as well as the volume of blood to be transfused and interval between both procedures (T). Although an estimated fetal Hct decline of approximately 1% / day, this parameter is quite variable and independent of the volume of blood to be transfused, as in the present study. The present authors support the results of study Mari *et al.* that the optimal interval between Doppler examination for MCA-PSV has not determined, but appears to be one or two weeks [6]. As Steel *et al.* reported, the wide range in pre-transfusion MCA MoM for fetuses with identical Hct, other factors such as, blood viscosity, cardiac output, and peripheral resistance must play an important role in determining MCA peak [18]. In that context, the present study did not demonstrate statistical significance between MCA-MoM-3 before the second IUIVT and the mean decline rate in fetal Hct levels between first and second IUIVT (expressed in percentage/day) (Figure 1) as well as the time interval between both procedures (T) (Figure 2). In this study, the authors described the prediction model as a mathematical formula:

Hct decline (%/day) = post-transfusion (post-2Hct) – pre-transfusion (pre-Hct-3)/ time interval between IUIVT-1 and IUIVT-2

As Scheier *et al.* confirmed, more precise predictive models have been investigated [3]. The present authors believe that this may not be a rule, but it can be useful for future investigations.

In the present authors' Department, in case of severe fetal anemia, ultrasound-directed fetal blood sampling (i.e. cordocentesis) allows direct access to the fetal circulation to obtain important laboratory values such as Hct, fetal blood type, reticulocyte count, and platelet count.

An increasing fetal Hct after IUIVT has effect on maximum MCA-PSV. The present study documented high sensitivity of pre-transfusion Hct and MCA-MoM before the first and second IUIVT in predicting severity of the fetal anemia. The wide range in pre-transfusion MCA-MoM in fetuses with identical Hct exist with other factors and must determine MCA peak or MoM-MCA. The measurements MCA MoM before every IUIVT can be useful for determining severity fetal anemia, but it cannot be useful in predicting the best time interval for the next IUIVT.

Monitoring of pregnancies complicated by hydrops fetalis should not rely solely on measuring blood flow in MCA, as indicator severity of fetal anemia, as also as predictor for the best time for the next IUIVT. In these cases, regardless of Doppler examination for MCA-PSV, IUIVT is the most effective treatment of fetal anemia due to maternal Rh D alloimmunization.

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