Diagnosis of Severe Fetomaternal Hemorrhage with Fetal Cerebral Doppler: Case Series and Systematic Review

Federica Bellussi Antonella Perolo Tullio Ghi Aly Youssef Gianluigi Pilu
Giuliana Simonazzi

Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

Key Words

Doppler ultrasound · Doppler velocimetry · Fetal anemia · Fetal diagnosis · Fetal monitoring · Fetomaternal hemorrhage · Intrauterine transfusion · Perinatal outcome · Prenatal counselling · Middle cerebral artery Doppler

Abstract

Objectives: To analyze the role of middle cerebral artery (MCA) peak systolic velocity (PSV) in the prediction of severe fetomaternal hemorrhage (FMH) and to compare it with standard biophysical assessment. **Data Sources:** Retrospective review of cases of FMH seen in our unit and systematic review of the literature. **Results:** We followed the MOOSE guidelines to review the literature. From 838 articles, 16 were selected. In total, 35 women, including 3 cases from our center and 32 obtained from the literature search were included. Diagnosis of FMH was always confirmed by laboratory tests. Patients were seen at 31 ± 5 weeks' gestation (range 16–39) and the most frequent indication for referral was decreased perception of fetal movements. Cardiotocography (CTG) upon admission was sinusoidal in 18 cases, nonreactive in 6, decelerative in 2 and tachycardic in one. MCA-PSV was abnormal in all cases but one. There were 2 perinatal deaths. The mean hemoglobin concentration at birth or at intrauterine transfusion was 4.8 ± 1.9 g/dl. **Discussion:** The most accurate predictor of FMH was fetal MCA-PSV. CTG was always

abnormal but the pattern was frequently nonspecific. We suggest including fetal cerebral Doppler in the evaluation of patients with decreased fetal movements, particularly in those cases with ambiguous results of biophysical testing.

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Objectives

Fetomaternal hemorrhage (FMH) is a well-established cause of fetal anemia. The reported incidence is variable depending on the method of ascertainment and the threshold employed and ranging from 0.3 to 1 in 1,000 births [1–4]. The consequences of FMH encompass a wide spectrum of severity from neonatal anemia to intrauterine demise. Severe FMH is a life-threatening complication and has been estimated to cause up to 14% of fetal deaths [5, 6].

Prenatal diagnosis of severe FMH is difficult. A decreased perception of fetal movements [7–12] and abnormal cardiotocography (CTG) [3, 10] are usually present. More recently, increased peak velocities in the middle cerebral arteries (MCA-PSV) detected by Doppler ultrasound have been described [8, 13–26]. Our objective was to evaluate the role of MCA-PSV in the prediction of severe FMH and to compare it with standard methods of biophysical assessment in our own experience and in a systematic review of the available literature.

Table 1. Clinical data of case series

Case	Indication for referral	Weeks' gestation	CTG pattern	MCA-PSV, MoM	Estimated Hb, g/dl	Hb at birth, g/dl	Mode of delivery	Birth weight, g	Clinical remarks
1	decreased fetal movements	35	decelerative	1.96	5.2	4	cesarean section	2,850	neonatal transfusion, respiratory distress syndrome, discharged in good condition
2	decreased fetal movements	32	sinusoidal	2.6	4.3	2.8	cesarean section	2,165	neonatal transfusion, respiratory distress syndrome, discharged in good condition
3	decreased fetal movements	37	nonreactive	1.86	6.3	5.7	cesarean section	3,000	neonatal transfusion, respiratory distress syndrome, discharged in good condition

Data Sources

FMH covers a wide span of severity. In our review, we considered severe those cases resulting in perinatal death, having severe neonatal anemia (hemoglobin concentration, Hb ≤ 9 g/dl) or requiring prenatal or postnatal transfusions.

Case Series

We conducted a retrospective review of the medical records of all pregnant women who delivered at our University Hospital with a confirmed diagnosis of FMH from January 2011 to December 2014. We included all cases that had undergone assessment of fetal MCA-PSV, obtained as previously described [27]. FMH was always confirmed by flow cytometry. In all cases, a detailed follow-up were obtained.

