Ultrasound Obstet Gynecol 2005; **25**: 323–330
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.1882

Opinion

Middle cerebral artery peak systolic velocity for the diagnosis of fetal anemia: the untold story

The use of the middle cerebral artery peak systolic velocity (MCA-PSV) for the diagnosis of fetal anemia has been one of the few discoveries in fetal medicine that is changing the standard of care in the management of affected pregnancies[1]. This has led to a more than 70% reduction in the number of invasive tests, which often cause fetal death, in the assessment of red-cell alloimmunized pregnancies[1].

Up to 2 years ago, I thought that only a few doctors in the world were relying upon the MCA-PSV for the diagnosis of fetal anemia. However, in 2003 at the Society for Maternal–Fetal Medicine (SMFM) meeting in San Francisco and a few months later at the American Institute of Ultrasound in Medicine (AIUM) meeting in Montreal, during my lectures on fetal anemia, I asked my colleagues, 'how many of you are using the middle cerebral artery peak systolic velocity in fetuses at risk of anemia?', and I was pleasantly surprised to see that about 70% of the participants raised their hands. I then realized that the use of the MCA-PSV in fetal medicine had become a reality.

The MCA-PSV story

A recent article published in the *New England Journal of Medicine* entitled 'Who's on first? – medical discoveries and scientific priority', illustrates that each achievement in science is usually attributed to the person who made the final contribution to a discovery[2]. However, behind this person there is the work of many other researchers who prepared the basis for the discovery, and without that work, the discovery would not have been possible. It is for this that I acknowledge the important contribution of many investigators that over the last 20 years have applied Doppler ultrasonography to describe the association between fetal anemia and a hyperdynamic fetal circulation[3–11].

For me, it all started in 1987 at Baylor College of Medicine, Houston, TX, USA. Along with other investigators, Dr Robert L. Carpenter, Dr Russell L. Deter, Dr Kenneth J. Moise, Jr and Dr Theodor Stefos, I was studying the effects of intravascular transfusion on the circulation of the fetus. We were using two-dimensional (2D) ultrasound equipment (GE PASS II, Milwaukee, WI, USA) that did not have a color Doppler system. I noticed that, in all fetal anemia cases, the MCA waveforms (following transfusion) had a lower PSV value than before transfusion. We reported this concept a number of years later[12,13]. I could obtain a clear and good signal from this vessel by placing the sample volume parallel to the greater wing of the sphenoid bone. The anatomy of the MCA suggested that this vessel could be sampled with an angle of zero degrees and, therefore, the blood velocity could be measured. We were able to confirm in every case that the velocity in anemic fetuses was higher than that found following transfusion. Our first study was presented at the Society for Gynecologic Investigation in 1990[14]. In this study, we suggested that, for the diagnosis of fetal anemia, the MCA-PSV was a better parameter than the pulsatility index.

In 1995, we reported in this Journal the first comprehensive study on the MCA-PSV[15]. Our data indicated that we could diagnose fetal anemia in all cases due to red-cell alloimmunization; however, the false-positive rate was approximately 50%. In any case, the measurement of the MCA-PSV could spare 50% of the fetuses at risk for anemia from invasive procedures.

I started to apply the MCA-PSV in my practice and I was able to reduce the number of invasive procedures. However, I did not yet understand something related to its application in clinical practice. When I worked at Yale, Dr Uku Oz – a fellow of mine – and I were looking at the correlation between the MCA-PSV and fetal hemoglobin. The data showed that a cubic function described the relationship between the two parameters (Figure 1). Suddenly, I understood what I had missed for a long time: the MCA-PSV does not diagnose all cases of fetal anemia because, in mildly anemic cases, the velocity does not necessarily change. However, the correlation between hemoglobin and MCA-PSV becomes more accurate as the severity of anemia increases[16]. Furthermore, when

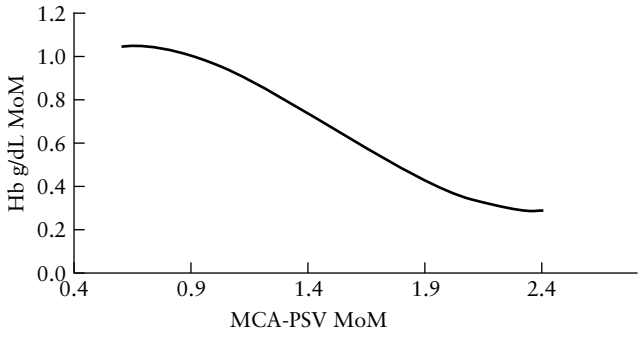

Figure 1 Cubic function describing the relationship between middle cerebral artery peak systolic velocity (MCA-PSV) and fetal hemoglobin (Hb). The values are expressed as multiples of the median (MoM). $y = 0.6835 + \text{MCA-PSV MoM} \times 1.2794 - 1.2885\ \text{MCA-PSV}^2 + 0.2861 \times \text{MCA-PSV}^3$.

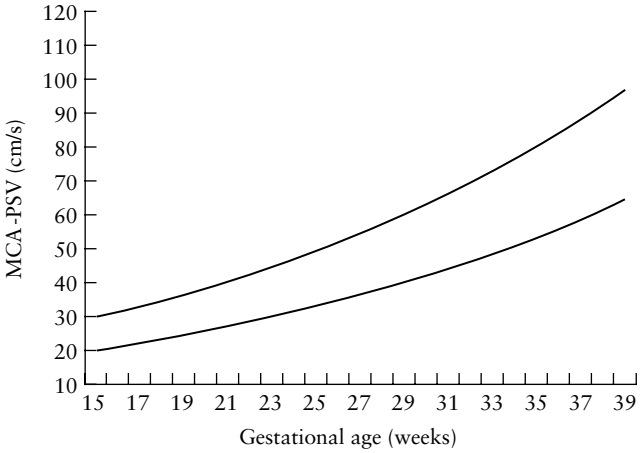

Figure 2 Peak velocity of systolic blood flow in the middle cerebral artery (MCA) with advancing gestation. The curves indicate the median (below) and 1.5 multiples of the median (MoM) (above) peak systolic velocity (PSV) in the MCA. (Reprinted from G. Mari *et al. N Engl J Med* 2000; **342**: 9–14[1], with permission. Copyright © 2000 Massachusetts Medical Society).

