British Journal of Obstetrics and Gynaecology
September 1990, Vol. 97, pp. 797–803

Middle cerebral artery flow velocity waveforms in fetal hypoxaemia

S. VYAS, K. H. NICOLAIDES, S. BOWER, S. CAMPBELL

Summary. In 81 small-for-gestational age fetuses (SGA) colour flow imaging was used to identify the fetal middle cerebral artery for subsequent pulsed Doppler studies. Impedence to flow (pulsatility index; PI) was significantly lower, and mean blood velocity was significantly higher, than the respective reference ranges with gestation. Fetal blood sampling by cordocentesis was performed in all SGA fetuses and a significant quadratic relation was found between fetal hypoxaemia and the degree of reduction in the PI of FVWs from the fetal middle cerebral artery. Thus, maximum reduction in PI is reached when the fetal PO_2 is 2–4 SD below the normal mean for gestation. When the oxygen deficit is greater there is a tendency for the PI to rise, and this presumably reflects the development of brain oedema.

Animal studies have shown that fetal hypoxaemia is associated with a relative redistribution of cardiac output resulting in preferential perfusion of the brain at the expense of the viscera (Cohn *et al.* 1974; Peeters *et al.* 1979). The aim of the study was to investigate this brain-sparing effect in human fetuses by relating umbilical cord blood gases, in samples obtained by cordocentesis, with Doppler indices of velocity and impedence to flow in the fetal middle cerebral artery.

Subjects and methods

Flow velocity waveforms (FVW) were obtained from the middle cerebral artery and measured on one occasion in 81 small-for-gestational age fetuses (SGA) at 19–38 weeks gestation and 162 appropriate-for-gestational age fetuses (AGA) at 18–42 weeks gestation. Gestational age was calculated from Naegele's rule and was confirmed by an ultrasonographic measurement of the fetal biparietal diameter at 16–20 weeks' amenorrhoea.

The 81 pregnancies with SGA fetuses were referred to our unit for cordocentesis for fetal karyotyping and blood gas analysis. In all pregnancies the fetal abdominal circumference was below the 2·5th centile of our reference range for gestation, which was constructed from the study of 1610 pregnancies. The Doppler studies were undertaken up to 30 min before cordocentesis, which was performed without maternal sedation or fetal paralysis (Nicolaides *et al.* 1986). The umbilical cord vessel was identified as either artery or vein by the ultrasonographically detectable turbulence produced after the intravascular injection of 0·4 ml normal saline. The umbilical artery was sampled in 12 fetuses and the umbilical vein in 69. Fetal blood gases were measured by an automated blood gas analyser (Radiometer ABL 330, Copenhagen, Denmark). All fetuses included in this study were morphologically and karyotypically normal.

Harris Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, King's College Hospital, Denmark Hill, London SE5 8RX, England
S. VYAS, *Research Fellow*
K. H. NICOLAIDES *Director*
S. BOWER, *Research Fellow*
S. CAMPBELL *Professor and Head of Dept.*

Correspondence: Dr K. H. Nicolaides.

