Using Middle Cerebral Artery Peak Systolic Velocity to Time In Utero Transfusions in Fetomaternal Hemorrhage

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BACKGROUND: Fetomaternal hemorrhage is a rare cause of fetal anemia and hydrops fetalis. Early and severe fetomaternal hemorrhage may benefit from in utero transfusion(s); however, hemorrhage rate is unpredictable, and reliable criteria are needed to identify recurrent anemia.

CASE: Fetal hydrops due to massive fetomaternal hemorrhage was diagnosed at 29 weeks. After the first in utero transfusion, daily monitoring of middle cerebral artery peak systolic velocity suggested recurrent fetal anemia, requiring two additional in utero transfusions at 1-week intervals. One day after the third in utero transfusion, a sudden increase in fetomaternal hemorrhage rate was suspected on a rapid elevation of middle cerebral artery peak systolic velocity, leading to immediate delivery at 32 weeks.

CONCLUSION: Middle cerebral artery peak systolic velocity is a relevant, noninvasive tool for the timing of repeated in utero transfusions and of fetal delivery in case of chronic fetomaternal hemorrhage.

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Fetomaternal hemorrhage is a known yet rare cause of nonimmune fetal hydrops. Several cases of successful management of early severe fetomaternal hemorrhage by repeated in utero transfusions have been reported. However, different criteria have been used to determine indications and timing of successive in utero transfusions[1–8]: diminished fetal body movements,[1,2] nonstress test anomalies, repeated cordocentesis, persistent positivity of Kleihauer-Betke test, persistent fetal hydrops, and middle cerebral artery peak systolic velocity. Middle cerebral artery peak systolic velocity is used routinely for the diagnosis of fetal anemia[9]; however, its predictive value after repeated in utero transfusions is being questioned.[10] We report a case of chronic fetomaternal hemorrhage monitored by repeated measurement of middle cerebral artery peak systolic velocity to determine the timing of repeated in utero transfusion, allowing detection of a sudden increase in fetomaternal hemorrhage rate.

CASE

A 26-year-old gravida 2 para 1 woman was referred to our department at 29 2/7 weeks of gestation for management of severe hydrops fetalis. During her first pregnancy, she had mild preeclampsia requiring labor induction at 39 weeks. She delivered vaginally a 3,070-g healthy male neonate. Her blood pressure was within normal range at the postpartum visit 6 weeks later.

The current pregnancy was uneventful until 28 weeks, when a 1.4 g/24-hour proteinuria was found, with a blood pressure of 130/80 mm Hg. The woman was admitted, and a course of betamethasone was administered. No other clinical or biological abnormalities were detected. An ultrasound scan revealed a severe hydrops fetalis with ascites, pericardial effusion, and prefrontal subcutaneous edema. Fetal movements were considered normal, as was the middle cerebral artery peak systolic velocity (53 cm/s, ie, 1.43 MoM). Maternal blood tests were negative for parvovirus B19 (positive immunoglobulin [Ig] G and negative IgM) and cytomegalovirus (negative IgG and IgM). The blood-group antibodies screening was negative in maternal blood. The Kleihauer-Betke stain revealed severe fetomaternal hemorrhage, with 150 fetal red blood cells for 10,000 maternal cells (ie, about 75 mL fetal blood). The woman then was referred to our center for management of severe fetomaternal hemorrhage at 29 2/7 weeks, with prior middle cerebral artery peak systolic velocity control at 58 cm/s (ie, 1.49 MoM).

On admission, ultrasound examination confirmed severe fetal hydrops likely due to anemia with a highly elevated middle cerebral artery peak systolic velocity at 71 cm/s (ie, 1.83 MoM). A first in utero transfusion was performed ~~on the same day~~. Initial fetal hemoglobin was 4.5 g/dL and was increased to 12.5 g/dL after in utero transfusion (Table 1). Immediate postprocedure middle cerebral artery peak systolic velocity was 55 cm/s (ie, 1.42 MoM; Fig. 1). Kleihauer-Betke stains performed on cord blood before and after the transfusion were, respectively, 100% and 27% fetal red blood cells. Further monitoring of the fetus consisted of nonstress tests twice daily and daily middle cerebral artery peak systolic velocity. Eight days later (30 4/7 weeks), a second in utero transfusion was performed when an elevation in middle cerebral artery peak systolic velocity at 80 cm/s (ie, 1.88 MoM) was noted,