the anemia becomes very severe (hemoglobin levels of 1–3 g/dL), the velocity does not increase further. With this information in hand, I organized a study at different medical centers, carried out by several investigators – expert sonologists or good sonographers acquainted with the sampling of the MCA. We measured the velocity prior to cordocentesis in fetuses that were suspected to have anemia, based on traditional criteria. This multicenter study demonstrated that 70% of the invasive procedures performed to diagnose anemia were not necessary because the fetuses were either non-anemic or only slightly anemic[1]. If we had used the MCA-PSV as the criterion for intervention, we could have avoided approximately 70% of the procedures (Figure 2). In this study, we reported that an exponential function expresses the changes of fetal hemoglobin with advancing gestation, and classified the degrees of anemia as follows: mild, moderate, and severe (Table 1). Because we did not base our decision to perform an invasive procedure on the value of the velocity, I therefore participated in another study with Dr Roland Zimmerman, chairman of Obstetrics and Gynecology at the University of Zurich, Switzerland, Dr Robert L. Carpenter from the Houston Medical Center, and Dr Peter Duerig from Bern University, Switzerland. Dr Zimmerman and I had discussed this project in 1996 but we had not pursued it. Now the time was right. In this study, we based our decision to perform an invasive procedure on an elevated MCA-PSV value[17]. We included 125 women at risk for having a fetus with anemia, and avoided any invasive procedure in 90 women. We detected all but two cases of moderate and severe anemia. The first was a case in which the last value of velocity was assessed 3.5 weeks prior to delivery. The fetus was delivered at 35.5 weeks and the hematocrit was 24.5%. The second case was that of a patient serially followed up to 35 weeks when the last measurement was obtained. The fetus was then delivered 2.5 weeks later and the hematocrit was 15%. The neonates were transfused and did well. We also induced labor in six patients after 35 weeks' gestation because the value of the velocity was above our cut-off point. The neonates were not anemic. This study taught us that in some fetuses the MCA-PSV should be evaluated more frequently than every 2–3 weeks, and following 35 weeks' gestation, the MCA-PSV false-positive rate increases. I believe that the reason why the MCA-PSV, following 35 weeks' gestation, may be falsely increased in normal, non-anemic fetuses is due to different behavioral states of the fetus in this period of gestation. For example, the MCA-PSV may be falsely increased when the measurement is performed during a period of rest that follows a period of fetal activity. For the management of the fetus at risk for anemia following 35 weeks, see Figures 3 and 4.

In a subsequent study, Detti *et al.* reported that the MCA-PSV could be used to diagnose anemia even in fetuses previously transfused once[18].

Is rhesus (Rh) alloimmunization still a problem?

The Rh blood group system was discovered by Landsteiner and Weiner in 1940[19] and its involvement in maternal alloimmunization and hemolytic disease of the fetus and neonate (HDFN) was first described by Levine *et al.* in 1941[20]. In 1953, Bevis first recognized that

Table 1 Reference range for fetal hemoglobin concentration in normal and anemic fetuses as a function of gestational age (GA)

	Fetal hemoglobin concentration (g/dL)			
GA (weeks)	*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	13.8	7.6	9.0	11.6

MoM, multiples of the median. Normal hemoglobin values are ≥ 0.84 MoM; fetal anemia is divided into mild (hemoglobin < 0.84 MoM), moderate (hemoglobin < 0.65 MoM) and severe (hemoglobin < 0.55 MoM). (Reprinted from G. Mari *et al. N Engl J Med* 2000; **342**: 9–14[1], with permission. Copyright © 2000 Massachusetts Medical Society).

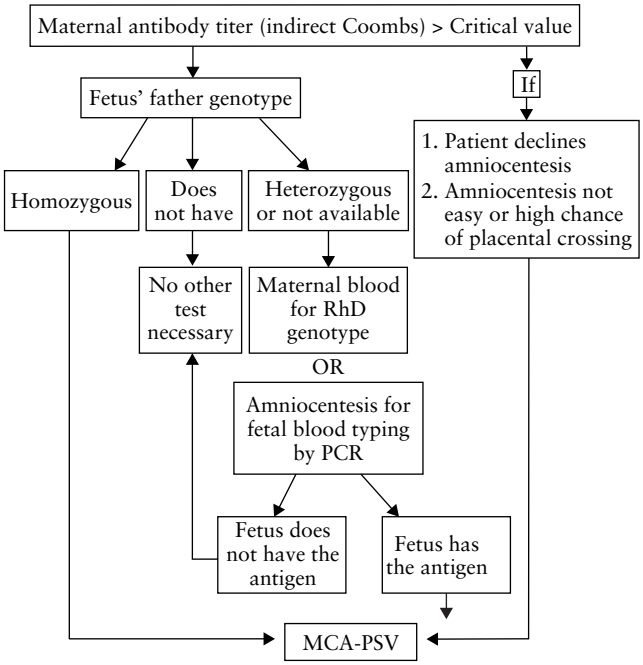

Figure 3 Algorithm for the management of red-cell alloimmunization (Part I). Although it is commonly reported that fetal anemia develops with an antibody titer of at least 1 : 16, with some antigens, i.e. Kell, severe fetal anemia may develop with a lower value (personal experience). MCA-PSV, middle cerebral artery peak systolic velocity; PCR, polymerase chain reaction; RhD, rhesus D.