Systematic Review

The systematic review was performed according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [28]. We systematically searched PubMed and Clinical-Trials.gov from April 1990 to June 2014 for the following terms: 'fetomaternal hemorrhage', 'fetomaternal hemorrhage and middle cerebral artery Doppler', 'fetal anemia and middle cerebral artery Doppler' and 'fetomaternal hemorrhage and ultrasound'.

We included all studies describing FMH resulting in fetal anemia evaluated antenatally with Doppler sonography MCA-PSV and confirmed by specific maternal tests (Kleihauer-Betke or flow cytometry test) from January 1990 to April 2014. The reference lists of the returned manuscripts were also evaluated. All of the identified articles were then limited to English language and human subjects. Duplicates were removed. Two independent authors (F.B. and G.S.) conducted the literature search. Identification of relevant studies was carried out through abstract screening. The full text of these articles was retrieved and studies which met inclusion criteria were selected. Inclusion criteria were: (1) English language; (2) documented MCA Doppler assessment; (3) laboratory confirmation of FMH. Disagreements about the decision to include a study were resolved by consensus, and in consultation with a third author (G.P.) if necessary. We investigated first the indication for referral, the CTG pattern and MCA-PSV value of all cases. When more than one sonographic assessment was performed, we collected data about the first one reported (the first MCA-PSV assessment and the subsequent hemoglobin concentration before intrauterine transfusion or at birth) [8, 10, 13, 14, 16–22, 24–26].

Secondly, we reviewed the antenatal and postnatal complications associated with this condition and the need for fetal or neonatal transfusions. We focused on the correlation between the fetal Hb calculated from the MCA-PSV and Hb at birth or at the time of intrauterine transfusion. Where not available, the estimated Hb value was retrieved from the MCA-PSV, as previously described [29]. When only hematocrit (Ht) was reported, Hb was calculated using the standard threefold conversion ($Hb = Ht/3$) [30].

Statistics

Descriptive statistics are provided. Data are presented as mean $\pm$ standard deviation (SD) unless otherwise specified.

Results

Case Series

A summary of clinical data of cases seen in our Unit is provided in table 1.

Case 1. A 38-year-old primigravida with an uncomplicated prenatal course was seen at 35 weeks and 3 days of gestation because of decreased fetal movements. The CTG was nonreactive with decelerations. Sonography revealed a fetus of normal size for gestation, with no movements, normal amniotic fluid volume and umbilical artery Doppler. MCA-PSV was 99 cm/s, or 1.9 multiples of the median (MoM) for gestational age (estimated Hb concentration 5.2 g/dl) [29]. A 2,850-gram female infant with Apgar score of 7 and 9 at 5 and 10 min was delivered by an emergency cesarean section. Hb was 4 g/dl and flow cytometry confirmed the presence of a severe FMH. The neonate was transfused and is in good health at 3 years of age.

Case 2. A 35-year-old primigravida at 32 weeks and 2 days of gestation was admitted because of decreased fetal movements. Computerized CTG revealed a sinusoidal tracing. Doppler sonography revealed normal fetal measurements, absence of movements, normal amniotic fluid

volume and umbilical artery waveforms. MCA-PSV was 114 cm/s or 2.6 MoM (estimated fetal Hb 4.3 g/dl) [29]. An emergency cesarean section was performed and a 2,165-gram male fetus with an Apgar score of 2 and 6 was delivered. Hb was 2.8 g/dl and flow cytometry confirmed the presence of a massive FMH. The infant was transfused and was eventually discharged in good condition.

Case 3. A 37-year-old primigravida at 37 weeks and 2 days of gestation was admitted because of decreased fetal movements. CTG upon admission was nonreactive. Ultrasound confirmed absence of fetal movements, but fetal size, amniotic fluid volume and umbilical artery Doppler were normal. MCA-PSV was 103 cm/s, corresponding to 1.86 MoM (estimated Hb 6.3 g/dl) [29]. A 3,000-gram female infant with Apgar scores of 8 and 9 and Hb of 5.7 g/dl was delivered by an emergency cesarean section. Flow cytometry confirmed the presence of severe FMH. The girl was transfused after birth and was eventually discharged in good condition.

