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Middle cerebral artery peak systolic velocity: a new Doppler parameter in the assessment of growth-restricted fetuses

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KEYWORDS: biophysical profile; middle cerebral artery; peak systolic velocity; pulsatility index

ABSTRACT

Objective *The aims of this study were to determine if there is a relationship between middle cerebral artery (MCA) peak systolic velocity (PSV) and perinatal mortality in preterm intrauterine growth-restricted (IUGR) fetuses, to compare the performance of MCA pulsatility index (PI), MCA-PSV and umbilical artery (UA) absent/reversed end-diastolic velocity (ARED) in predicting perinatal mortality, to determine the longitudinal changes that occur in MCA-PI and MCA-PSV in these fetuses, and to test the hypothesis that MCA-PSV can provide additional information on the prognosis of hypoxemic IUGR fetuses.*

Methods *This was a retrospective cross-sectional study of 30 IUGR fetuses (estimated fetal weight < 3rd percentile; UA-PI > 95% CI) in which the last MCA-PI, MCA-PSV and UA values were obtained within 8 days before delivery or fetal demise. Among the 30 fetuses, there were 10 in which at least three consecutive measurements were performed before delivery and these were used for a longitudinal study. MCA-PSV and MCA-PI values were plotted against normal reference ranges and were considered abnormal when they were above the MCA-PSV or below the MCA-PI reference ranges.*

Results *Gestational age at delivery ranged between 23+1 and 32+5 (median, 27+6) gestational weeks. Birth weight ranged from 282 to 1440 (median, 540) g. There were 11 perinatal deaths. Forward stepwise logistic regression indicated that MCA-PSV was the best parameter in the prediction of perinatal mortality (odds ratio, 14; 95% CI, 1.4–130;* $P < 0.05$*) (Nagerlke* $R^2 = 31$*). In the 10 fetuses studied longitudinally, an abnormal MCA-PI preceded the appearance of an abnormal MCA-PSV. In these fetuses, the MCA-PSV consistently showed an initial increase in velocity; before demise or the appearance of a non-reassuring test in seven fetuses, there was a decrease in blood velocity. The MCA-PI presented an inconsistent pattern.*

Conclusions *In IUGR fetuses, the trends of the MCA-PI and MCA-PSV provide more clinical information than does one single measurement. A high MCA-PSV predicts perinatal mortality better than does a low MCA-PI. We propose that MCA-PSV might be valuable in the clinical assessment of IUGR fetuses that have abnormal UA Doppler. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Fetuses that are intrauterine growth-restricted (IUGR), secondary to placental insufficiency, redistribute their blood flow from the periphery to the brain[1], and Doppler ultrasound of the umbilical artery (UA) and fetal brain arteries can be used to determine these changes[2,3]. In IUGR, the pulsatility index (PI) of the UA is increased, while that of the cerebral arteries is decreased. Because it is simple to access, the most studied fetal brain artery is the middle cerebral artery (MCA). We have previously reported nomograms of the MCA-PI and MCA peak systolic velocity (PSV) with advancing gestation in appropriate-for-gestational-age fetuses[4,5] and, along with other researchers, we have also reported that the MCA-PI is decreased in fetuses at risk for perinatal morbidity and mortality[4,6]. A preliminary study also reported that MCA-PSV increased in a subset of IUGR fetuses, suggesting that it could be a good predictor of perinatal mortality[7].

The aims of this study were four-fold: to determine if there is a relationship between the MCA-PSV and

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perinatal mortality in preterm IUGR fetuses that have an abnormal UA-PI, to compare the performance of the MCA-PI, MCA-PSV, and UA absent or reversed end-diastolic flow velocity (ARED) in the prediction of perinatal mortality in these fetuses, to determine the longitudinal changes that occur in the MCA-PI and MCA-PSV in these fetuses, and to test the hypothesis that the MCA-PSV can provide additional information on the prognosis of hypoxemic IUGR fetuses.

MATERIAL AND METHODS

This study included a retrospective and a prospective assessment of the MCA-PSV and MCA-PI. All patients were enrolled into research protocols approved by a human investigation committee.