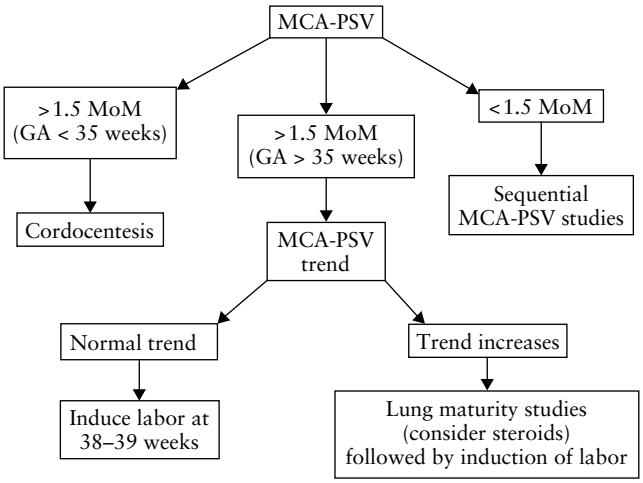

Figure 4 Algorithm for the management of red-cell alloimmunization (Part II). GA, gestational age; MoM, multiples of the median; MCA-PSV, middle cerebral artery peak systolic velocity.

spectrophotometric measurements of amniotic fluid appeared to change at optical density 450 nm in fetuses who were shown to have HDFN[21]. In 1956, Liley performed the first amniocentesis in a human to assess the fetal bilirubin through a spectrophotometric analysis in a pregnancy at risk for anemia, and in 1960 he described the technique and complications of amniocentesis[22]. In 1961, Liley described a method which uses the observed change in the optical density at 450 nm (delta OD450) to predict the severity of HDFN in fetuses[23], and in 1963 this investigator performed the first intrauterine transfusion (intraperitoneal) in an anemic fetus using X-ray guidance[24]. In 1964, Freda *et al.* performed the first intravascular transfusion in a fetus at 26 weeks' gestation[25]. This was the first case of open fetal surgery. Early in the 1970s, Carlo Valenti performed the first fetoscopy and also the first umbilical blood sampling under fetoscopy guidance[26,27]. This technique was extensively used in Europe by Dr Charles Rodeck and his group[28], and in the United States by Dr John Hobbins and Dr Jeremiah Mahoney[29]. In 1983, fetal blood sampling under ultrasound guidance was described by Daffos *et al.*[30] and it remains the current technique used for fetal blood transfusion.

Despite the introduction of Rh(D) immune globulin for the prevention of hemolytic disease of the fetus/newborn following the studies of Vincent Freda and collaborators[31–33], who received the Lasker award in 1980, Rh alloimmunization remains a major problem in several areas of the world.

Maternal Rh alloimmunization occurs when a pregnant woman develops an immunological response to a paternally derived red blood cell antigen (D) foreign to the mother and inherited by the fetus. The antibodies may cross the placenta, bind to antigens present on the fetal erythrocytes, and cause hemolysis. Hemolysis of the erythrocytes causes anemia in the fetus, and if severe, may result in edema, hydrops fetalis, and fetal death. Hemolytic disease of the fetus/neonate can also be caused by other antigens of the Rh blood group system and by the so-called 'irregular antigens' of the non-rhesus blood group system. Therefore, the term red-cell alloimmunization is more commonly used. Red-cell alloimmunization remains the most common cause of fetal anemia even in the USA, as a recent review of the 2001 birth certificates by the Centers for Disease Control and Prevention indicates that Rh sensitization still affects 6.7 out of every 1,000 live births[34]. This number, added to the other causes of red-cell alloimmunization (Kell, Kidd, Duffy, etc.), suggests that each year in the USA there are more than 30 000 fetuses at risk for anemia due to red-cell alloimmununization.

Is the delta OD450 better than MCA-PSV or vice versa?

In 1997, we reported that the MCA-PSV is superior to amniocentesis in detecting anemia in cases at risk of anemia[35]. Pereira *et al.* in 2003, confirmed these results[36]. A recent, comprehensive, multicenter study by Oepkes *et al.*, in which MCA-PSV and amniocentesis were performed prior to cordocentesis, has reported that the sensitivity and specificity of the MCA-PSV for detection of anemia are better than amniocentesis, which was considered the standard of care to diagnose fetal anemia in red-cell alloimmunization cases, and MCA can be safely used for timing a cordocentesis and possible fetal transfusion[37]. In their study, the authors used both the Liley[23] and the Queenan[38] curves. Bullock *et al.* have reported, in this issue of the Journal, that MCA-PSV and

delta OD450 have similar test accuracy in detecting fetal anemia[39]. However, they conclude that the MCA-PSV is a preferable screening method for fetal anemia because it is non-invasive.

The MCA-PSV diagnoses fetal anemia, even in cases of Kell sensitization, in which the problem is not the hemolysis but the suppression of the erythroid precursor in the bone marrow. We found a good correlation between the blood velocity and the hemoglobin values ($R^2 = 55\%$)[1]. Van Dongen *et al.*, in this issue of the Journal, concisely confirm that MCA-PSV can be used even in cases of Kell alloimmunization[40]. This is another advantage of using the MCA-PSV, because in cases of Kell alloimmunization, delta OD450 is not accurate[41–43].

Where do we need to sample the MCA-PSV?

I do not see any problem with investigators expressing the concept of anemia in SD or in absolute values, or when they develop reference ranges for the MCA-PSV in the normal fetuses in their population. However, I do see a problem when investigators – not trained to correctly sample this parameter – perform a study on fetuses at risk for anemia, and try to predict this condition by using the MCA-PSV. This can be misleading, which is highlighted in the article by Bartha *et al.*, reported in this issue of the Journal[44]. The sensitivity of the MCA-PSV for the diagnosis of fetal anemia ranged from 7% to 100% in the hands of different operators[1,40,44–50]. Therefore, the operators should be trained to correctly sample the MCA-PSV, for if the measurement is done well, the intra- and interobserver variabilities are small. Another important issue is determining what part of the MCA should be sampled. I completed a study on the intra- and interobserver variabilities of the MCA with Dr Alfred Abuhamad, Dr Mekibib Altaye, and three of my former fellows: Dr Erich Cosmi, Dr Maria Segata, and Dr Masashi Akiyama[51]. The results indicate that any segment of the MCA, with the exception of the area close to its division into terminal branches, can be sampled with good results. The reason why the distal area of the MCA does not have good reproducibility is due to a technical factor: any minimal movement of the fetal head can displace the sample volume in one of the terminal branches. There are usually two or three terminal branches but in my experience there can be as many as five (Figure 5). The MCA-PSV should be sampled at its proximal point, soon after its origin from the internal carotid artery, avoiding the need for angle correction, because measurement at this point is associated with the lowest intra- and interobserver variabilities[51]. The sample volume should be placed at the