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Table 1. Summary of Serial Transfusion Data and Evolution of Fetomaternal Hemorrhage Rate

	GA (wk)	Pre-IUT Hb (g/dL)	Post-IUT Hb (g/dL)	Fetal Hemorrhage Rate (g Hb/24 h)	Pre-IUT MCA-PSV (cm/s)	Post-IUT MCA-PSV (cm/s)
IUT 1	29 3/7	4.5	12.5	—	0.71	0.55
IUT 2	30 4/7	4.2	16.2	1.0	0.80	0.35
IUT 3	31 4/7	6.3	15.5	1.4	0.66	0.35
Birth	31 5/7	10.2	—	5.3	0.60	

GA, gestational age; IUT, in utero transfusion; Hb, hemoglobin; MCA-PSV, middle cerebral artery peak systolic velocity.

suggesting persistent fetomaternal hemorrhage; ascites and pericardial effusion had almost fully resolved, however. Fetal hemoglobin was 4.2 g/dL and increased to 16.2 g/dL (Table 1), and middle cerebral artery peak systolic velocity decreased immediately to 35 cm/s (0.82 MoM; Fig. 1). Kleihauer-Betke stains showed 43% and 5.8% fetal red blood cells before and after in utero transfusion, respectively. At 31 weeks, a second course of antenatal corticosteroids was decided on because of ongoing fetomaternal hemorrhage. A fetal magnetic resonance imaging scan was performed to detect possible neurological consequences of fetal anemia. No signs of cerebral ischemia were found.

A third in utero transfusion was decided on at 31 4/7 weeks, indicated by an elevation of the middle cerebral artery peak systolic velocity at 66 cm/s (1.50 MoM) without signs of hydrops. Fetal hemoglobin was 6.3 g/dL initially and increased to 15.5 g/dL after in utero transfusion (Table 1), with Kleihauer-Betke stains at 27% and 7.7% fetal red blood cells, respectively.

On the next day, a sharp elevation of the middle cerebral artery peak systolic velocity at 60 cm/s, although lower than 1.5 MoM (1.41 MoM), suggested a sudden increase in fetal hemorrhage rate (Fig. 1). Two subsequent measurements performed on the same day confirmed the rapid increase in middle cerebral artery peak systolic velocity. A cesarean delivery then was decided on. A 1,530-g female neonate was delivered, with Apgar scores of 8 at 1 minute and 7 at 5 minutes. Neonatal hemoglobin was 10.2 g/dL. One postnatal transfusion was performed, and the neonate required respiratory assistance for 24 hours. Neurological examinations at birth and at 6 months were normal. Placental pathological examination showed no histologic abnormalities.

COMMENT

Fetomaternal hemorrhage is an uncommon cause of fetal anemia. The diagnosis often is made retrospectively when searching for the cause of a fetal death. In rare cases, severe fetomaternal hemorrhage may benefit from in utero therapy to avoid early delivery and prematurity.

Eight cases of successful in utero management of fetal anemia due to chronic fetomaternal hemorrhage by repeated in utero transfusion have been reported