Among 55 fetuses diagnosed with IUGR, we selected singletons that had: (a) an estimated weight $< 3^{rd}$ percentile (confirmed at birth), (b) a UA-PI $> 95^{th}$ CI, (c) normal anatomy and (d) an MCA Doppler examination determined with an angle close to 0° within 8 days before delivery or fetal demise. All were delivered at < 33 weeks' gestation.

Thirty fetuses met the entry criteria. The gestational age at the time of the Doppler study ranged between 23+0 and 32+4 (median, 27+2) weeks, based on the last menstrual period for women with a recorded history or on a second-trimester scan. Delivery was indicated in the presence of: (a) non-reassuring fetal testing, (b) fetal demise, or (c) worsening maternal or fetal conditions as determined by the managing physician. Non-reassuring fetal testing was defined as the presence of either continuous late decelerations or a biophysical profile < 4. When delivery was indicated and the fetus was < 500 g in weight, the patient was counseled on the poor prognosis and offered the option of non-intervention. For fetal weight, we utilized the normal reference ranges established by Hadlock *et al.*[8].

Doppler studies

Pulsed-wave Doppler ultrasound studies were performed with four color Doppler systems (Sequoia, Siemens Medical Solutions, Mountain View, CA, USA; Voluson 530 or 730 Expert, GE Medical Systems, Milwaukee, WI, USA; HDI 5000, Philips Medical Systems, Bothell, WA, USA) using 3.5- or 5-MHz probes with spatial peak temporal average intensities of < 100 mW/cm^2 in both imaging and Doppler modes. All recordings were obtained in the absence of fetal breathing and fetal movements. For each vessel, an average of three consecutive Doppler velocity waveforms was used for statistical analysis. A free loop of the UA was sampled, and the PI was used to analyze the waveforms[9]. The MCA was studied with an angle close to 0° between the ultrasound beam and the direction of blood flow, as reported previously[5]. The MCA waveforms were quantified using the PI as well as the PSV. The MCA-PI was considered abnormal if the measurements were below the lower limit of normal as reported previously[4]; the MCA-PSV was considered abnormal if the measurements were above the upper limit of normal, as established previously[5]. A UA-PI > 95% CI for gestational age of our reference range was also considered abnormal, as was ARED in the UA.

Prospective longitudinal study

Of the 30 IUGR fetuses, we prospectively assessed 10 in which the MCA-PI and the MCA-PSV were recorded longitudinally from the time the diagnosis was made until delivery. The number of measurements in these fetuses ranged from 3 to 8 (median, 5). Gestational ages at entrance into the study ranged from 20+6 to 26+4 (median, 23+5) weeks, and gestational ages at delivery were between 23+1 and 28+6 (median, 26+1) weeks.

Perinatal outcome endpoints included: (a) perinatal mortality, defined as mortality occurring between 20 weeks' gestation and 28 days after birth and

Table 1 Demographics of the study population ($n = 30$)

Characteristic	*Median (range)*
GA at Doppler study (weeks)	27+2 (23+0–32+4)
Interval between last scan and delivery (days)	1 (0–8)
GA at delivery (weeks)	
Total population	27+6 (23+1–32+5)
Perinatal deaths ($n = 11$)	25+5 (23+1–28+6)
IUFDs ($n = 6$)	25+8 (23+1–28+6)
NDs ($n = 5$)	25+0 (24+6–28+1)
Survivors ($n = 19$)	29+2 (25+2–32+5)
Birth weight (g)	
Total population	540 (282–1440)
Perinatal deaths ($n = 11$)	440 (282–660)
IUFDs ($n = 6$)	430 (282–472)
NDs ($n = 5$)	471 (300–660)
Survivors ($n = 19$)	760 (360–1440)

GA, gestational age; IUFD, intrauterine fetal demise; ND, neonatal death.

