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Prediction of Fetal Anemia in Subsequent Transfusions: Is There a Need to Change the Threshold of the Peak Systolic Velocity of the Middle Cerebral Artery?

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Keywords
Cordocentesis · Fetal hemoglobin · Fetal transfusion · Doppler ultrasound · Intrauterine transfusion · Middle cerebral artery · Red cell alloimmunization · Rhesus alloimmunization · Peak systolic velocity

Abstract

Introduction: Peak systolic velocity (PSV) of the middle cerebral artery (MCA) shows 100% sensitivity for predicting fetal anemia before the first intrauterine transfusion (IUT). However, its ability to predict subsequent transfusions has remained mostly controversial. ***Objectives:*** To assess if there is a need to change the threshold of MCA-PSV from 1.5 to 1.69 multiples of the median (MoM) to predict fetal anemia and the need for subsequent IUT. ***Methods:*** This is a retrospective audit, wherein case records of mothers who underwent IUT at the Bangalore Fetal Medicine Centre between April 2008 and May 2017 were reviewed; 86 cases were included, and the data were analyzed using MS Excel. The MCA-PSV and pretransfusion Hb were converted into MoM. 40 fetuses that had more than 1 IUT were included in the analysis. ***Results:*** 31/40 fetuses that had >1 IUT had an MCA-PSV >1.5 MoM, of which 29 were anemic according to the post-IUT Hb MoM. 20/29 (69%) had an MCA-PSV >1.69, whereas 9/29 (31%) had an MCA-PSV between 1.5 and 1.69 MoM. Our study shows that changing the MCA-PSV threshold from 1.5 to 1.69 MoM will reduce the detection of fetal anemia and hence the need for repeat IUT by 31%. ***Conclusions:*** Increasing the fetal MCA-PSV threshold from 1.5 to 1.69 will miss out one-third of the fetuses that will require a 2nd, 3rd, or 4th IUT. This is more relevant in geographical areas where the parents must travel long distances for IUTs, which are performed in tertiary fetal care centers.

Introduction

Fetal anemia is an uncommon occurrence and can result from several pathologic processes in the maternofetal circulation. Fetuses with severe anemia invariably develop fetal hydrops and die in utero if untreated. Maternal Rh(D) alloimmunization continues to be an important

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cause of fetal anemia despite the development and implementation of anti-D immunoglobulin prophylaxis. Other causes include parvovirus infection, inherited conditions such as α-thalassemia and genetic or metabolic disorders, and acquired conditions, such as fetomaternal hemorrhage. Fetal anemia in monochorionic twins can result from the twin-twin transfusion syndrome [1]. Fetal blood sampling for the assessment of fetal hemoglobin (Hb) allows accurate quantification of the degree of fetal anemia [2]. However, cordocentesis, an invasive procedure, carries a procedure-related risk of fetal loss and fetomaternal hemorrhage, which can further increase the antibody levels. Noninvasive methods to detect fetal anemia have gained significant importance in the last 2 decades. Doppler ultrasound of the middle cerebral artery (MCA) to measure the peak systolic velocity (PSV) has been evaluated in several studies as an index of the hyperdynamic circulation to predict fetal anemia with high sensitivity and specificity [3–9]. MCA-PSV >1.5 multiples of the median (MoM) will identify fetuses with mild-to-severe anemia with a sensitivity of 100% and a false-positive rate of 12% [10, 11]. This holds true to identify the anemic fetus and plan the first intrauterine transfusion (IUT). However, there are contradictory opinions in the literature about the threshold of MCA-PSV that can be used for the detection of fetal anemia after 1 blood transfusion and the timing of subsequent fetal blood transfusions. A study published by Detti et al. [12] recommended a threshold of 1.69 MoM to identify correctly those fetuses with severe fetal anemia that needed a 2nd IUT with a false-positive rate of 6%. However, following more transfusions, the sensitivity of the MCA-PSV to predict fetal anemia requiring IUT is reduced with increasing false positives [13–16]. Another study by Ghesquière et al. [17] contradicted the use of MCA-PSV suggesting a lower sensitivity after the 2nd transfusion and recommended the use of formulae to calculate the estimated decline in fetal Hb. The Society for Maternal-Fetal Medicine (SMFM) clinical guideline of 2015 on the diagnosis and management of a fetus at risk of anemia cited that following an initial transfusion, the recommended threshold for the diagnosis of fetal anemia requiring a second transfusion is higher (MoM >1.69), most likely because of the contribution of donor blood given as part of IUT. As an alternative, if the posttransfusion hematocrit (Hct) is known or can be estimated, the timing of the next transfusion can be calculated using the expected decline in fetal Hct [1].