Systematic Review

The systematic research yielded a total of 838 citations. Identification of potentially relevant studies was carried out through abstract scanning and the full text of 628 articles was retrieved. Of these, after removal of duplicates, 16 studies were deemed appropriate to be included in the final review [8, 10, 13–26]. Studies were found suitable for inclusion in the systematic review after critical appraisal according to the published guidelines we used [28]. A flowchart depicting the process from initial literature search to inclusion in the present manuscript is presented in figure 1. The selected articles included case reports, case series, one letter to the editor, one retrospective and one prospective study, and there were no randomized controlled trials. Table 2 shows the characteristics of studies included in this review and a flowchart describing the process of selection of cases included is presented in figure 2. Overall, from the 118 cases collected from 16 articles, 32 pregnant women at 31 ± 5 weeks' gestation (range 16–39) were included in this systematic review. Ten of the 32 cases were derived from the only prospective series retrieved from the literature [16]. The maternal age, when available, was 31 ± 5 years. Indications for referral were available in 28 cases and included decreased fetal movements (12 cases), maternal trauma (10 cases), fetal hydrops (3 cases), and uterine contractions, fetal right atrial enlargement, and twin-twin transfusion syndrome (1 case each). The remaining 4 cases were retrieved from a retrospective analysis of intrauterine transfusions. CTG upon admission was described in 24 cases and was

Table 2. Characteristics of studies included in this systematic review

First author	Year	Study design	Patients, n	Patients included, n
Baschat	1998	case report	1	1
Sueters	2003	case reports	2	2
Weisberg	2004	case reports	4	3
Wong	2005	case report	1	1
Rubod	2006	case report	1	1
Malcus	2006	case report	1	1
Eichbaum	2006	case report	1	1
Votino	2008	case report	1	1
Aso	2009	case report	1	1
Sikafis	2010	case report	1	1
Huissoud	2010	letter to the editor	3	2
Siemer	2010	case reports	2	2
Friszer	2010	case report	1	1
Amann	2011	retrospective	82	4
Cosmi	2012	prospective	15	10
Singh	2014	case report	1	1

Fig. 1. Flowchart of literature review process.

categorized as sinusoidal in 17, nonreactive in 5, with decelerations and tachycardic in 1 case each. MCA-PSV was 82 ± 19 cm/s (1.9 ± 0.3 MoM). FMH was confirmed by Kleihauer-Betke test in 27 cases and flow cytometry in 4

and both tests were used in the remaining case. The Hb value was available in all cases but one [15] and in this case, we retrieved it from the Ht [30]. Gestational age at delivery was available in 22 cases and it was 32 ± 4 weeks. A cesarean section was performed in all cases in which the mode of delivery was described (19/32) [13, 16, 21]. There was one fetal [21] and one neonatal death [14]. Fetuses/neonates had an initial hemoglobin (Hb) concentration of 4.82 ± 1.9 g/dl.

In all cases in which these data were available (20 cases), the fetuses/neonates were transfused only in utero (5 cases) [2, 8, 17, 21, 24, 25], only after birth (9 cases) [14, 19, 20, 22, 23, 25, 26] or both (2 cases) [10, 15]. In 4 cases, fetuses were transfused but data about postnatal transfusion were not available [13]. In the remaining 12 cases, data about transfusion were not available [16, 18].

Combined Series

Data from all cases included in our analysis (32 cases from the literature review and our own 3 cases) are provided in tables 1 and 3. The mean gestational age at admission was 31 ± 5 weeks. In the available cases, the mean gestational age at delivery was 33 ± 4 weeks. CTG was described in 27 cases and was categorized as sinusoidal in 18, nonreactive in 6, with decelerations in 2 and tachycardic in one. MCA-PSV was >1.5 MoM in all cases but one and >2 MoM in 14 cases (see fig. 3). The only case with a normal MCA-PSV had a borderline value (1.45 MoM) [19] at 39 weeks. Mean Hb at fetal blood sampling or at delivery was 4.8 ± 1.9 g/dl. There was one fetal demise [21] and one neonatal death [14]. Follow-up information was available in 27 cases and all infants were in good condition.