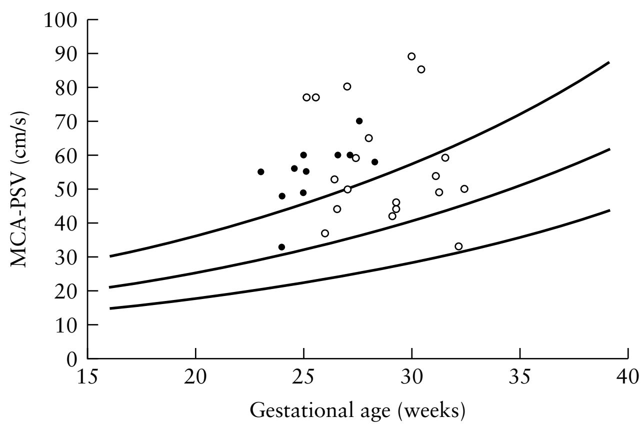

Figure 1 Middle cerebral artery peak systolic velocity (MCA-PSV) in 30 growth-restricted fetuses plotted on the normal reference range[5], showing fetuses which died (●) and those which survived (○).

Table 2 Individual characteristics of the study population

Case	Maternal pathology	Gestational age (weeks) at Doppler	Gestational age (weeks) at delivery	MCA-PI	MCA-PSV	UA-ARED	Indication for delivery	Birth weight (g)	Perinatal morbidity (BPD)	Perinatal mortality
1	CHtn	30+0	30+0	A	A	A	NRFT	600	Yes	No
2	None	25+1	25+5	A	A	A	IUFD	308	—	IUFD
3	None	27+1	27+2	N	A	A	IUFD	472	—	IUFD
4	CHtn	24+6	24+6	A	N	A	NRFT	300	—	Died in NICU (1 day)
5	CHtn	25+5	25+5	A	A	A	S-PE	360	Yes	No
6	CHtn	23+0	23+1	N	A	A	IUFD	282	—	IUFD
7	CHtn	25+0	25+0	A	A	A	HELLP	440	—	Died in NICU (1 day)
8	None	30+4	30+6	A	A	N	S-PE	1080	No	No
9	CHtn	26+0	26+5	A	N	A	NRFT	510	No	No
10	None	32+4	32+5	N	N	N	HELLP	1440	No	No
11	None	29+2	29+2	A	N	A	NRFT	1000	Yes	No
12	CHtn	26+4	26+4	A	A	A	NRFT	460	Yes	No
13	None	32+1	32+2	N	N	N	HELLP	1380	No	No
14	CHtn	31+3	31+3	A	N	N	S-PE	1240	Yes	No
15	None	25+1	25+2	A	A	A	NRFT (PE)	530	Yes	No
16	None	27+6	28+1	N	A	A	NRFT S-PE	471	—	Died in NICU (8 days)
17	CHtn	26+6	28+0	A	N	A	NRFT	700	Yes	No
18	CHtn	26+6	26+6	A	A	A	NRFT	660	—	Died in NICU (3 days)
19	CHtn	28+0	28+0	A	A	A	NRFT	467	Yes	No
20	None	28+1	28+4	A	A	A	NRFT (S-PIH)	840	Yes	No
21	None	28+3	28+6	N	A	A	IUFD	440	—	IUFD
22	Hypth	24+0	24+1	N	A	A	IUFD	440	—	IUFD
23	Lupus	25+0	26+1	A	A	A	IUFD	420	—	IUFD
24	CHtn	31+6	32+0	A	N	A	NRFT	1100	No	No
25	SCD	31+1	31+6	A	N	N	S-PIH	1150	No	No
26	None	29+1	29+4	A	N	N	S-PIH	820	No	No
27	None	27+0	27+1	A	A	A	S-PE	550	Yes	No
28	None	29+3	29+4	N	N	N	S-PE	760	No	No
29	None	24+6	24+6	A	A	A	S-PE	505	—	Died in NICU (8 days)
30	None	27+3	27+3	A	N	A	NRFT (S-PE)	620	Yes	No

A, abnormal; BPD, bronchopulmonary dysplasia; CHtn, chronic hypertension; HELLP, hemolysis, elevated liver function tests, low platelets; Hypth, hyperthyroidism; IUFD, intrauterine fetal demise; MCA-PI, middle cerebral artery pulsatility index; MCA-PSV, middle cerebral artery peak systolic velocity; N, normal; NICU, neonatal intensive care unit; NRFT, non-reassuring fetal testing; PE, pre-eclampsia; PIH, pregnancy-induced hypertension or gestational hypertension; S, severe; SCD, sickle cell disease; UA-ARED, absent/reversed end-diastolic flow velocity.