A recently published international, multicenter, randomized trial done across 13 centers in Australia, New Zealand, Canada, the United Kingdom, Ireland, Belgium, and Argentina showed no statistically significant differences between fetuses monitored with MCA-PSV and fetuses monitored by calculation of fetal Hct decreases with regard to adverse infant outcomes related to alloimmunization or procedure-related complications. They concluded that both Doppler measurement of MCA-PSV and estimation of the decrease in fetal Hct or Hb can be used to determine the timing of second and subsequent IUTs in fetuses with red cell alloimmunization [18].

Our study aimed to audit our practice of IUT and assess if there is a need to change the threshold of the MCA-PSV for the prediction of fetal anemia in subsequent transfusions or change to calculating the estimated Hct/Hb decline as suggested in some studies. This is relevant to our practice as most of our patients travel long distances to have the IUT in specialized centers and also includes medical expenses in addition to travel expenditure.

Materials and Methods

This is an audit study of fetal blood transfusions that were performed for rhesus isoimmunization in the Bangalore Fetal Medicine Centre (BFMC) from April 2008 to May 2017. A total of 86 IUTs performed for rhesus isoimmunization leading to fetal anemia were initially included in the study, in whom the pre- and posttransfusion MCA-PSV and Hb were available for this audit. Fetuses with anemia resulting from any other cause were excluded. The final analysis included only 40 fetuses, which had >1 IUT. The average gestation age at IUT was 28 weeks (17–36 weeks). All fetuses were evaluated for any sign and symptom of fetal anemia with a detailed ultrasound scan. Fetal Doppler assessment included MCA-PSV measurement according to the standard guidelines performed by experienced fetal medicine specialists.

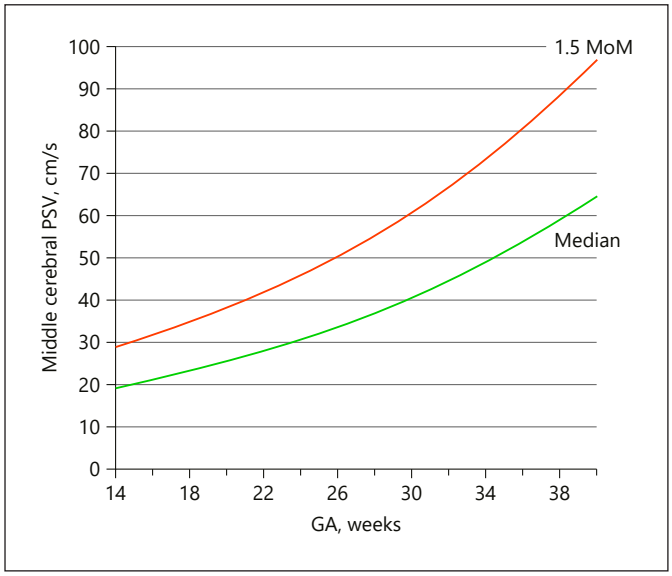
To assess MCA-PSV, an axial plane of the fetal brain at the level of the sphenoid bones, just caudal to the level at which the biparietal diameter is measured, is taken during a period of fetal rest. The circle of Willis is identified with color Doppler. The MCA of the cerebral hemisphere proximal to the ultrasound transducer is identified at its origin from the internal carotid artery, and the ultrasound probe is placed over it such that the angle of insonation is as close to 0° as possible. A 2-mm pulsed Doppler gate is placed over the vessel just as it bifurcates from the carotid siphon. The distal part of the MCA should not be used as it leads to false depression of the real PSV; 3–5 measurements are taken consistently, and the best and highest measurement was recorded. The serial trend in values consistently >1.5 MoM was considered as an indication for a repeat IUT.