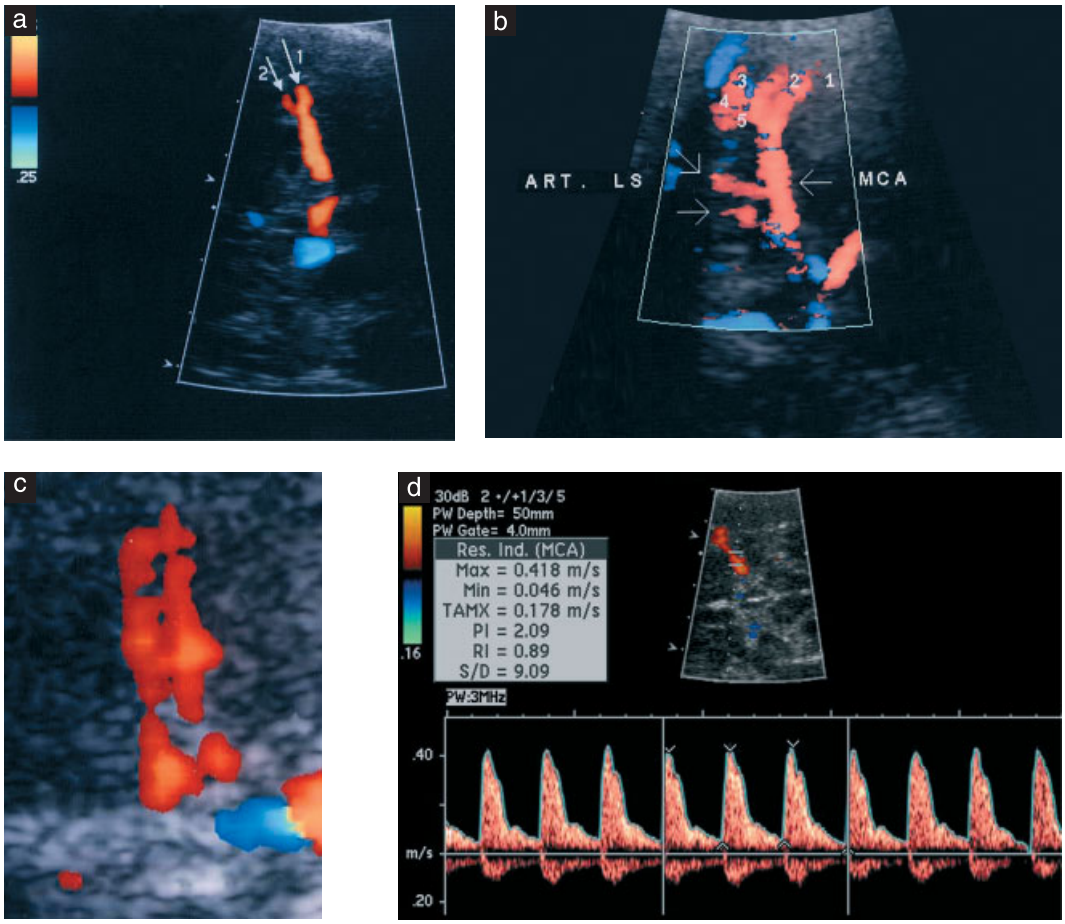

Figure 5 Color Doppler ultrasound image showing the middle cerebral artery (MCA). (a) The main trunk divides into two terminal branches (indicated by arrows 1 and 2); (b) it divides into five terminal branches (1 to 5); (c) double MCA (normal variant); (d) color Doppler of the MCA (top); flow velocity waveforms of the MCA (above the baseline) and lenticulostriates arteries (ART-LS) (below the baseline).

center of the vessel (Figure 6). If this Doppler parameter is correctly measured, the differences in the MCA-PSV reference ranges that different investigators might find would be minimal. Although the possibility exists that I may miss a case of severe anemia in the future, I feel very fortunate because, to date, while managing patients at risk for fetal anemia using the MCA-PSV reference ranges previously reported, I have never missed a case of moderate or severe anemia. Therefore, I do not believe that the cut-off points we have previously generated should be modified, since the curve was obtained with data gathered by several experienced investigators at different centers.

When the MCA is sampled, it is important to be aware and recognize the possible variants of this vessel (double MCA), or the waveforms of its collaterals (lenticulostriates arteries) (Figure 5).

Why is the velocity increased in MCA-PSV?

I believe that the blood velocity is increased in any vessel of the severely anemic fetus, as also suggested by the study by Van Dongen *et al*. reported in this issue of the Journal[40]. The advantage of studying the MCA is that it is easy to get an angle of zero degrees between the ultrasound beam and the direction of blood flow. In the diagnosis of severe anemia, there is one finding – tricuspid regurgitation – that precedes the development of ascites and hydrops. Use of this parameter could be of help in decreasing the false-negative cases. If a fetus at risk for anemia has a normal MCA-PSV and tricuspid regurgitation is present, it would be important to follow that fetus very closely, because it could be anemic. Although tricuspid regurgitation can be found in normal and non-anemic fetuses, in my experience, it is very unlikely to be found in fetuses at risk for anemia, especially when there is holosystolic regurgitation.

Is the MCA-PSV standard of care for the diagnosis of fetal anemia secondary to red-cell alloimmunization?

I believe that if a sonologist is well trained in the measurement of the MCA-PSV, the management of a patient at risk for fetal anemia can be based on the MCA-PSV; if the sonologist is not trained properly, it is better to use a different strategy to diagnose fetal anemia. For example, the patient could be referred to the closest center that has sonologists or sonographers trained to correctly measure the MCA-PSV. If there are no close centers that perform the MCA-PSV assessment, the patient should be informed of this limitation. The option of assessing fetal anemia with an invasive and less sensitive procedure than MCA-PSV assessment, such as amniocentesis, should be presented to the patient.