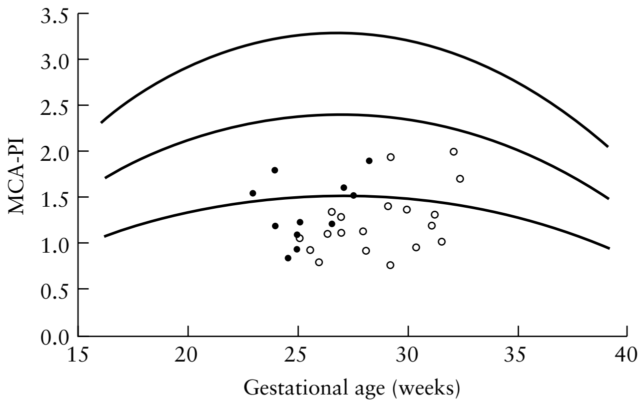

Figure 2 Middle cerebral artery pulsatility index (MCA-PI) in 30 growth-restricted fetuses plotted on the normal reference range[4], showing fetuses which died (●) and those which survived (○).

(b) major neonatal complications, defined as intracerebral hemorrhage (IVH) Grades III or IV according to the Papile classification[10] or bronchopulmonary dysplasia (BPD).

Table 3 Predictive value for perinatal mortality of middle cerebral artery peak systolic velocity (MCA-PSV) above the normal range for gestational age

Test result	Perinatal mortality (n)	No perinatal mortality (n)	Total (n)
MCA-PSV (abnormal)	10	8	18
MCA-PSV (normal)	1	11	12
Total	11	19	30

Sensitivity, 91%; specificity, 58%; positive predictive value, 56%; negative predictive value, 92% (odds ratio, 14; 95% CI, 1.4–130; $P < 0.05$).

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 14.0 (SPSS, System for Windows, Chicago, IL, USA). We evaluated the MCA-PI, MCA-PSV and UA-ARED obtained at the last examination against the outcomes of perinatal mortality or major neonatal complications by forward stepwise logistic regression. Due to the small number of fetuses that survived,

