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INTRAUTERINE GROWTH RETARDATION AND FETAL TRANSVERSE CEREBELLAR DIAMETER

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SUMMARY

In 103 small-for-gestational age (SGA) fetuses, the transverse cerebellar diameter (TCD), abdominal circumference (AC), head circumference (HC), and femur length (FL) were measured and their ratios calculated. In addition, umbilical venous blood samples were obtained by cordocentesis for measurements of fetal blood pH and erythroblast count. Compared with the AC, HC, and FL, the TCD was relatively mildly reduced. However, in the 28 fetuses with TCD >2 SDs (standard deviations) below the normal mean, the degrees of growth retardation, acidaemia, and erythroblastosis were more severe, and the incidence of perinatal death was higher than in the group with a normal sized TCD. Although in the group with TCD >2 SDs below the normal mean the TCD/AC ratio was increased, in the most severely growth-retarded fetuses this ratio was usually within the normal range. Thus, in intrauterine growth retardation (IUGR), cerebellar size is reduced in proportion to the severity of the disease and therefore the TCD cannot be used to obtain reliable information on the gestational age of small fetuses and the TCD/AC ratio does not provide reliable information as to whether or not fetuses are growth-retarded.

KEY WORDS—Intrauterine growth retardation, transverse cerebellar diameter, uteroplacental insufficiency, cordocentesis.

INTRODUCTION

When the fetal abdominal circumference (AC) is found to be below the fifth centile for gestational age, it is necessary to determine whether the problem is one of incorrect dating of the pregnancy or the fetus is small for gestational age (SGA). If the diagnosis SGA is made, it remains to be established whether the fetus is constitutionally small or growth-retarded (IUGR) due to either uteroplacental insufficiency or fetal abnormality.

It has been suggested that measurements of the fetal head circumference (HC) or femur length (FL), and the ratio HC/AC or FL/AC may help to distinguish between the different causes of smallness (Campbell and Thoms, 1977; Hadlock *et al.*, 1983). Thus, in the group with incorrect dating, as well as in constitutionally small and abnormal small fetuses, all dimensions were thought to be equally reduced (symmetrical SGA), whereas in IUGR, due to uteroplacental insufficiency, the abdomen would be affected more than the head and femur (asymmetrical SGA). However, recent evidence suggests that the HC/AC and FL/AC ratios do not provide reliable information as to the cause of smallness, because in severe uteroplacental insufficiency the HC and FL are reduced to the extent that HC/AC and FL/AC are within the normal range, and furthermore chromosomally abnormal fetuses are often asymmetrically small (Snijders *et al.*, 1993).

Reece *et al.* (1987) examined 19 SGA fetuses and reported that the transverse cerebellar diameter (TCD) was always within the normal range for gestation. On the basis of this finding, they concluded that the cerebellum is unaffected by growth retardation and suggested that the TCD may serve as an independent and reliable correlate of

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gestational age. Confirmation of their finding would imply that measurement of the TCD allows distinction between fetuses that appear small due to wrong dates and SGA fetuses. However, subsequent studies have provided conflicting results. Hill *et al.* (1990) examined 44 SGA fetuses, found the TCD to be reduced in 59 per cent of the cases, and concluded that this parameter cannot be used to assess gestational age in SGA fetuses. Lee *et al.* (1991) examined 19 SGA fetuses and reported that the TCD is a reliable predictor of gestational age in fetuses with asymmetric IUGR, because in all six of their cases the TCD was normal, but not in fetuses with symmetric IUGR, because five of these 13 fetuses had a reduced TCD.

The aim of the present study was to investigate TCD and TCD/AC in SGA fetuses thought to be growth-retarded due to uteroplacental insufficiency, and to relate the findings to other biometrical parameters, indices of fetal oxygenation, and pregnancy outcome.

