Renal function and bone biochemistry in three children after ifosfamide treatment

	Plasma phosphate (mmol/l)	Plasma alkaline phosphatase (U/l)	Plasma potassium (mmol/l)	Plasma calcium (mmol/l)	Plasma magnesium (mmol/l)	Fractional excretion of phosphate* (%)	Fractional excretion of glucose (%)	Glomerular filtration rate† (ml/min/1·73 m²)
Case 1‡	0·39	475	2·3	2·66	0·71	90·7	41·6	66
Case 2	0·49	536	3·4	2·29	0·87	12·2	16·1	162
Case 3§	0·34	439	2·4	2·43	0·96	32·6	50·3	76
Approximate normal range	1·00-1·75	71-212	3·3-4·7	2·13-2·62	0·7-1·0			89-165

*Fractional excretion of a substance (s) in urine calculated by $U_s/P_s \times P_{cr}/U_{cr} \times 100$, where U=urine concentration, P=plasma concentration, Cr=creatinine.
†Glomerular filtration rate measured by clearance of edetic acid labelled with chromium-51.
‡Plasma bicarbonate concentration 14·0 mmol/l; urine pH 6·1; osmolality of early morning urine sample 329 mmol/kg.
§Osmolality of random urine sample 275 mmol/kg; plasma osmolality 283 mmol/kg.

phosphatase activity (table). She continued to receive ifosfamide for a further three months, but the limp persisted and radiographs of her wrists and knees two months later showed signs of rickets.

Case 3—A 3 year old girl with a malignant epithelial schwannoma of the nose received ifosfamide (total dose 124 g/m²), adriamycin, vincristine, and etoposide. Nine months after diagnosis she developed severe nephrogenic diabetes insipidus and the ifosfamide was stopped. She also had more generalised renal tubular damage, and investigation two months later showed phosphaturia, hypophosphataemia, hypokalaemia, glycosuria, and a diminished glomerular filtration rate; serum alkaline phosphatase activity was high (table). Four months later she developed a limp, and radiographs of her wrists and knees confirmed rickets.

Other cases—Investigation of renal function in a further 10 children receiving high dose ifosfamide showed hypophosphataemia in two and considerable phosphaturia in three.

Comment

The three children described developed symptoms and radiological features of rickets with hypophosphataemia despite a normal plasma calcium concentration. The low plasma phosphate concentrations were due to renal tubular damage that resulted in phosphaturia. All were treated with oral phosphate supplements. The two adults previously reported with Fanconi's syndrome after chemotherapy with ifosfamide both had pronounced hypophosphataemia.[2,3] In contrast, the renal tubular damage caused by cisplatin leads to hypomagnesaemia, which was not present in our patients.

The renal tubular problems in our three children were probably caused by ifosfamide. The children all received 9 g/m² per course, given by continuous infusion over three days with mesna and hydration of 3 l/m²/day. This dose schedule has not been widely used elsewhere but is included in the current study of Ewing's tumour by the United Kingdom Children's Cancer Study Group. The short term toxicity of this regimen is tolerable,[5] but this is the first report of long term toxicity.

Hypophosphataemia causes muscle weakness, and rickets develops over several months. These cases and the pronounced phosphaturia found in a further three of 10 children receiving high dose ifosfamide treatment suggest that up to 45% of children receiving this treatment are at risk of developing rickets. Plasma phosphate concentrations should be measured regularly in all such children and phosphate supplements given if hypophosphataemia develops. Further follow up will determine whether the renal damage is reversible.

We thank the North of England Children's Cancer Research Fund, the Leukaemia Research Fund, and the special trustees of Newcastle Health Authority for financial help.

1 Van Dyk JJ, Falkson HC, van der Merve AM, Falkson G. Unexpected toxicity in patients treated with iphosphamide. *Cancer Res* 1972;**32**:921-4.
2 De Fronzo RA, Abeloff M, Braine H, Humphrey RL, Davis PJ. Renal dysfunction after treatment with isophosphamide (NSC-109724). *Cancer Chemother Rep* 1974;**58**:375-82.
3 Sangster G, Kaye SB, Calman KC, Dalton JF. Failure of 2-mercaptoethane sulphonate sodium (mesna) to protect against ifosfamide nephrotoxicity. *Eur J Cancer Clin Oncol* 1984;**20**:435-6.
4 Pinkerton CR. Rogers H, James C, *et al*. A phase II study of ifosfamide in children with recurrent solid tumours. *Cancer Chemother Pharmacol* 1985;**15**: 258-62.
5 Davies SM, Pearson ADJ, Craft AW. Toxicity of high dose ifosfamide in children. *Cancer Chemother Pharmacol* (in press).