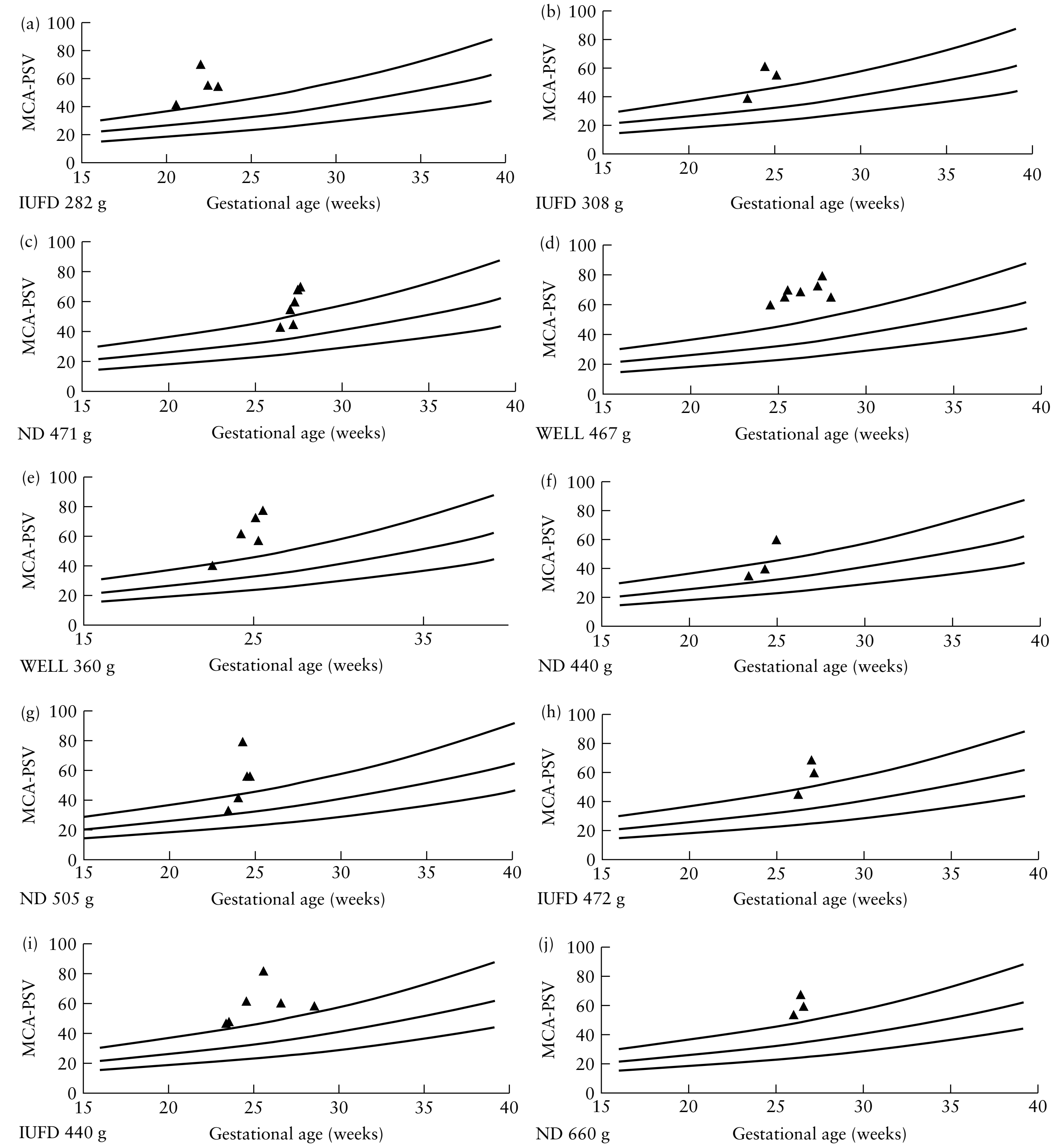

Figure 3 Individual longitudinal values for the middle cerebral artery peak systolic velocity (MCA-PSV in cm/s) in 10 growth-restricted fetuses plotted on the reference range[5]. An accurate velocity value could not be determined in some studies because an appropriate angle between the ultrasound beam and the direction of the blood flow could not be obtained. At the bottom left of each graph, the fetal outcome is indicated: intrauterine fetal demise (IUFD), well at the time of writing (WELL) or neonatal death (ND), with the weight at delivery in grams.

two-tailed chi-square or Fisher's exact tests were employed to analyze the relationship between the Doppler parameters and perinatal morbidity. Student's *t*-test for independent samples was used to compare whether or not a difference in gestational age existed at delivery among the babies who survived and those who died, either *in utero* or within the first 4 weeks of life. This test was also used to compare whether a difference in gestational age existed at delivery among the infants who developed major neonatal complications and those who did not. A probability value of $P < 0.05$ was considered statistically significant.

We also calculated the sensitivity, specificity, positive predictive value and negative predictive value for the parameters selected by the forward stepwise logistic regression analysis, with the tests' status being abnormal