PATIENTS AND METHODS

The TCD, AC, FL, and HC were measured and the TCD/AC, HC/AC and AC/FL ratios were calculated in 103 SGA fetuses presumed to be growth-retarded due to uteroplacental insufficiency. The patients were referred to our centre for further assessment because ultrasound examination at the referring hospital had demonstrated severe fetal growth retardation. Our diagnostic protocol in such cases includes (i) detailed ultrasound examination for fetal biometry, the diagnosis of fetal malformations, and assessment of amniotic fluid volume; (ii) continuous wave Doppler ultrasound studies (Doptek Ltd, Chichester, U.K.) of the uterine and umbilical arteries; and (iii) cordocentesis for fetal karyotyping and measurement of blood pH and erythroblast count.

The selection criteria for the patients in the present study were (i) fetal AC and subsequently birth weight below the fifth centile of the appropriate reference range for gestation (Yudkin *et al.*, 1987); (ii) the presence of an early diastolic notch in the waveform from at least one of the uterine arteries, and/or the absence of end diastolic frequencies in the waveform from the umbilical arteries (Aristidou *et al.*, 1990; Nicolaides *et al.*, 1988); (iii) normal fetal anatomy; and (iv) normal fetal karyotype. The gestational age at referral was 19–39 (mean=31) weeks, and this was determined from the maternal menstrual history ($n=96$) or, for those with uncertain or irregular periods ($n=7$), by an ultrasound scan at <16 weeks' gestation.

In all cases, umbilical venous blood samples were obtained by cordocentesis, which was performed without maternal sedation or fetal paralysis (Nicolaides *et al.*, 1989a). Fetal blood (250 and 180 μl) was collected into heparinized syringes for measurement of pH (Radiometer ABL 330, Copenhagen, Denmark), and into syringes with 20 μl of isotonic edetic acid solution for full blood cell count (Coulter Stacker Counter, Coulter Electronics plc, Luton, U.K.). Blood films were stained with May–Grünwald–Giemsa on an automatic processing machine and the number of erythroblasts per 100 leucocytes was counted to calculate the erythroblast count.

Statistical analysis

In normal pregnancy, the fetal TCD, AC, HC, FL, blood pH, erythroblast count, and birth weight change with gestation (Yudkin *et al.*, 1987; Nicolaides *et al.*, 1989a,b; Snijders and Nicolaides, 1994). Therefore, values obtained from the SGA pregnancies were expressed as the number of standard deviations by which the individual values differed from the appropriate normal mean for gestation (delta values; SDs). Student's *t*-test was applied to determine if the mean values in the SGA fetuses were significantly different from the appropriate normal mean for gestation. Regression analysis was applied to examine the significance of associations between delta TCD and delta values for the other biometrical parameters. Furthermore, a chi-square test was applied to examine the significance of differences between fetuses with a TCD < -2 SDs and $\geqslant -2$ SDs, respectively.

RESULTS

In the 103 SGA fetuses, the mean TCD, AC, HC, FL, and umbilical venous blood pH were significantly below the appropriate normal mean for gestation, and the mean HC/AC, TCD/AC, and erythroblast count were increased (Figs 1–3). In 38 cases, there was oligohydramnios (no vertical pool of amniotic fluid >1 cm in diameter), and in an additional 37 cases, the amniotic fluid volume was subjectively assessed by ultrasonography to be reduced. In 16 cases there was intrauterine death,

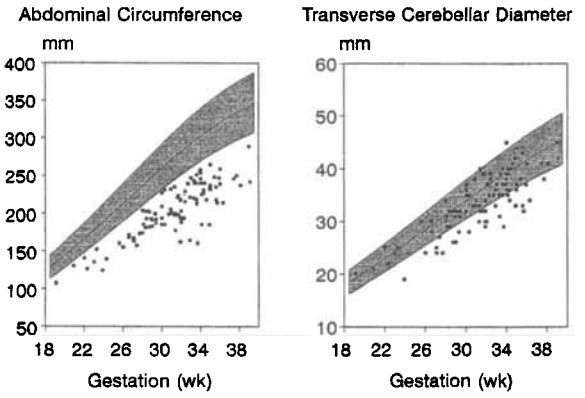

Fig. 1—Abdominal circumference and transverse cerebellar diameter of 103 growth-retarded fetuses plotted on the appropriate reference range (mean, fifth, and 95th centiles) for gestation