Fig. 2. Flowchart of cases included in this systematic review.

Fig. 3. MCA-PSV distribution of fetuses included in this study, plotted on the reference range of Mari et al. [27]. Black circles indicate systematic reviews, open squares indicate case series.

Discussion

This review of the literature on fetal MCA-PSV obtained in cases of fetal anemia secondary to FMH shows that this Doppler parameter was abnormal in all cases but one that we analyzed. This is not surprising as MCA-PSV is a good indicator of severe fetal anemia independently from the etiology [27, 31–33]. Indeed, all cases in our review but one had an MCA-PSV exceeding 1.5 MoM, the commonly accepted threshold that indicates severe fetal anemia [27], and in 14 of the cases (40%) the value exceeded 2 MoM. Abnormal CTG was present in all cases

but was frequently not specific. A sinusoidal cardiotocogram, which carries the strongest although not exclusive correlation with fetal anemia, was found in 66% of available cases (18/27) [10, 14–16, 19, 23, 25]. In the remaining, nonreactive tracings, decelerations or tachycardia were found [8, 20, 22, 24]. Indeed, the clinical presentation of massive FMH typically includes inconsistent fetal variables: absence of movements, nonreassuring fetal CTG, normal fetal size, normal amount of amniotic fluid, normal umbilical artery Doppler waveforms. Interpretation of such findings is usually a dilemma, and decision-making is a major challenge particularly in pregnancies

Table 3. Clinical data of cases from the systematic review of the literature

Case	Indication for referral	GAa	GAd	CTG pattern	MCA-PSV, MoM	eHb, g/dl	rHb, g/dl	Mode of delivery	Birth weight, g	IUT	NT	Clinical remarks
Baschat, 1998	labor	29	29	sinusoidal	2.37	3.6	3.7	CS	1,250	yes	yes	IVH, PVL, RDS
Sueters, 2003-1	DFM	36	36	sinusoidal	2.29	3.9	3.1	CS	2,465	no	yes	none
Sueters, 2003-2	DFM	30	30	sinusoidal	2.24	3.8	1.9	CS	1,630	no	yes	RDS
Weisberg, 2004-1	DFM	36	36	NA	2.1	4.6	2.7	CS	2,540	yes	no	none
Weisberg, 2004-2	DFM	34	34	sinusoidal	2.4	3.8	4.9	CS	2,380	no	yes	pulmonary hypertension
Wong, 2005	DFM	33	33	nonreactive	1.7	6.8	3.2	CS	2,005	no	yes	none
Eichbaum, 2006	DFM	32	32	sinusoidal	1.77	6.4	4	CS	1,860	yes	yes	none
Malcus, 2006	DFM	39	39	sinusoidal	1.45	9.6	3	CS	4,130	no	yes	NA
Rubod, 2006	DFM	28	28	decelerations	2.1	4.2	2.2	CS	3,400	yes	no	none
Votino, 2008	fetal hydrops	26	33	nonreactive	2.19	3.8	2.9	CS	2,075	yes	no	none
Aso, 2009	DFM	37	37	sinusoidal	2.2	4.1	3.6	CS	2,450	no	yes	neonatal death
Sifakis, 2010	fetal hydrops	24	24	NA	2.7	5	2.5	NA	NA	yes	\	fetal demise
Huissoud, 2010-1	DFM	29	29	tachycardic	1.52	8.5	8.6	CS	1,430	no	NA	NA
Huissoud, 2010-2	maternal trauma	28	28	NA	1.6	8.2	9	CS	1,170	no	NA	NA
Siemer, 2010-1	DFM	37	37	nonreactive	1.9	5.7	3.7	CS	3,150	no	yes	none
Siemer, 2010-2	DFM	37	37	nonreactive	1.77	6.7	5	CS	3,020	no	yes	none
Friszer, 2010	fetal hydrops	29	32	NA	1.8	5.7	4.5	CS	1,530	yes	No	none
Amann, 2011-1	NA	29	29	NA	2.2	3.8	3.3	NA	NA	yes	NA	NA
Amann, 2011-2	NA	29	29	NA	2.3	3.6	3.1	NA	NA	yes	NA	NA
Amann, 2011-3	NA	16	34	NA	2.7	4	7.7	NA	NA	yes	NA	NA
Amann, 2011-4	NA	30	30	NA	1.5	8.6	6.5	CS	NA	yes	NA	NA
Cosmi, 2012-1	TTTS	26	NA	sinusoidal	1.8	5.9	6	CS	NA	no	NA	RDS, BPD
Cosmi, 2012-2	maternal trauma	24	NA	sinusoidal	1.9	4.6	4.7	NA	NA	no	NA	RDS, NEC
Cosmi, 2012-3	maternal trauma	26	NA	sinusoidal	2	4.5	5	NA	NA	no	NA	RDS, BPD
Cosmi, 2012-4	maternal trauma	27	NA	sinusoidal	1.9	5.1	5.1	NA	NA	no	NA	RDS
Cosmi, 2012-5	maternal trauma	30	NA	sinusoidal	1.7	6.9	6.5	NA	NA	no	NA	RDS
Cosmi, 2012-6	maternal trauma	30	NA	sinusoidal	1.7	6.7	6.2	NA	NA	no	NA	RDS
Cosmi, 2012-7	maternal trauma	31	NA	sinusoidal	1.6	7.4	6.9	NA	NA	no	NA	RDS
Cosmi, 2012-8	maternal trauma	32	NA	sinusoidal	1.7	7	6.7	NA	NA	no	NA	RDS
Cosmi, 2012-9	maternal trauma	33	NA	sinusoidal	1.6	7.7	7.2	NA	NA	no	NA	RDS
Cosmi, 2012-10	maternal trauma	36	NA	sinusoidal	1.7	7.2	7.1	NA	NA	no	NA	RDS
Singh, 2014	fetal cardiopathy	38	38	nonreactive	1.82	6.3	4	CS	NA	no	yes	NA