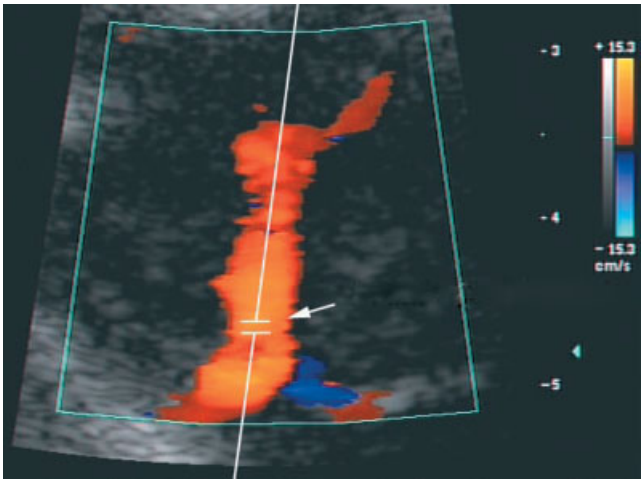

Figure 6 Color Doppler ultrasound image showing the middle cerebral artery. The sample volume (arrow) is placed in the center of the vessel after its origin from the internal carotid artery.

Primum non nocere – Which patients are candidates for the assessment of the MCA-PSV?

It is important to emphasize that MCA-PSV assessment should be reserved for those patients who are at risk of having an anemic fetus – indiscriminate use of the MCA-PSV without a clear indication may cause more harm than good. It is neither wise nor good medical care to screen every patient with the MCA-PSV and if the value is elevated, to assume that the fetus is anemic. This may create unnecessary anxiety and iatrogenic investigation. For example, if fetal–maternal hemorrhage is suspected, because of absent fetal movements and sinusoidal fetal heart rate tracing, an elevated MCA-PSV may strengthen the suspicion. On the other hand, an elevated MCA-PSV, in the presence of a reassuring fetal heart rate tracing and no anemia risk, does not indicate pathology – it may represent a false-positive case. Therefore, no intervention is indicated when an elevated MCA-PSV value is found in the absence of the risk of fetal anemia.

How do sonologists and sonographers achieve good training?

Since our first studies on the cerebral circulation of the anemic fetus, we have sampled the MCA following its origin from the internal carotid artery[1,15]. Recently, we have emphasized the steps for the correct measurement of the MCA-PSV: a) an axial section of the head is obtained at the level of the sphenoid bones; b) color Doppler identifies the circle of Willis; c) the image of the circle of Willis is enlarged; d) the color box is placed around the MCA; e) the MCA is zoomed; f) the MCA flow velocity waveforms are displayed and the highest point of the waveform (PSV) is measured. The waveforms should be all similar. The above sequence is repeated at least three times in each fetus[51].

I have trained many sonographers and sonologists on the use of the MCA-PSV. In the USA, it is not plausible to request board-certified physicians to demonstrate their skill in the measurement of the MCA-PSV. However, I feel that each sonographer and sonologist interested in the measurement of the MCA-PSV should have the possibility of contacting one center for advice. I believe that the first step for achieving good training should be a course on the application of MCA-PSV for the diagnosis of fetal anemia; this should be followed by practical application, i.e. availability to compare the measurement with that

obtained by a trained sonographer or sonologist. Our center, in Detroit, Michigan, USA, is available for review of both images and tapes to sonographers and sonologists interested in improving their skill.

How do we use the information of the MCA-PSV in red-cell alloimmunization?

Today, I manage patients at risk for anemia because of red-cell alloimmunization, as indicated in Figures 3 and 4. Two known methods are used in assessing the sequential studies of the MCA-PSV given in these flow charts. The first method requires a mathematical approach.

When, for the first time, I meet a patient who is at risk of having an anemic fetus due to red-cell alloimmunization, I measure the MCA-PSV. If the value is below 1.5 multiples of the median (MoM) (Figure 2), I reassess the MCA-PSV in 1 week. If the value remains below 1.5 MoM, I reassess the parameter the following week. Afterwards, I perform a linear regression analysis on the three values, and if the line is to the right of the thin curve shown in Figure 7, I repeat the study at intervals that vary between 2 and 4 weeks, based on the risk of the patient[52]. For example, if I see a patient for the first time at 16 weeks and (a) she has an anti-c value of 1 : 16, (b) the father of her baby is heterozygous for the c factor, (c) she is not interested in having an amniocentesis to know if the fetus is c positive, and (d) she does not have a history of a previous baby affected by anemia, I reassess the MCA-PSV in 4 weeks. Afterwards, I base my decision for a repeat test on the trend of the MCA-PSV. If the line remains to the right of the thin curve shown in Figure 7, and the value remains below 1 : 128, I repeat the scan every 2 weeks until 35 weeks. At this gestational age, if the value remains below the cut-off of 1.5 MoM, I continue to follow the MCA-PSV on a weekly basis. If the value is above 1.5 MoM, I evaluate the trend of the MCA-PSV and if it increases, following the administration of steroids to the mother, I induce labor, as indicated in Figure 4.

Of note is that, if the patient is Rh negative, I perform a maternal blood test to check for RhD genotype of the fetus. This new technique is very accurate and avoids the risk of the amniocentesis[53–55].

Figure 7 Average regression line for non-anemic fetuses (dashed line, $y = -17.28 + 1.99x$); mildly anemic fetuses (thin line, $y = -53.54 + 4.17x$) and severely anemic fetuses (thick line, $y = -76.82 + 5.26x$). (Reprinted from Detti L. *et al.*[52], © 2002, with permission from Elsevier).

An alternative to the above management is to assess the MCA-PSV on a weekly basis. If it becomes higher than 1.5 MoM, one should repeat the study in 2–3 days, and if the value continues to increase, one should perform a cordocentesis and be ready for intravascular transfusion. The MCA–PSV median and 1.5 MoM are reported in Table 2.

Is the MCA-PSV reliable for the diagnosis of fetal anemia due to other causes?