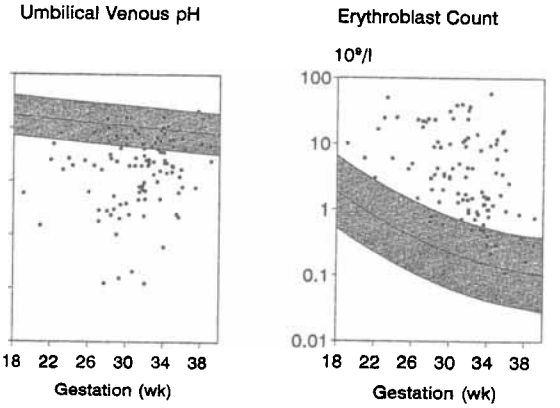

Fig. 3—Umbilical venous blood pH and erythroblast count in 103 growth-retarded fetuses plotted on the appropriate reference range (mean, fifth, and 95th centiles) for gestation

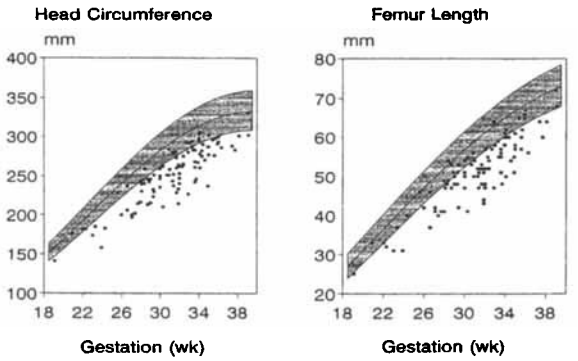

Fig. 2—Head circumference and femur length of 103 growth-retarded fetuses plotted on the appropriate reference range (mean, fifth, and 95th centiles) for gestation

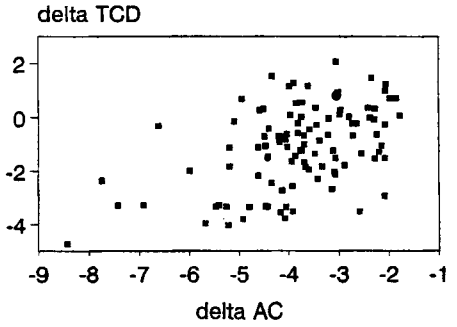

Fig. 4—Association between transverse cerebellar diameter (TCD) and fetal abdominal circumference (AC). Individual values are expressed as the number of standard deviations from the appropriate normal mean for gestation (delta values)

Table I—Relationship of delta transverse cerebellar diameter (TCD) to delta abdominal circumference (AC), head circumference (HC), femur length (FL), HC/AC, FL/AC, TCD/AC, umbilical venous blood pH, erythroblast count, and birth weight in 103 growth-retarded fetuses

	r	Residual SD	*P*
Abdominal circumference	0·479	1·122	<0·0001
Head circumference	0·519	1·350	<0·0001
Femur length	0·452	1·529	<0·0001
HC/AC	−0·108	1·278	ns
FL/AC	0·092	1·074	ns
TCD/AC	0·555	1·054	<0·0001
Blood pH	0·231	2·684	<0·05
Erythroblast count	−0·387	1·646	<0·0001
Birth weight	0·391	0·687	<0·0001

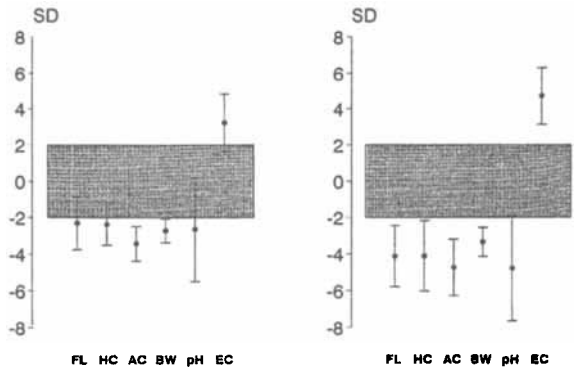

Fig. 5—Mean deviation (± 1 SD) of the femur length (FL), head circumference (HC), abdominal circumference (AC), birth weight (BW), umbilical venous blood pH, and erythroblast count (EC) in 75 growth-retarded fetuses with a normal transverse cerebellar diameter (TCD; left) and in 28 fetuses where the TCD was more than 2 SDs below the normal mean (right)

eight infants died in the neonatal period, and 79 (77 per cent) infants are alive.