The pre- and posttransfusion Hb levels were available for all procedures. These were correlated with the MCA-PSV values. The MCA-PSV and the pre- and post-Hb levels were converted into MoM for comparison. The fetus was considered anemic if the fetal Hb was <0.84 MoM according to the gestational age-based reference ranges published in the SMFM guidelines of 2015 (Fig. 1).

An MCA-PSV >1.5 MoM according to Mari [19] standardized charts (Fig. 2) was used as a screening test to identify an anemic fetus for the 1st IUT. For the subsequent blood transfusions also, a

GA, weeks	1.0 MoM, median	0.55 MoM	0.65 MoM	0.84 MoM
18	10.6	5.8	6.9	8.9
19	10.9	6.0	7.1	9.1
20	11.1	6.1	7.2	9.3
21	11.4	6.2	7.4	9.5
22	11.6	6.4	7.5	9.7
23	11.8	6.5	7.6	9.9
24	12.0	6.6	7.8	10.0
25	12.1	6.7	7.9	10.2
26	12.3	6.8	8.0	10.3
27	12.4	6.8	8.1	10.4
28	12.6	6.9	8.2	10.6
29	12.7	7.0	8.3	10.7
30	12.8	7.1	8.3	10.8
31	13.0	7.1	8.4	10.9
32	13.1	7.2	8.5	11.0
33	13.2	7.2	8.6	11.1
34	13.3	7.3	8.6	11.1
35	13.4	7.4	8.7	11.2
36	13.5	7.4	8.7	11.3
37	13.5	7.5	8.8	11.4
38	13.6	7.5	8.9	11.4
39	13.7	7.5	8.9	11.5
40	18.3	7.6	9.0	11.6

Fig. 1. Reference ranges for fetal hemoglobin (Hb) concentrations (g/dL) as a function of gestational age (GA). Normal Hb: ≥0.84 multiples of the median (MoM); mild anemia: Hb 0.65–0.84 MoM; moderate anemia: Hb 0.55–0.64 MoM; severe anemia: Hb ≤0.55 MoM [adapted from ref. 1].



Color version available online

Fig. 2. Peak velocity of systolic blood flow in the middle cerebral artery (MCA) with advancing gestational age (GA). The curves indicate the median and 1.5 multiples of the median (MoM) peak systolic velocity (PSV) in the MCA. Reprinted from Mari et al. [7].

persistent MCA-PSV >1.5 MoM was considered as an indication for repeat IUT as this was the unit protocol during the study period.

All IUTs are performed by 2 senior fetal medicine specialists as an outpatient procedure under local anesthesia. The majority of the procedures are intravascular, i.e., into the placental insertion end of the umbilical cord or fetal hepatic vein under continuous ultrasound guidance. Fetal anesthesia was only used when IUT was performed into the intrahepatic portion of the umbilical vein. All procedures were uncomplicated, and in the group that had subsequent IUTs, there were no fetal losses. O-negative packed cells with a Hct of 75–80%, irradiated and tested negative for infections, acquired from a single blood bank, were used for all IUTs.

Results

Of the total 86 IUTs included initially, 46 with only 1 IUT were excluded from further analyses. Of the 40 fetuses included in the final analysis, almost half of them (n = 22) required 2 IUTs, one-fourth of them (n = 10) 3 IUTs, while 8 fetuses had 4 IUTs (Table 1).

The majority of the fetuses (n = 31; 77.5%) had an MCA-PSV measurement ≥1.5 MoM, taken just prior to the IUT; 93.5% of these (that is, 29 out of 31) had mild-to-severe anemia (mild = 8, moderate = 3, and severe = 18). The severity of anemia was confirmed by Hb MoM ≤0.84 MoM. Furthermore, out of these 29 fetuses with mild-to-severe anemia, 20 (68.9%) had an MCA-PSV >1.69 MoM, and 9 (31.1%) fetuses had an MCA-PSV of 1.5–1.68 (Table 2). In our sample, the MCA-PSV was not predictive of the degree of anemia for just 2 fetuses (both in 3rd IUT) with mild anemia, and they had an MCA-PSV of 1.51 and 1.68 MoM, respectively.

A small number of fetuses (n = 5) had Hb >0.84 MoM. Out of these, 2 fetuses had an MCA-PSV of 1.64 and 1.65 MoM in the 2nd and 4th IUT, with a Hb MoM of 0.88 and 0.87 MoM, respectively, giving a 12.5% false-negative rate for the method (Table 3). One of these fetuses required yet another IUT, even after the 4th one.