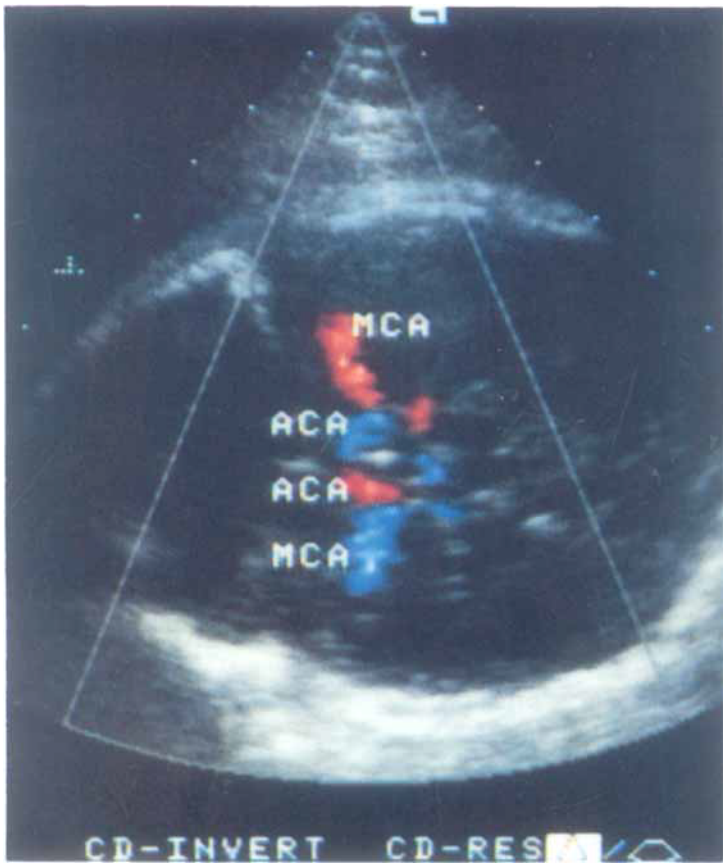

Fig. 1. Colour flow imaging of the fetal intra-cranial vasculature demonstrating by the anterior (ACA) and middle cerebral (MCA) arteries.

Reference ranges of the Doppler variables with gestational age were obtained from the cross-sectional study of 162 AGA fetuses. The women were recruited from the routine antenatal clinic and had uncomplicated singleton pregnancies. An ultrasound scan performed at the time of the Doppler study showed all fetuses to be morphologically normal and the head and abdominal circumferences to be between the 2·5th and 97·5th centiles of our reference ranges for gestation.

Colour flow imaging was used to identify the fetal middle cerebral artery for subsequent pulsed Doppler studies (Acuson 128, Acuson, California, USA; 5 MHz linear array and 3·5 MHz sector transducers). The high pass filter was set at 125 Hz and the transmitted power output level, in the low power output mode used throughout the study, was 36 and 50 mW/cm^2 SPTA in colour and pulsed Doppler modes respectively. During the studies care was taken to apply minimal pressure to the maternal abdomen with the transducer, as fetal head compression is associated with alterations of intra-cranial arterial FVWs, (Vyas *et al.* 1989).

For Doppler studies the woman was placed in a semi-recumbent position and a transverse view of the fetal brain was obtained at the level of the biparietal diameter. The transducer was then moved towards the base of the skull at the level of the lesser wing of the sphenoid bone. Using colour flow imaging, the middle cerebral artery could be seen as a major lateral branch of the circle of Willis running anterolaterally towards the lateral edge of the orbit (Fig. 1). The pulsed Doppler sample gate was then placed on the proximal portion of this vessel to obtain FVWs. The angle of vessel insonation was 0–35° and the Doppler gate size was 4–6 mm. All Doppler studies were performed in the absence of gross fetal body or breathing movements (Marsal *et al.* 1984).

The FVWs were analysed by an on-line spectrum analyser (Doptek, Doptek, UK) when

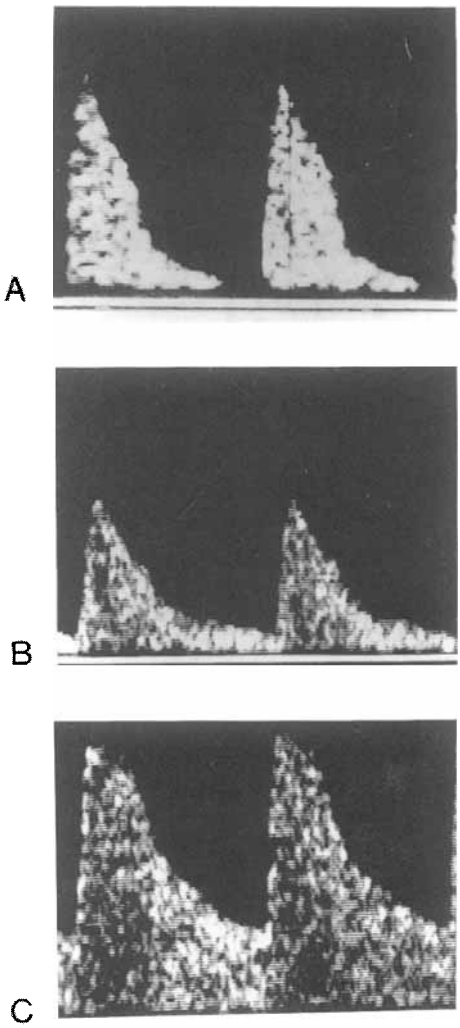

Fig. 2. Flow velocity waveforms from the fetal middle cerebral artery: (a) at 22 weeks gestation with end-diastolic frequencies absent; (b) at 37 weeks gestation with end-diastolic frequencies present, and (c) in a hypoxaemic fetus at 28 weeks gestation where EDF were increased.