(Accepted 12 April 1989)

Fetal haemodynamic response to acute maternal hyperoxygenation as predictor of fetal distress in intrauterine growth retardation

Domenico Arduini, Giuseppe Rizzo, Carlo Romanini, Salvatore Mancuso

Department of Obstetrics and Gynaecology and Laboratory of Fetal Physioloy, Università Cattolica S Cuore, Rome, Italy
Domenico Arduini, MD, *deputy director of perinatal medicine centre*
Giuseppe Rizzo, MD, *assistant*
Salvatore Mancuso, MD, *professor and chairman of department*
Department of Obstetrics and Gynaecology, Università di Ancona, Italy
Carlo Romanini, MD, *professor and chairman of department*

Br Med J 1989;**298**:1561-2

Doppler ultrasound has confirmed the redistribution of blood flow that occurs secondary to chronic hypoxia (the so called brain sparing effect) in fetuses with intrauterine growth retardation.[1] We recently found that acute transmaternal treatment with oxygen induced pronounced haemodynamic modifications in these fetuses with temporary return of blood flow velocity waveforms towards normal.[2] This paper reports an investigation assessing the diagnostic value, if any, of the fetal vascular response to transmaternal oxygen as a method of grading fetoplacental compromise in fetuses with retarded growth.

Patients, methods, and results

After getting informed consent we studied 22 fetuses fulfilling the following criteria: (*a*) ultrasonic evidence of abdominal circumference below the fifth centile[3]; (*b*) no evidence of congenital abnormality; (*c*) Doppler velocity waveforms in umbilical artery, descending thoracic aorta, and internal carotid artery abnormal (below the 10th and above the 90th centiles) compared with our reference ranges (see figure); (*d*) reactive cardiotocograms at the time of Doppler measurements.

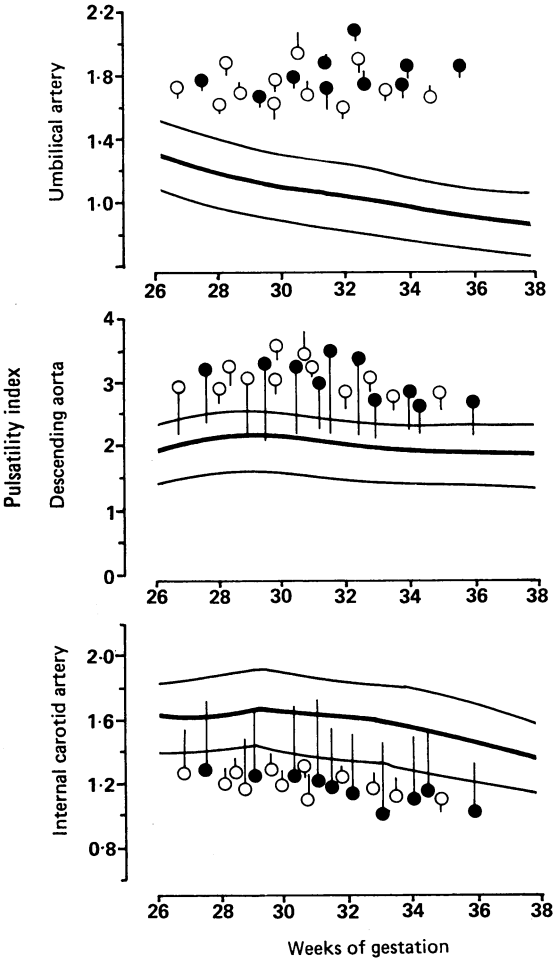
Fetal blood flow velocity waveforms were recorded from the umbilical artery, descending aorta, and internal carotid artery by means of a commercially available pulsed Doppler system (Ansaldo Esacord 80). Waveforms were obtained as described[2] and

vascular resistance evaluated over 10 consecutive cardiac cycles by means of the pulsatility index—that is, (systolic velocity−diastolic velocity)/mean velocity. Maternal oxygen (60% humidified) was delivered through a facemask with the mother semirecumbent. Recordings were made before and 20 minutes after oxygen delivery. Changes in the pulsatility index were considered relevant when values differed by more than 20% from basal. The clinicians in charge were not told the outcome of the blood flow measurements. Results are expressed as mean values and 1 SD. Statistical analysis was by paired and unpaired *t* tests, χ^2 test, and the Wilcoxon rank sum test.