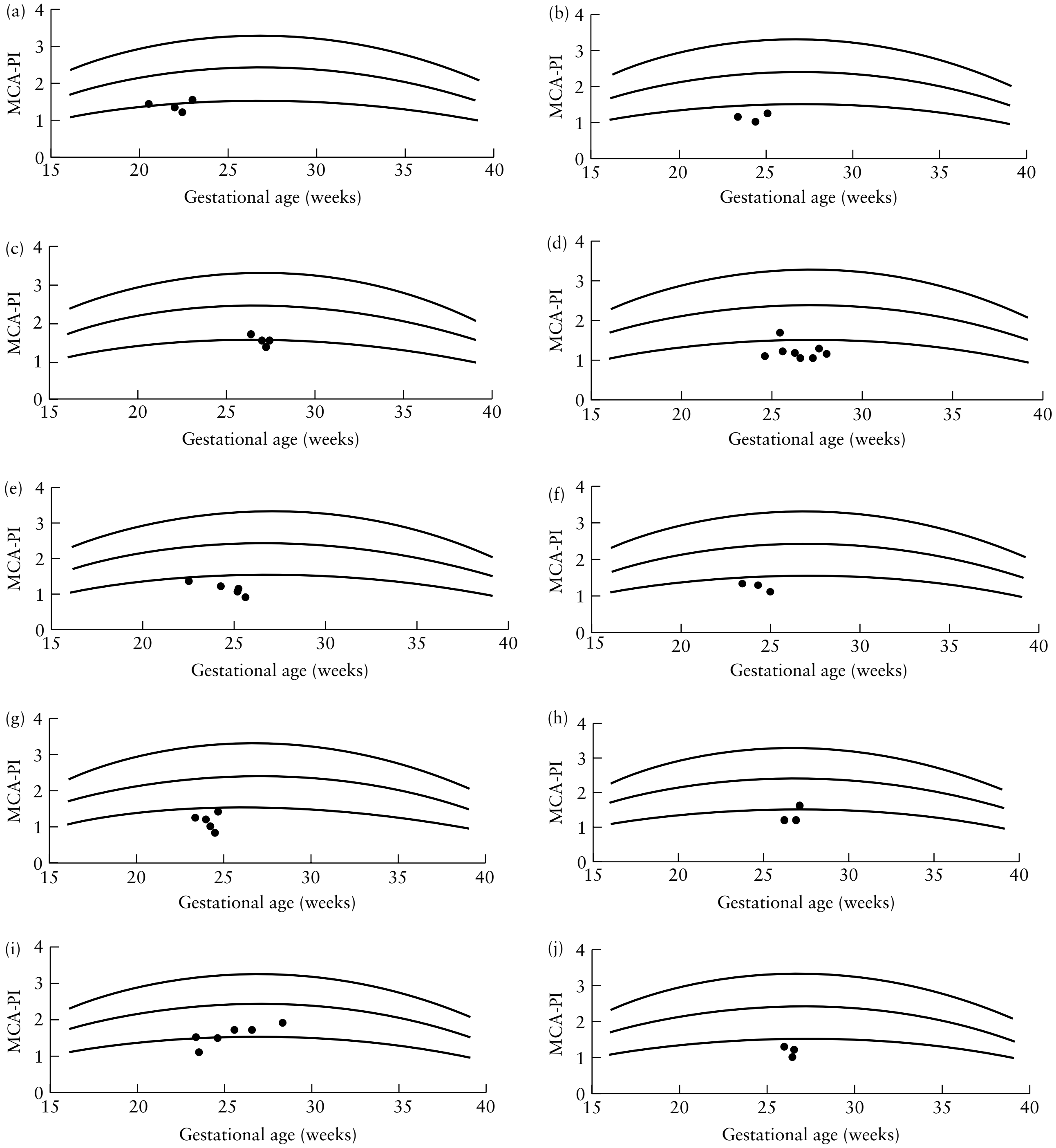

Figure 4 Individual longitudinal values for the middle cerebral artery pulsatility index (MCA-PI) in the same 10 growth-restricted fetuses as in Figure 3, plotted on the reference range[4].

Doppler parameter and the outcome status being presence or absence of perinatal death.

For the 10 fetuses that were followed longitudinally, we plotted the MCA-PI and the MCA-PSV values on our reference ranges to determine the trend of these two parameters with advancing gestational age in IUGR fetuses.

RESULTS

The characteristics of the study population and the perinatal morbidity and mortality data are reported in Tables 1 and 2. There were six fetal demises and in all cases the mothers opted for no intervention following counseling due to extreme prematurity and low birth weight. With the exception of those that died *in utero*, all but one of the fetuses were delivered by Cesarean section. The forward stepwise logistic regression indicated that the MCA-PSV predicted the perinatal mortality (odds ratio, 14; 95% CI, 1.4–130; $P < 0.05$) (Nagerlke $R^2 = 31$).