three consecutive FVWs of satisfactory quality had been obtained. To compute the pulsatility index (PI) the maximum frequency envelope of the FVW was outlined using a light pen. The time-averaged intensity-weighted mean blood velocity (Vm) was calculated after the angle of vessel insonation had been determined from the frozen image. The mean value of three FVWs was recorded for all further analyses. The PI was measured in all 81 SGA and 162 AGA fetuses. However, the fetal middle cerebral artery Vm was measured only in the last 58 SGA and 106 AGA fetuses because the software required to calculate this variable was unavailable in the earlier part of the study.

The intra-observer coefficients of variation for the measurement of Vm and PI of FVWs from the fetal middle cerebral artery were determined by performing 10 consecutive examinations on three AGA fetuses within a 1-h period. These were 5·3% for the measurement of PI and 11·1% for the measurement of Vm.

Statistical analysis

For the AGA group, reference ranges (mean, 2·5th and 97·5th centiles) of the Vm and PI of FVWs from the fetal middle cerebral artery with gestation were derived by regression analysis (Statistics package for personal computers, Timberlake Clark Ltd, 40b Royal Hill, London SE10).

Because in normal fetuses blood PO_2, PCO_2, pH (Nicolaides *et al.* 1989) and both Doppler variables change with gestation, the individual measurements in the SGA fetuses were expressed as the number of standard deviations (SD's) from the respective normal mean for gestation ($\triangle PO_2$, $\triangle PCO_2$, $\triangle$pH, $\triangle$PI and $\triangle$Vm). The one sample Student's *t*-test was used to examine whether the mean $\triangle$PI and $\triangle$Vm of the SGA group were significantly different from zero.

Results

In the AGA group, the FVW is highly pulsatile and the presence of end-diastolic frequencies (EDF) becomes more common with advancing gestation. Thus, EDF were present in 32 of 43 (75%) fetuses at 18–25 weeks, 38 of 50 (76%) at 26–33 weeks and all 69 fetuses examined at >34 weeks gestation (Fig. 2). The relation of PI with gestation was best described by a quadratic equation (Fig. 3). The data on Vm were made Gaussian by $\log_{10}$ transformation and the relation with gestation was best described by a linear equation (Fig. 4). In the 106 fetuses in whom both PI and Vm were measured, there was a significant association between the two variables (r= 0·67, P<0·0001, constant = 25·92, slope = 6·454, residual SD = 4·012).

In the 81 SGA fetuses, the mean $\triangle$PI (−2·035 SD) was significantly lower than zero (Fig. 5; t_{80} = 22·23, P<0·0001) and there was a significant relation between $\triangle$PI and $\triangle PO_2$ (Fig. 6). Similarly, there was a significant relation