MCA-PSV can be used to diagnose fetal anemia due to other causes. Delle Chiaie *et al.*[46] and Cosmi *et al.*[45] reported that this parameter is useful in cases of fetal anemia secondary to parvovirus infection. Senat *et al.*[56] reported that MCA-PSV diagnoses anemia secondary to twin–twin transfusion syndrome (TTTS), and others have reported that MCA-PSV diagnoses anemia secondary to fetomaternal hemorrhage[57,58], and fetal hydrops[59,60].

In cases with parvovirus infection, I perform an ultrasound every week for 10 weeks following the exposure. I look for signs of anemia and I evaluate the MCA-PSV. If the value of the velocity becomes higher than 1.5 MoM, I repeat the ultrasound examination twice a week, and look for tricuspid regurgitation and ascites.

Table 2 Reference range of fetal middle cerebral artery peak systolic velocity (MCA-PSV) median and 1.5 multiples of the median (MoM) values during pregnancy

	MCA-PSV (cm/s)	
GA (weeks)	*Median*	*1.5 MoM*
14	19.3	28.9
15	20.2	30.3
16	21.1	31.7
17	22.1	33.2
18	23.2	34.8
19	24.3	36.5
20	25.5	38.2
21	26.7	40.0
22	27.9	41.9
23	29.3	43.9
24	30.7	46.0
25	32.1	48.2
26	33.6	50.4
27	35.2	52.8
28	36.9	55.4
29	38.7	58.0
30	40.5	60.7
31	42.4	63.6
32	44.4	66.6
33	46.5	69.8
34	48.7	73.1
35	51.1	76.6
36	53.5	80.2
37	56.0	84.0
38	58.7	88.0
39	61.5	92.2
40	64.4	96.6

GA, gestational age. (Modified from G Mari *et al. N Engl J Med* 2000; **342**: 9–14[1], with permission. Copyright © 2000 Massachusetts Medical Society)

Often, I do not intervene in cases of parvovirus infection based solely on the MCA-PSV because the fetus would not necessarily become hydropic, and the anemia might resolve spontaneously without intervention.

Fetal–maternal hemorrhage usually occurs in the third trimester. When I diagnose fetal–maternal hemorrhage, I perform a Cesarean delivery. The MCA-PSV is elevated in cases of fetal–maternal hemorrhage, but as indicated above, I utilize other signs that might suggest fetal–maternal hemorrhage (absence of fetal movements, sinusoidal pattern in the fetal heart rate tracing) prior to assessing the MCA-PSV.

In non-immune hydrops, if the MCA-PSV is below the cut-off point of 1.5 MoM, I do not perform a cordocentesis.

The preliminary data of Senat *et al*. appear promising for the use of MCA-PSV in the management of monochorionic twins following the death of the co-twin[56].

Recently, Robyr *et al*. have reported that in TTTS, feto-fetal hemorrhage from recipient to donor occurs in 10% of cases with double survivors as a result of incomplete laser coagulation of anastomoses[61]. Therefore, this parameter should be used for follow-up cases of TTTS following laser therapy.

In conclusion, the MCA-PSV has been shown to be an excellent tool for the diagnosis of fetal anemia. The *condicio sine qua non* for correctly measuring this parameter is the training of sonographers and sonologists. I believe that centers managing anemic fetuses should become comfortable with the diagnosis of fetal anemia using the MCA-PSV.

ACKNOWLEDGMENTS

I would like to thank Dr Russell L. Deter and Dr Roberto Romero for their lifelong support and friendship.

G. Mari
Professor of Obstetrics and Gynecology, Director of Diagnostic Endoscopy and Fetal Therapy, Department of Obstetrics and Gynecology, Wayne State University, Perinatology Research Branch, NICHD, NIH, DHHS, Detroit, MI, USA
(e-mail: gmari@med.wayne.edu)