The fetuses that died were at a significantly lower gestational age at the time of delivery than were those that survived (25+6 ± 1+6 weeks vs. 29+0 ± 2+3 weeks;

$P = 0.001$). There were no survivors at $\leq 25+0$ weeks' gestation (two intrauterine (IUFD) and three neonatal deaths), whereas at > 29 weeks' gestation all the fetuses survived ($n = 10$), and between 25 and 29 weeks six died (four fetal demises and two neonatal deaths).

Figures 1 and 2 show the MCA-PSV and MCA-PI, respectively, plotted on our reference ranges[4,5]. Table 3 gives the sensitivity, specificity, and positive and negative predictive values of MCA-PSV above the normal range for perinatal mortality.

Among the infants who survived, none developed IVH Grade III or IV, whereas 11 developed BPD. The gestational age at delivery was lower in the infants who developed BPD (27+6 ± 1+6 weeks vs. 30+3 ± 2+1 weeks; $P < 0.05$). BPD was significantly related to an abnormal MCA-PSV (odds ratio, 12; 95% CI, 1.1–139; $P = 0.037$), and UA-ARED (odds ratio, 30; 95% CI, 2.2–405; $P = 0.006$). The MCA-PI odds ratio was 0.6 (95% CI, 0.4–1.1; $P = 0.058$).

In the 10 fetuses followed longitudinally, the abnormal MCA-PI preceded the appearance of an abnormal MCA-PSV. In six of these 10 fetuses, the last MCA measurements were obtained within 12 h of delivery or fetal demise. In two other fetuses, measurements were performed within 2 days of delivery; one of these two fetuses died *in utero*. In the last two fetuses, measurements were performed within 4 days of delivery; both fetuses died *in utero*. In all 10 fetuses, the MCA-PSV showed an initial increase in velocity and it decreased before demise or the appearance of non-reassuring testing in seven fetuses (Figure 3). In the other three fetuses, the MCA-PSV had the highest velocity value before birth and a normal arterial pH value was recorded at birth[11], with Apgar scores at 5 min of 7, 8 and 9. These three infants did well initially, but two died within 8 days of delivery; the third infant, who had a birth weight of 360 g, did well. The MCA-PI did not have a consistent pattern: initially, it was abnormal in most of the fetuses; in three fetuses it decreased progressively with advancing gestation, in another six fetuses, it increased towards normal before delivery and in one fetus, it remained more or less unchanged (Figure 4).

DISCUSSION

In this cross-sectional and longitudinal assessment of the MCA-PI and MCA-PSV in IUGR fetuses, our data have shown that, although the MCA waveforms change in IUGR fetuses, the MCA-PSV predicts perinatal mortality more accurately than does the MCA-PI. The reason for this difference can be found in the evaluation of our longitudinal data. Initially, the MCA-PI was abnormal in most of the fetuses, but in six an increased MCA-PI with a tendency towards normalization occurred before delivery or fetal demise. In three other fetuses, the MCA-PI progressively decreased up to delivery, and in one fetus it changed little. The MCA-PSV, on the other hand, exhibited a well-defined pattern, progressively increasing with advancing gestation in all fetuses, with a tendency to slightly decrease, just before delivery or the occurrence of fetal demise, in seven fetuses. Despite this decrease, however, the MCA-PSV value remained above the upper limit of normal until a few hours prior to delivery or fetal demise.

The MCA-PI together with the UA-PI, has long been considered the gold standard for the assessment of fetuses with IUGR. Our findings, though, suggest that not only does the MCA-PSV complement the information provided by the MCA-PI, but that it actually provides clearer information than does the MCA-PI. In IUGR fetuses with an abnormal MCA-PI and a normal MCA-PSV, the IUGR condition is less severe than in cases in which both parameters are abnormal. However, when the IUGR condition intensifies, the MCA-PSV increases and becomes abnormal. Our data also suggest that when an MCA-PI value is increasing or an MCA-PSV value is decreasing, the fetus starts to decompensate. For example, four fetuses died following a drop in MCA-PSV value, and in each case the MCA-PI increased before the fetal demise occurred.