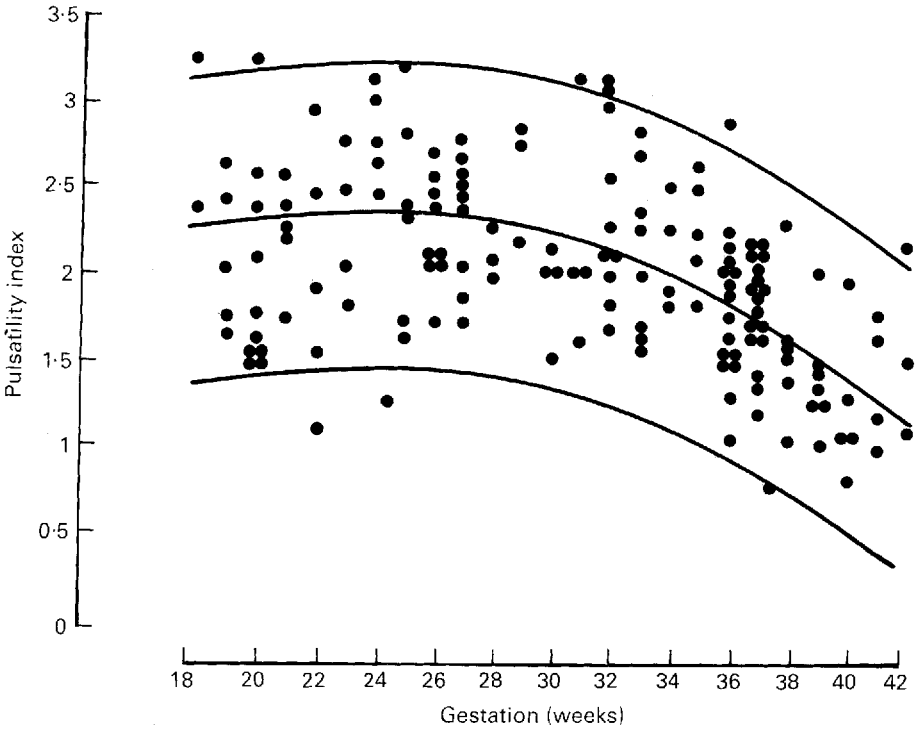

Fig. 3. Reference range (mean and individual 95% CI) of fetal middle cerebral artery pulsatility index with gestation, constructed from a cross-sectional study of 162 appropriate-for-gestational age fetuses (●). [$r = 0{\cdot}57$; $P<0{\cdot}0001$; constant = −0·611; linear coefficient = 0·228; quadratic coefficient = −0·004; residual SD = 0·444].

between △PI and △pH ($r = 0{\cdot}47$, $P<0{\cdot}01$, constant = −1·461, linear coefficient = 0·358, quadratic coefficient = 0·030, residual SD = 0·732).

In the 58 SGA fetuses, the mean △Vm (2·045 SD) was significantly higher than zero (Fig. 7; $t_{57} = 12{\cdot}27$, $P<0{\cdot}0001$) and there were significant associations between △Vm and $\triangle PO_2$ (Fig. 8), and △Vm and △pH ($r = 0{\cdot}491$, $P<0{\cdot}01$, constant = 0·763, linear coefficient = −0·782, quadratic coefficient = −0·074, residual SD = 1·135). In the 58 SGA fetuses in which both △PI and △Vm were measured, there was a significant association between the two variables ($r = -0{\cdot}37$, $P<0{\cdot}01$, constant = −1·731, slope = 0·200, residual SD = 0·652). There were no significant associations between $\triangle PCO_2$ and △PI or △Vm ($n = 81$, $r = -0{\cdot}05$ and $n = 58$, $r = -0{\cdot}05$ respectively).

Discussion

In normal pregnancy there is a gestation related fall in the PI, and by implication impedence to flow, in the fetal middle cerebral artery. This

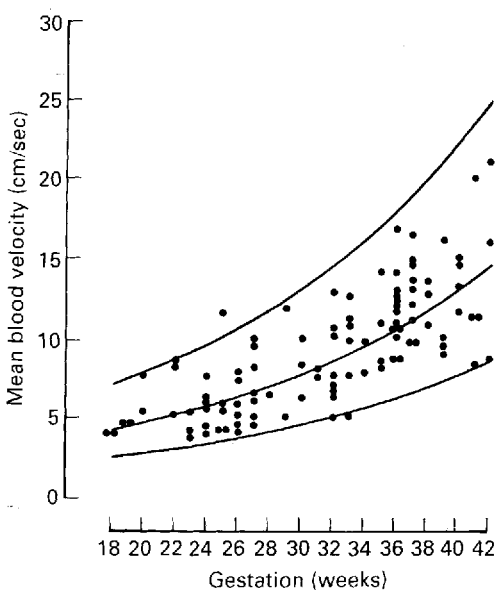

Fig. 4. Reference range (mean and individual 95% CI) of fetal middle cerebral artery mean blood velocity with gestation, constructed from a cross-sectional study of 106 appropriate-for-gestation age fetuses (●). [$r = 0{\cdot}79$; $P<0{\cdot}0001$; constant = 0·173; slope 0·023; residual SD = 0·119].