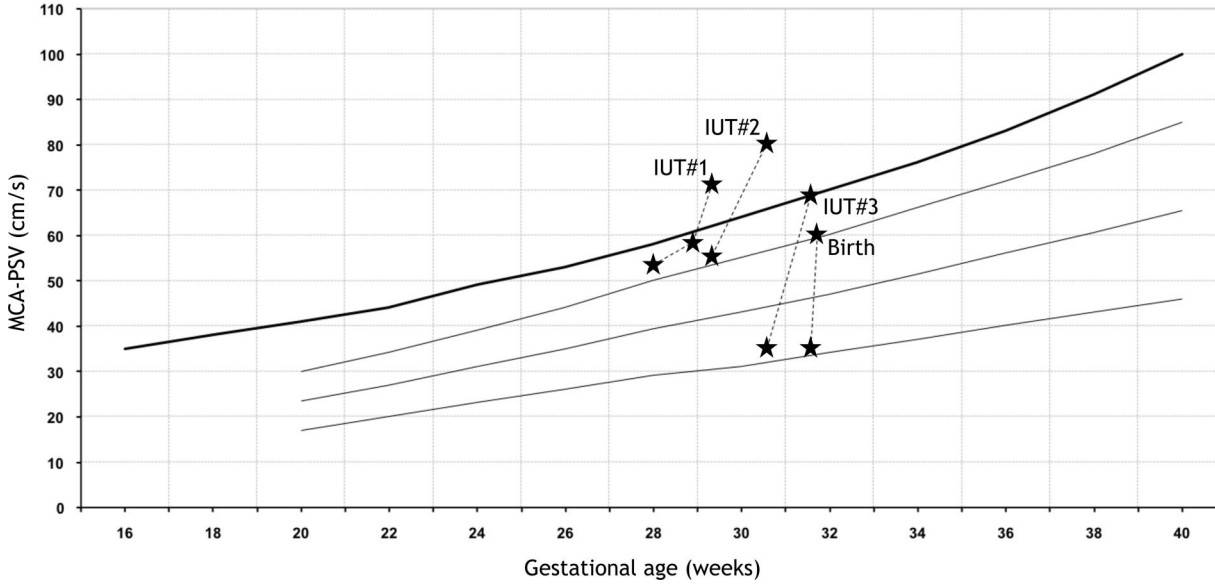

Fig. 1. Evolution of middle cerebral artery peak systolic velocity over time and summary of serial transfusion data.
Friszer. Fetomaternal Hemorrhage and Cerebral Doppler. Obstet Gynecol 2010.

previously.[1–8] The criteria or combination of criteria used to determine the timing of the successive in utero transfusions were different in all of these reports. Yet, each one bears disadvantages: fetal movements are perceived subjectively by the mother and are often a delayed sign of fetal anemia; the classical sinusoidal fetal heart rate pattern is also a very late manifestation of a bleeding fetus; repeated Kleihauer-Betke test is unreliable because the adult red blood cells transfused to the fetus cannot be distinguished from maternal blood; repeated cordocentesis, although the most accurate method, is an invasive procedure with a high risk of complications.

In contrast, middle cerebral artery peak systolic velocity Doppler measurement has proved its ability to diagnose moderate or severe fetal anemia in maternal red cell alloimmunization.[9] Indeed, a peak systolic velocity of 1.5 times the median or higher is a strong predictor of anemia, regardless of its cause. However, recent data suggest that middle cerebral artery peak systolic velocity could be inaccurate in the diagnosis of fetal anemia after previous in utero transfusion, with a high rate of false-positive results.[10] In previously reported cases, middle cerebral artery peak systolic velocity always was used in association with other criteria and never as a sole indicator for repeated in utero transfusions.[7,8] In the present case, neither fetal movements nor fetal heart rate monitoring was altered at the time of repeated in utero transfusions, despite confirmation of severe fetal anemia. Middle cerebral artery peak systolic velocity was thus the only altered parameter at the time when repeated transfusions were decided on, without prior invasive procedure to confirm anemia.

The evolution profile of the fetomaternal hemorrhage is variable; it may consist of a single episode of transplacental passage of fetal blood or of chronic hemorrhage, whether by ongoing bleeding or by repeated acute episodes. The rate of fetomaternal hemorrhage cannot be known before the second in utero transfusion. In our case, it was approximately 1 g/dL hemoglobin per day between the first and second transfusions. This rate increased moderately, at 1.4 g/dL/d after the second transfusion. Then, a sharp increase in middle cerebral artery peak systolic velocity in only 24 hours led us to suspect a sudden increase in the fetomaternal hemorrhage rate. This was confirmed by the neonatal hemoglobin rate of 10 g/dL, representing a drop in fetal hemoglobin of more than 5 g/dL in only 24 hours. This sharp increase in the fetomaternal hemorrhage rate may have occurred spontaneously, but it also could have been induced by the in utero transfusion because the access to the umbilical cord was transplacental.

In conclusion, the fetomaternal hemorrhage rate may vary dramatically and requires daily monitoring. Even if less accurate after previous transfusions, middle cerebral artery peak systolic velocity remains the only relevant, noninvasive tool for the timing of subsequent in utero transfusions or for delivery of the fetus in case of chronic fetomaternal hemorrhage.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES **1**

1—Author: Please review and approve the figure.

2—Author: Should 30 4/7 weeks be 9 days later (initial presentation was at 29 2/7 weeks)?