Most of our data were collected within 48 h before delivery or fetal demise, when the MCA-PI had normalized in some fetuses. This might explain why the MCA-PI predicted the perinatal mortality less well than did the MCA-PSV. UA-ARED, on the other hand, was present in most IUGR fetuses and might explain why the MCA-PSV that was normal in most of the fetuses that survived and abnormal in most of the fetuses that died predicted the perinatal mortality better than did the UA-ARED.

Although we confirmed that gestational age plays an important role in the perinatal mortality of IUGR fetuses, we found that among IUGR fetuses delivered at $\leq 25+0$ weeks' gestation, there were no survivors, while all IUGR fetuses survived when they were delivered at > 29 weeks' gestation. In terms of survival rate, the IUGR group delivered at > 25 and < 29 weeks' gestation was the most uncertain group. Interestingly, although the MCA-PI at this gestational age was abnormal in 12/15 fetuses, none of the fetuses died when the MCA-PSV was normal. These outcomes reinforce the concept that the MCA-PSV is a better predictor of perinatal mortality than is the MCA-PI.

We have reported previously that the MCA-PSV is a reliable predictor of moderate and severe fetal anemia, whereas it is less sensitive in predicting mild anemia[12]. While IUGR fetuses can be anemic at birth, they are rarely severely anemic, although they can also be polycythemic[13]. This is probably the reason why a previous study on mild and non-anemic IUGR fetuses was unable to find a correlation between anemia and MCA-PSV[14].

We would like to propose here that the pathophysiological explanation for the observed high MCA-PSV in IUGR fetuses and anemic fetuses is different. In anemic fetuses, as reported previously, the high MCA-PSV is most likely secondary to a raised cardiac output and decreased blood viscosity[12], whereas in IUGR fetuses, the increased MCA-PSV reflects increased blood flow to the brain through an elevated left cardiac output[15] and an increased placental vascular resistance.

Although betamethasone can affect blood velocity[16], it is unlikely that this was the cause of high MCA-PSV in our study because betamethasone was administered to all our patients.

Our data, combined with previously reported data, allow us to postulate that in fetuses with IUGR secondary to placental insufficiency, the following occurs. Initially, a low MCA-PI might reflect decreased brain vascular resistance and a slight increase in blood flow. With increased severity, the MCA-PSV increases, as a consequence of increased left cardiac output[15]. When the process becomes more severe, a portion of the blood ejected from the right ventricle is shifted to the brain through the aortic isthmus because of a high vascular resistance in the descending aorta[17]. Although the MCA-PSV decreased before IUFD in four of the fetuses we studied, it remained above the normal range. This might have been a consequence of the exaggerated vasodilatation or vasoconstriction that occurs in the overstressed fetus. We cannot currently conclude if blood pressure also plays a role in these cerebral blood flow changes.

The gestational age was lower in the group that developed BPD. Because of the small number of neonates that survived ($n = 19$), we did not perform logistic regression analysis, and we were not able to subdivide these IUGR fetuses based on gestational age. We believe that studies with a larger number of fetuses should be undertaken to further explore whether the MCA-PSV and the UA-ARED are better correlated with perinatal morbidity than is the MCA-PI.

It is important to emphasize that the IUGR group reported here represented a heterogeneous group because the maternal pathology present before the pregnancy and the pathology occurring during the pregnancy influenced the time of delivery in many of our fetuses. Therefore, a study that includes only idiopathic IUGR fetuses (cases in which no cause can be found for the placental insufficiency), as reported previously for other Doppler parameters[18], is warranted.

In summary, our data indicate that: (a) the trends of the MCA-PSV and MCA-PI provide more information than does one single measurement of either, and (b) the MCA-PSV might be clinically more informative than is the MCA-PI in the management of IUGR fetuses. We believe that prospective longitudinal studies in IUGR fetuses with documented long-term outcome and aimed at assessing the correlation of the longitudinal changes of the MCA-PSV with those of other vessels, such as the aortic isthmus and ductus venosus, could be profitable.

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