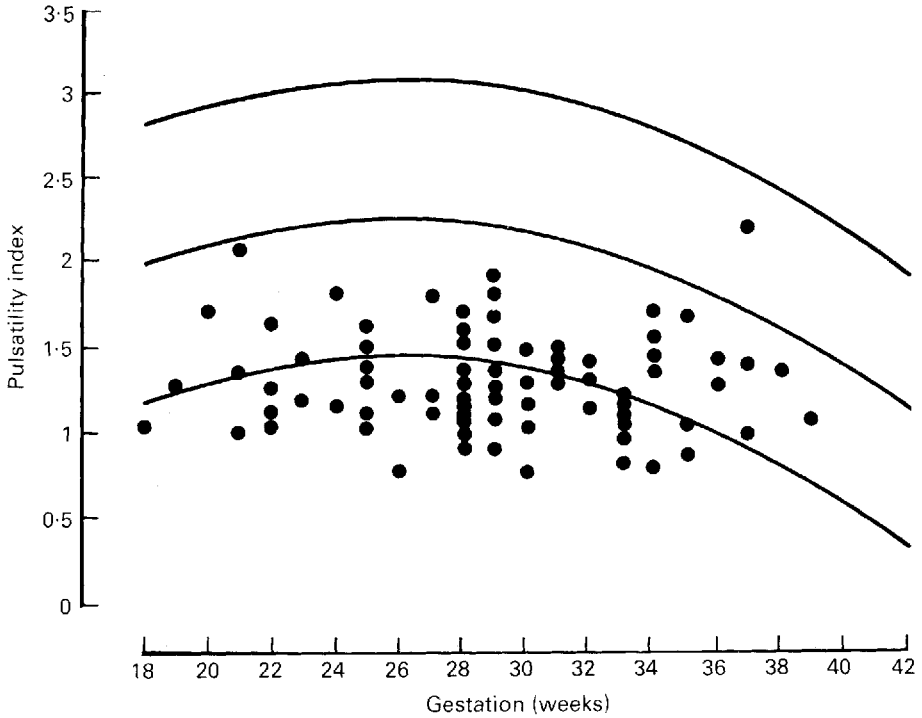

Fig. 5. Middle cerebral artery pulsatility index of the 81 SGA fetuses (●) plotted on the reference range.

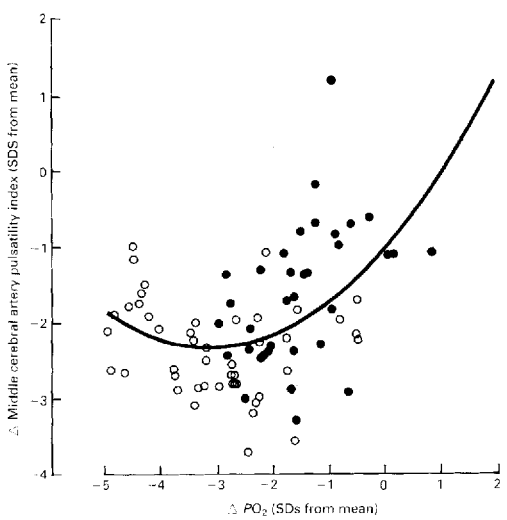

Fig. 6. The relation between fetal hypoxaemia and fetal middle cerebral artery pulsatility index, both expressed as the number of SD by which the observed values differed from the respective normal mean for gestation. The open circles indicate acidaemic fetuses and the closed circles represent non-acadaemic fetuses. [$r = 0{\cdot}46$; $P<0{\cdot}001$; constant = $-1{\cdot}021$; linear coefficient = 0·844; quadratic coefficient = 0·135; residual SD = 0·740].

finding is in agreement with those of Kirkinen *et al.* (1987) and Van Den Wijngaard *et al.* (1989) who examined 83 and 55 fetuses respectively at 25–41 weeks gestation. Both studies noted the

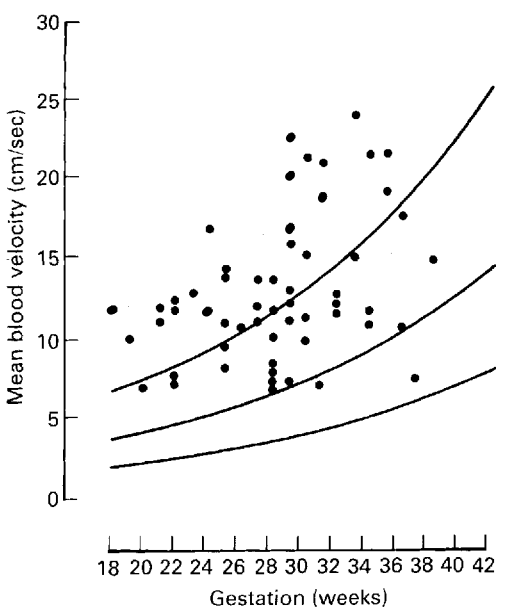

Fig. 7. Middle cerebral artery mean blood velocity of the 58 SGA fetuses (●) plotted on the reference range.