We observed that 15% (n = 6) of the fetuses had a Hb MoM <0.84, but they also showed an MCA-PSV <1.5 MoM. Four of them were in the 2nd IUT, while 2 were in the 4th IUT (Table 4). Nearly half the fetuses (that is, 15/35, 42.8%) with Hb <0.84 MoM had an MCA-PSV <1.69 MoM. Out of these 15 fetuses, 6 were <1.5 MoM.

Table 1. Fetuses that had >1 IUT and their corresponding pretransfusion Hb MoM (n = 40)

Fetus No.	IUT, n	MCA MoM	Hb MoM	Degree of anemia
1	2	1.1	1.12	no anemia
2	2	1.3	0.75	mild
3	2	1.33	1.11	no anemia
4	2	1.38	0.43	severe
5	2	1.4	0.81	mild
6	2	1.43	0.33	severe
7	2	1.62	0.34	severe
8	2	1.64	0.88	no anemia
9	2	1.65	0.47	severe
10	2	1.68	0.44	severe
11	2	1.69	0.45	severe
12	2	1.7	0.16	severe
13	2	1.74	0.36	severe
14	2	1.75	0.71	mild
15	2	1.76	0.56	moderate
16	2	1.77	0.40	severe
17	2	1.88	0.42	severe
18	2	1.93	0.15	severe
19	2	1.93	0.48	severe
20	2	1.97	0.68	mild
21	2	2.23	0.42	severe
22	2	2.35	0.55	moderate
23	3	1.51	0.37	severe
24	3	1.51	0.72	mild
25	3	1.55	0.50	severe
26	3	1.68	0.84	mild
27	3	1.69	0.58	moderate
28	3	1.73	0.45	severe
29	3	1.77	0.48	severe
30	3	1.81	0.70	mild
31	3	1.85	0.73	mild
32	3	1.87	0.38	severe
33	4	1.28	0.89	no anemia
34	4	1.46	0.75	mild
35	4	1.49	0.83	mild
36	4	1.64	0.49	severe
37	4	1.65	0.87	no anemia
38	4	1.66	0.52	severe
39	4	1.7	0.79	mild
40	4	1.77	0.76	mild

However, if we were to consider 1.69 as a threshold for repeat IUT, then 9 (25.7%; mild = 2; severe = 7) fetuses would have missed being transfused (Table 5). Considering a higher threshold of MCA-PSV of 1.69 MoM for repeat IUT, the detection rate would have dropped by 31%.

Table 2. Fetuses with anemia predicted by various thresholds of MCA-PSV MoM

	2nd IUT (n = 22)	3rd IUT (n = 10)	4th IUT (n = 8)
Fetal anemia Hb <0.84 MoM	19/22 (86.4%)	10 (100%)	6 (75%)
MCA-PSV <1.5 MoM	4	0	2
MCA-PSV >1.5 MoM	15 (78.9%)	10 (100%)	4 (66.7%)
MCA-PSV >1.69 MoM	12 (63.2%)	6 (60%)	2 (33.3%)
MCA-PSV 1.51–1.68	3 (21.1%)*	4 (40%)#	2 (33.3%)*

* Severe fetal anemia. # 2 severe and 2 mild anemia.

Table 3. MCA-PSV of nonanemic fetuses

IUT, n	MCA MoM	Hb MoM	Degree of anemia
2	1.1	1.12	no anemia
4	1.28	0.89	no anemia
2	1.33	1.11	no anemia
2	1.64	0.88	no anemia
4	1.65	0.87	no anemia

Discussion

Our study is an audit of the practice that we have followed for nearly 10 years. The primary reason for continuing with MCA Doppler assessment for subsequent transfusion requirement arises from the fact that most of our patients come from outstation referred by their obstetrician. After the first IUT, the couple travels back to their local area where the obstetrician is monitoring the MCA-PSV with the help of a local sonologist every week. When the MCA-PSV crosses 1.5 MoM for the gestational age, they are immediately referred for subsequent IUT. At the center, compatible blood must be pre-arranged.