In all cases the eventual birth weight was below the 10th centile for Italian population standards. Twelve mothers had pregnancy induced hypertension, in four cases complicated by proteinuria (>0·5 g/l), the remaining 10 having no obvious cause for retarded fetal growth. No fetus showed a relevant change in the pulsatility index at the level of the umbilical artery (figure). Moreover, though the pulsatility index from the descending aorta decreased in 12 fetuses (basal value 2·98 (SD 0·33), after oxygen 2·2 (0·14); paired *t* test, p<0·001), no such change occurred in the remaining 10 (basal value 2·90 (0·4), after oxygen 2·82 (0·5)). At the level of the internal carotid artery the pulsatility index returned towards normal in the 12 fetuses with a decrease in vascular resistance from the descending aorta (basal value 1·23 (0·08), after oxygen 1·56 (0·1); paired *t* test, p<0·001), whereas the fetuses with no changes in the descending aorta showed no such response (basal value 1·20 (0·05), after oxygen 1·25 (0·07)).

There was no significant difference in gestational age at the time of the Doppler recordings (31·4 (SD 2·96) weeks *v* 31·6 (2·58) weeks) or in eventual birthweight centile (6·11 (2·47)) *v* 5·33 (3·38)) between the oxygen responders and non-responders. The interval between Doppler examination and delivery, however, was shorter (median 6 days (range 3-9) *v* 18 (7-28); Wilcoxon test, p<0·001) in the non-responders. In this group of fetuses the indication for delivery was invariably acute fetal distress (as shown by abnormal cardiotocograms), whereas among the fetuses showing haemodynamic modifications after maternal oxygen only two suffered this complication (χ^2=12·1; p<0·0005). Furthermore, the fetuses responding to oxygen were in better condition at birth in terms of their Apgar score at 1 minute (7·56 (SD 1·13) *v* 6·11 (1·41); unpaired *t* test, p<0·05) and umbilical artery pH (7·26 (0·03) *v* 7·22 (0·03); unpaired *t* test, p<0·05).

As an aid to predicting acute fetal distress, the absence of a fetal haemodynamic response to maternal oxygen had a specificity of 100%, a sensitivity of 83·3%, and an efficiency of 90·9%.



Pulsatility index from umbilical artery, descending aorta, and internal carotid artery before (points) and 20 minutes after (bars) giving mother 60% humidified oxygen. Open points represent fetuses that developed acute distress. Normal range for gestation shown as median with 10th and 90th centiles.

Comment

Abnormalities in fetal blood flow velocity waveforms seem to precede the appearance of pathological cardiotocographic findings, but the time interval between these two events is difficult to establish because of wide intraindividual differences.[4] In this study basal values of pulsatility index from the different vessels investigated did not aid the prediction of fetal outcome; by contrast, monitoring fetal vascular responses to maternal oxygen clearly distinguished fetuses at high risk, those not responding to oxygen developing acute fetal distress within nine days. These findings suggest that in non-responders either placental transfer of oxygen or fetal response to oxygen is severely impaired, and such fetuses may require early delivery. On the other hand, the trend of a change in values towards normal after maternal oxygen proves maintained placental transfer, which might justify continued treatment of these fetuses with maternal oxygen.[5]

Our findings suggest a potential role of the fetal vascular response to maternal oxygen as a test to obtain better insight into the functioning of the feto-placental unit.

Correspondence to: Dr Domenico Arduini, Ist Cl Ostetrica e Ginecologica, Università Cattolica S Cuore, Largo A Gemelli 8, 00168 Rome, Italy.

1 Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. *Br J Obstet Gynaecol* 1986;**93**:471-5.
2 Campbell S, Wilkin D. Ultrasonic measurement of fetal abdominal circumference in estimation of fetal weight. *Br J Obstet Gynaecol* 1975;**82**:680-6.
3 Arduini D, Rizzo G, Romanini C, Mancuso S. Short-term effects of maternal oxygen administration on blood flow velocity waveforms in healthy and growth retarded fetuses. *Am J Obstet Gynecol* 1988;**159**:1077-80.
4 Laurin J, Marsal K, Persson PH, Lingman G. Ultrasound measurement of fetal blood flow in predicting fetal outcome. *Br J Obstet Gynaecol* 1987;**94**:940-8.
5 Nicolaides KH, Campbell S, Bradley RJ, Bilardo CM, Soothill PW, Gibb D. Maternal oxygen therapy for intrauterine growth retardation. *Lancet* 1987;i: 942-5.

(Accepted 21 February 1989)