REFERENCES

1. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, Dorman KF, Ludomirsky A, Gonzalez R, Gomez R, Oz U, Detti L, Copel JA, Bahado-Singh R, Berry S, Martinez-Poyer J, Blackwell SC. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. *N Engl J Med* 2000; **342**: 9–14.
2. Markel H. "Who's on first?" – medical discoveries and scientific priority. *N Engl J Med* 2004; **351**: 2792–2794.
3. Abdel-Fattah SA, Soothill PW, Carroll SG, Kyle PM. Noninvasive diagnosis of anemia in hydrops fetalis with the use of middle cerebral artery Doppler velocity. *Am J Obstet Gynecol* 2001; **185**: 1411–1415.
4. Abdel-Fattah SA, Soothill PW, Carroll SG, Kyle PM. Middle cerebral artery Doppler for the prediction of fetal anaemia in cases without hydrops: a practical approach. *Br J Radiol* 2002; **75**: 726–730.
5. Bahado-Singh R, Oz U, Deren O, Kovanchi E, Hsu CD, Copel J, Mari G. Splenic artery Doppler peak systolic velocity predicts severe fetal anemia in rhesus disease. *Am J Obstet Gynecol* 2000; **182**: 1222–1226.
6. Copel JA, Grannum PA, Green JJ, Belanger K, Hobbins JC. Pulsed Doppler flow-velocity waveforms in the prediction of fetal hematocrit of the severely isoimmunized pregnancy. *Am J Obstet Gynecol* 1989; **161**: 341–344.
7. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, arterial, and intracardiac blood flows in red blood cell isoimmunization. *Obstet Gynecol* 1995; **85**: 122–128.
8. Kirkinen P, Jouppila P, Eik-Nes S. Umbilical vein blood flow in rhesus-isoimmunization. *Br J Obstet Gynaecol* 1983; **90**: 640–643.
9. Nicolaides KH, Bilardo CM, Campbell S. Prediction of fetal anemia by measurement of the mean blood velocity in the fetal aorta. *Am J Obstet Gynecol* 1990; **162**: 209–212.
10. Rightmire DA, Nicolaides KH, Rodeck CH, Campbell S. Fetal blood velocities in Rh isoimmunization: relationship to gestational age and to fetal hematocrit. *Obstet Gynecol* 1986; **68**: 233–236.
11. Vyas S, Nicolaides KH, Campbell S. Doppler examination of the middle cerebral artery in anemic fetuses. *Am J Obstet Gynecol* 1990; **162**: 1066–1068.
12. Mari G, Rahman F, Oloffson P, Oczan T, Copel JA. Increase of fetal hematocrit decreases the middle cerebral artery peak systolic velocity in pregnancies complicated by rhesus alloimmunization. *J Matern Fetal Med* 1997; **6**: 206–208.
13. Stefos T, Cosmi E, Detti L, Mari G. Correction of fetal anemia on the middle cerebral artery peak systolic velocity. *Obstet Gynecol* 2002; **99**: 211–215.
14. Mari G, Moise JK, Kirshon B, Deter R, Gounsolin W, Carpenter RJ Jr. Middle cerebral artery pulsatility index and maximal velocity as indicators of fetal anemia. 37th Annual Meeting of the Society for Gynecologic Investigation, St Louis, MO, USA, 1990; Abstract 253.
15. Mari G, Adrignolo A, Abuhamad AZ, Pirhonen J, Jones DC, Ludomirsky A, Copel JA. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. *Ultrasound Obstet Gynecol* 1995; **5**: 400–405.
16. Mari G, Detti L, Oz U, Zimmerman R, Duerig P, Stefos T. Accurate prediction of fetal hemoglobin by Doppler ultrasonography. *Obstet Gynecol* 2002; **99**: 589–593.
17. Zimmerman R, Carpenter RJ, Jr., Durig P, Mari G. Longitudinal measurement of peak systolic velocity in the fetal middle cerebral artery for monitoring pregnancies complicated by red cell alloimmunisation: a prospective multicenter trial with intention-to-treat. *BJOG* 2002; **109**: 746–752.
18. Detti L, Oz U, Guney I, Ferguson JE, Bahado-Singh RO, Mari G. Doppler ultrasound velocimetry for timing the second intrauterine transfusion in fetuses with anemia from red cell alloimmunization. *Am J Obstet Gynecol* 2001; **185**: 1048–1051.
19. Landsteiner K, Weiner S. An agglutinable factor in human blood recognized by immune sera for Rhesus blood. *Proc Soc Exp Biol Med* 1940; **43**: 223.
20. Levine P, Katzin EM, Burnham L. Isoimmunization in pregnancy: its possible bearing on the etiology of erythroblastosis fetalis. *JAMA* 1941; **116**: 825–827.
21. Bevis DC. The composition of liquor amnii in haemolytic disease of the newborn. *J Obstet Gynaecol Br Emp* 1953; **60**: 244–251.
22. Liley AW. The technique and complications of amniocentesis. *Northwest Med* 1960; **59**: 581–586.
23. Liley AW. Liquor amnil analysis in the management of the pregnancy complicated by resus sensitization. *Am J Obstet Gynecol* 1961; **82**: 1359–1370.