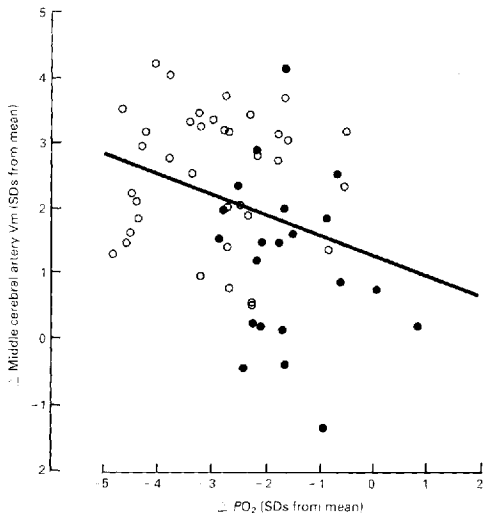

Fig. 8. The relation between fetal hypoxaemia and fetal middle cerebral artery mean blood velocity, both expressed as the number of SD by which the observed values differed from the respective normal mean for gestation. The open circles indicate acidaemic fetuses and the closed circles represent non-acidaemic fetuses. [$r = -0{\cdot}31$; $P<0{\cdot}05$; constant= 1·279; slope = −0·311; residual SD = 1·216].

presence of EDF in all fetuses; in the current study, EDF were absent in 24% of the examinations at 26–33 weeks. This discrepancy may be due to the different high pass filters used; 100 Hz in their studies, compared with 125 Hz in the current study.

The PI of FVWs from the fetal common carotid artery falls with advancing gestation (Bilardo *et al.* 1988). The present study demonstrates that there is a similar fall in impedence to flow in the middle cerebral artery suggesting that changes in the common carotid artery, during normal pregnancy, are predominantly due to a reduction in impedence to flow in the cerebral vasculature.

The blood velocity increases with advancing gestation, and this increase is significantly associated with the decrease in PI. Mean blood velocity in the intracranial vasculature has not been reported previously, possibly due to difficulties in B-mode imaging and therefore accurate measurement of the angle of vessel insonation. This problem has been overcome by the use of colour flow imaging.

In SGA fetuses, the PI of FVWs from the fetal middle cerebral artery is reduced and the degree of this reduction is significantly related to the degree of fetal hypoxaemia. The PI of FVWs represents downstream impedence to flow (Gosling & King 1975) and our data provide evidence of vasodilatation in the cerebral vasculature during mild to moderate hypoxaemia. With severe degrees of hypoxaemia (2–4 SD below the normal mean for gestation), usually with associated acidaemia, the reduction in PI reaches a maximum which probably represents maximum vessel dilatation. In extreme hypoxaemia (>4 SD below the normal mean for gestation) the reduction in PI is proportionally less (Fig. 5). It could be hypothesized that in severely hypoxaemic SGA fetuses the vasodilatation mediated decrease in PI is blunted by increased intracranial pressure due to cerebral oedema. It has been shown that fetal head compression, and therefore increased intracranial pressure, is associated with an increase in the PI of FVWs from the middle cerebral artery (Vyas *et al.* 1990).

Blood velocity in the middle cerebral artery is higher in the SGA than the AGA group, and there are significant associations between the increased blood velocity and fetal hypoxaemia and acidaemia. However, the relation between the increase in mean blood velocity and the decrease in PI is weaker in SGA than AGA fetuses ($r = -0{\cdot}37$ and $r = -0{\cdot}67$ respectively). These findings suggest that in SGA fetuses blood velocity is not determined by downstream impedence to flow alone and that other factors, such as cardiac contractility, vessel compliance and blood viscosity may also play a role.

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Received 24 October 1989
Accepted 20 March 1990