GAa = Gestational age at admission; GAd = gestational age at delivery; eHb = estimated Hb value; rHb = real Hb value (at delivery or at fetal blood sampling); IUT = intrauterine transfusion; NT = neonatal transfusion; DFM = decreased fetal movements; TTTS = twin-to-twin transfusion syndrome; CS = cesarean section; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; NEC = necrotizing enterocolitis; NA = not available.

remote from term. In our own case series and in the review of the published literature, MCA-PSV was by far the most effective predictor of severe FMH.

We do acknowledge that our review has a major weakness in that it depends largely upon case reports that certainly favor the inclusion of cases with positive Doppler findings. Indeed, both the sensitivity and positive predictive value of MCA-PSV in our review approach 100%, which is probably unrealistic. The available data do not allow estimating the accuracy, particularly the specificity, of MCA-PSV assessment in the diagnosis of severe FMH. Only a large prospective study would allow appropriate calculations, but given the low prevalence of severe FMH, an enormous number of patients need to be examined. Experience with fetal erythroblastosis suggests that MCA-PSV has a high sensitivity in the prediction of fetal anemia, but a relatively low positive predictive value [34]. We suggest, however, that an increased MCA-PSV, which can be obtained and interpreted rapidly, could at least indicate the need for a maternal blood test to diagnose FMH, such as a Kleihauer-Betke or flow cytometry.

In most countries, pregnant patients are recommended to report rapidly decreased perception of fetal movements, because this is associated with an increased risk of adverse outcome [35–38]. However, there is not a general consensus on which test to perform in these cases. Usually, the first approach is CTG and ultrasound evaluation of fetal size, movements and amniotic fluid volume [39]. A similar diagnostic workup is recommended after maternal trauma [40]. Severe FMH may occur in both circumstances and we therefore suggest that in such cases it would be reasonable to obtain MCA-PSV. This may rapidly provide a major clue to the diagnosis of an otherwise elusive obstetric complication that is potentially fatal and yet can be treated easily and effectively.

Disclosure Statement

The authors deny conflicts of interest in connection with this article.

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