24. Liley AW. Intrauterine transfusion of foetus in haemolytic disease. *Br Med J* 1963; **5365**: 1107–1109.
25. Freda VJ, Adamson SK Jr. Exchange transfusion *in utero*: report of a case. *Am J Obstet Gynecol* 1964; **89**: 817–821.
26. Valenti C. Endoamnioscopy and fetal biopsy: a new technique. *Am J Obstet Gynecol* 1972; **114**: 561–564.
27. Valenti C. Antenatal detection of hemoglobinopathies. A preliminary report. *Am J Obstet Gynecol* 1973; **115**: 851–853.
28. Rodeck CH, Kemp JR, Holman CA, Whitmore DN, Karnicki J, Austin MA. Direct intravascular fetal blood transfusion by fetoscopy in severe Rhesus isoimmunisation. *Lancet* 1981; **1**: 625–627.
29. Hobbins JC, Mahoney MJ. Fetoscopy and fetal blood sampling: the present state of the method. *Clin Obstet Gynecol* 1976; **19**: 341–352.
30. Daffos F, Capella-Pavlovsky M, Forestier F. A new procedure for fetal blood sampling in utero: preliminary results of fifty-three cases. *Am J Obstet Gynecol* 1983; **146**: 985–987.
31. Freda VJ, Gorman JG, Pollack W. Successful prevention of experimental Rh sensitization in man with an Anti-Rh Gamma2-Globulin antibody preparation: A preliminary report. *Transfusion* 1964; **77**: 26–32.
32. Freda VJ, Gorman JG, Pollack W. Suppression of the primary Rh immune response with passive Rh IgG immunoglobulin. *N Engl J Med* 1967; **277**: 1022–1023.
33. Freda VJ, Gorman JG, Pollack W, Robertson JG, Jennings ER, Sullivan JF. Prevention of Rh isoimmunization. Progress report of the clinical trial in mothers. *JAMA* 1967; **199**: 390–394.
34. Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM, Sutton PD. Births: final data for 2001. *Natl Vital Stat Rep* 2002; **51**: 1–102.
35. Mari G, Penso C, Sbracia M, Kern L, Levi D'Ancona R, Copel J. Delta OD450 and Doppler velocimetry of the middle cerebral artery peak velocity in the evaluation for fetal alloimmune hemolytic disease: Which is best? *Am J Obstet Gynecol* 1997; **180** (Suppl.)): 18.
36. Pereira L, Jenkins TM, Berghella V. Conventional management of maternal red cell alloimmunization compared with management by Doppler assessment of middle cerebral artery peak systolic velocity. *Am J Obstet Gynecol* 2003; **189**: 1002–1006.
37. Oepkes D, Seaward G, Vandenbussche F, Kingdom J, Windrim R, Beyene J, Kanhai H, Ohlsson A, Ryan G, for the Diamond Study Group. Minimally invasive management of Rh Alloimmunization: Can Amniotic fluid delta OD450 be replaced by Doppler studies? A prospective multicenter trial. *Am J Obstet Gynecol* 2004; **191** (Suppl.): S2; Abstract 3.
38. Queenan JT, Tomai TP, Ural SH, King JC. Deviation in amniotic fluid optical density at a wavelength of 450 nm in Rh-immunized pregnancies from 14 to 40 weeks' gestation: a proposal for clinical management. *Am J Obstet Gynecol* 1993; **168**: 1370–1376.
39. Bullock R, Martin WL, Coomarasamy A, Kilby MD. Prediction of fetal anemia in pregnancies with red-cell alloimmunization: comparison of middle cerebral artery peak systolic velocity and amniotic fluid OD450. *Ultrasound Obstet Gynecol* 2005; **25**: 331–334.
40. Van Dongen H, Klumper FJCM, Sikkel E, Vandenbussche FPHA, Oepkes D. Non-invasive tests to predict fetal anemia in Kell-alloimmunized pregnancies. *Ultrasound Obstet Gynecol* 2005; **25**: 341–345.
41. Babinszki A, Lapinski RH, Berkowitz RL. Prognostic factors and management in pregnancies complicated with severe kell alloimmunization: experiences of the last 13 years. *Am J Perinatol* 1998; **15**: 695–701.
42. Leggat HM, Gibson JM, Barron SL, Reid MM. Anti-Kell in pregnancy. *Br J Obstet Gynaecol* 1991; **98**: 162–165.
43. Weiner CP, Widness JA. Decreased fetal erythropoiesis and hemolysis in Kell hemolytic anemia. *Am J Obstet Gynecol* 1996; **174**: 547–551.
44. Bartha JL, Illanes S, Abdel-Fattah S, Hunter A, Denbow M, Soothill PW. Comparison of different reference values of fetal blood flow velocity in the middle cerebral artery for predicting fetal anemia. *Ultrasound Obstet Gynecol* 2005; **25**: 335–340.
45. Cosmi E, Mari G, Delle CL, Detti L, Akiyama M, Murphy J, Stefos T, Ferguson JE 2nd, Hunter D, Hsu CD, Abuhamad A, Bahado-Singh R. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia resulting from parvovirus infection. *Am J Obstet Gynecol* 2002; **187**: 1290–1293.
46. Delle Chiaie L, Buck G, Grab D, Terinde R. Prediction of fetal anemia with Doppler measurement of the middle cerebral artery peak systolic velocity in pregnancies complicated by maternal blood group alloimmunization or parvovirus B19 infection. *Ultrasound Obstet Gynecol* 2001; **18**: 232–236.
47. Deren O, Onderoglu L. The value of middle cerebral artery systolic velocity for initial and subsequent management in fetal anemia. *Eur J Obstet Gynecol Reprod Biol* 2002; **101**: 26–30.
48. Dukler D, Oepkes D, Seaward G, Windrim R, Ryan G. Noninvasive tests to predict fetal anemia: a study comparing Doppler and ultrasound parameters. *Am J Obstet Gynecol* 2003; **188**: 1310–1314.
49. Scheier M, Hernandez-Andrade E, Carmo A, Dezerega V, Nicolaides KH. Prediction of fetal anemia in rhesus disease by measurement of fetal middle cerebral artery peak systolic velocity. *Ultrasound Obstet Gynecol* 2004; **23**: 432–436.
50. Teixeira JM, Duncan K, Letsky E, Fisk NM. Middle cerebral artery peak systolic velocity in the prediction of fetal anemia. *Ultrasound Obstet Gynecol* 2000; **15**: 205–208.
51. Mari G, Abuhamad A, Cosmi E, Segata M, Altaye M, Akiyama M. Middle cerebral peak systolic velocity: Technique and variability. *J Ultrasound Med* 2005; **24**: 425–430.
52. Detti L, Mari G, Akiyama M, Cosmi E, Moise KJ Jr, Stefor T, Conaway M, Deter R. Longitudinal assessment of the middle cerebral artery peak systolic velocity in healthy fetuses and in fetuses at risk for anemia. *Am J Obstet Gynecol* 2002; **187**: 937–939.
53. Daniels G, Finning K, Martin P, Soothill P. Fetal blood group genotyping from DNA from maternal plasma: an important advance in the management and prevention of haemolytic disease of the fetus and newborn. *Vox Sang* 2004; **87**: 225–232.
54. Finning K, Martin P, Daniels G. A clinical service in the UK to predict fetal Rh (Rhesus) D blood group using free fetal DNA in maternal plasma. *Ann N Y Acad Sci* 2004; **1022**: 119–123.
55. Gautier E, Benachi A, Giovangrandi Y, Ernault P, Olivi M, Gaillon T, Cost JM. Fetal RhD genotyping by maternal serum analysis: a two-year experience. *Am J Obstet Gynecol* 2005; **192**: 666–669.
56. Senat MV, Loizeau S, Couderc S, Bernard JP, Ville Y. The value of middle cerebral artery peak systolic velocity in the diagnosis of fetal anemia after intrauterine death of one monochorionic twin. *Am J Obstet Gynecol* 2003; **189**: 1320–1324.
57. Mari G, Detti L. Doppler ultrasound – Application to fetal Medicine. In *The principles of ultrasonography in obstetrics and gynecology*, Manning FA, Fletcher A, Romero R, Jeanty P (eds). Appleton & Lange: New York; 2001.
58. Sueters M, Arabin B, Oepkes D. Doppler sonography for predicting fetal anemia caused by massive fetomaternal hemorrhage. *Ultrasound Obstet Gynecol* 2003; **22**: 186–189.
59. Hernandez-Andrade E, Scheier M, Dezerega V, Carmo A, Nicolaides KH. Fetal middle cerebral artery peak systolic velocity in the investigation of non-immune hydrops. *Ultrasound Obstet Gynecol* 2004; **23**: 442–445.
60. Cosmi E, Dessole S, Uras L, Capobianco G, D'Antona D, Andrisani A, Litta P, Ambrosini G. Middle cerebral artery peak systolic and ductus venosus velocity waveforms in the hydropic fetus. *J Ultrasound Med* 2005; **24**: 209–213.
61. Robyr R, Lewi L, Yamamoto M, Deprest J, Ville Y. Permanent feto-fetal transfusion from the recipient to the donor twin. A complication of laser surgery in twin–twin-transfusion syndrome. *Am J Obstet Gynecol* 2005; **191** (Suppl.1): 163.