Reassessment of the baby is conducted by a senior specialist, and if the MCA-PSV is still above 1.5 MoM, IUT is performed. Most of the time, the mother travels back home the same evening. Our audit affirmed that we should continue with our current practice and not change the threshold as there was a good correlation between the MCA-PSV and fetal Hb in fetuses even after they have undergone ≥2 transfusions. Our findings confirm that in these circumstances Doppler assessment of the MCA can continue to be used to monitor red cell alloimmunized pregnancies.

Table 4. Fetuses with MCA-PSV <1.5 MoM and their corresponding Hb MoM

IUT, *n*	MCA MoM	Hb MoM	Degree of anemia
2	1.1	1.12	no anemia
4	1.28	0.89	no anemia
2	1.3	0.75	mild
2	1.33	1.11	no anemia
2	1.38	0.43	severe
2	1.4	0.81	mild
2	1.43	0.33	severe
4	1.46	0.75	mild
4	1.49	0.83	mild

Table 5. Fetuses with MCA-PSV <1.69 MoM and their corresponding Hb MOM

IUT, *n*	MCA MOM	Hb MOM	Degree of anemia
2	1.3	0.75	mild
2	1.38	0.43	severe
2	1.4	0.81	mild
2	1.43	0.33	severe
4	1.46	0.75	mild
4	1.49	0.83	mild
3	1.51	0.37	severe
3	1.51	0.72	mild
3	1.55	0.50	severe
2	1.62	0.34	severe
4	1.64	0.49	severe
2	1.65	0.47	severe
4	1.66	0.52	severe
2	1.68	0.44	severe
3	1.68	0.84	mild

Our audit shows that if we change our threshold to travel and transfuse the fetus from 1.5 to 1.69 MoM, then we are likely to miss nearly 31% of the fetuses that need an earlier IUT. In addition, the MCA-PSV was not predictive of the degree of anemia, as mild anemia had a higher MCA-PSV (fetuses 14, 20, 24, 26, 30, 31, 39, and 40), and, on the other hand, severe anemia had lower MCA-PSV (fetuses 4, 6, 7, 9, 10, 23, 25, 36, and 38). This may be explained by the different rate of red cell breakdown in different fetuses of alloimmunized pregnancies. The timing of the subsequent IUTs was also variable as some fetuses required quick subsequent IUT, especially the first 3, and then the inter-IUT interval increased, whereas some fetuses had longer inter-IUT intervals even after the 2nd IUT. This may be attributable to the red cell breakdown in the fetus and the maternal antibody types and titers. In our area, we also find other atypical antibodies in addition to anti-D antibodies in the mother, commonly anti-c and -C antibodies.

Specialized fetal procedures are available only at tertiary centers in our country. Hence, interim surveillance can be continued locally as MCA Doppler monitoring is a simple tool that can be mastered by good sonologists. Also, this will reduce unnecessary early travel to the tertiary center as the alternate method proposed to estimate the Hb decline rate has a higher false-positive rate and, more importantly, not all fetuses would follow the same pattern of red cell breakdown in vivo. We plan to assess the neonatal follow-up Hb of the transfused babies and the need for exchange transfusion as part of our ongoing audit.

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Statement of Ethics

This research paper has been prepared based on an audit undertaken at our center, wherein we have retrospectively analyzed data (which have been anonymized and do not reveal the identities of the patients). All patients undergoing treatment at BFMC receive counseling before any procedure, and all procedures are carried out only after obtaining informed verbal and written consent from the patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have collectively conceptualized the research paper. The manuscript has been reviewed and revised by each of the authors. The final contents of the submission have been approved by all the authors, and each of them can act as a guarantor for the integrity of this research.

Dr. Prathima Radhakrishnan is the BFMC Director and is the prime author of this paper. She has performed the maximum IUT number in this center.

Dr. Shailaja Venkataravanappa is a clinical fellow at BFMC and has prepared the first draft of the manuscript with the literature search.

Dr. Veena Acharya is a consultant at BFMC and the 2nd operator to perform the IUT in this center.

Dr. Reeth Sahana is a consultant at BFMC who has contributed largely in assisting IUT procedures and in assessing the accuracy of the data.

Dr. Anitha Shettikeri is a consultant at BFMC who has contributed largely in performing the fetal scans prior to IUT procedures and in assessing the accuracy of the data.

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