The mean fetal AC was severely reduced (mean = − 3·8 SDs), the HC and FL were moderately reduced (mean = − 2·9 SDs and − 2.8 SDs, respectively), while the decrease in TCD was relatively mild (mean = − 1·1 SDs). Delta TCD was significantly associated with delta AC (Fig. 4), delta HC, delta FL, delta pH, and delta erythroblast count (Table I).

In the 28 fetuses with TCD >2 SDs below the normal mean, the FL, HC, AC, blood pH, and birth weight were lower and the erythroblast count was higher than in the fetuses with a TCD within the normal range (Fig. 5). Furthermore, in this group the degree of uteroplacental insufficiency was more severe, and the incidence of perinatal death was higher than in the 75 where the TCD was within the normal range (Table II). The TCD/AC ratio was within the normal range in 10 (36 per cent) of the 28 cases, and if the gestational age was calculated from the TCD, the AC, HC, and FL would have been within the normal range in 14 (78 per cent) of the remaining 18 cases.

DISCUSSION

This study investigated a group of SGA fetuses who were most probably intrauterine growth-retarded, due to uteroplacental insufficiency. In all cases, the gestation was certain; detailed scan and fetal karyotyping ruled out morphological or chromosomal abnormalities; and there was Doppler evidence of impaired placental perfusion.

The results confirm that the TCD is affected in IUGR due to uteroplacental insufficiency and thus cannot be used to assess gestational age (Hill *et al.*, 1990). The deficit in TCD was proportional to the degree of growth retardation; acidaemia and erythroblastosis were more severe; and the perinatal outcome was poorer in fetuses with a TCD below the normal range. The finding of Reece *et al.* (1987) that the TCD remains within the normal range may merely reflect that their group of SGA fetuses was not severely growth retarded; the birth weights were below the tenth centile and they all survived.

In mild to moderate IUGR, the TCD/AC ratio was increased, but in severely affected cases the ratio was often within the normal range. Therefore, like TCD alone, the combination of TCD and TCD/AC does not provide a reliable distinction between IUGR fetuses and fetuses that appear

Table II—Comparison of findings in fetuses with a transverse cerebellar diameter (TCD) more than 2 SDs below the normal mean with those in fetuses with a normal sized TCD, for incidence of 'asymmetrical' growth retardation (head circumference (HC)/abdominal circumference (AC) or TCD/AC more than 2 SDs above the normal mean or AC/femur length (FL) more than 2 SDs below the normal mean), absent end diastolic frequencies in the umbilical arteries (UA EDF negative), oligohydramnios, and perinatal death

	TCD > − 2 SDs (n=75)	TCD < − 2 SDs (n=28)	Chi	P
Delta HC/AC >2 SDs	56 (75%)	20 (71%)	0·1	ns
Delta AC/FL < − 2 SDs	32 (43%)	13 (46%)	0·1	ns
Delta TCD/AC > − 2 SDs	59 (79%)	10 (36%)	16·1	<0·001
UA EDF negative	37 (49%)	25 (89%)	11·6	<0·001
Oligohydramnios	23 (31%)	15 (54%)	6·2	<0·05
Perinatal death	13 (17%)	11 (39%)	8·6	<0·01

small due to wrong dates; redating the 18 fetuses with a small TCD but normal TCD/AC would have resulted in a false reassurance of normal growth in 14 (78 per cent) of the most severely affected cases.

Although the TCD was reduced, cerebellar size was less affected than AC, FL and HC. This finding is compatible with data from animal studies which have demonstrated that in IUGR blood flow to the brain is relatively spared, compared with that of other parts of the body; within the brain, blood flow to the cerebellum, brainstem, and midbrain is higher than that to the cerebrum (Behrman *et al.*, 1970). In evolutionary terms, it was obviously more important to protect those centres that control cardiac and respiratory activity rather than those involved in cerebral function. Despite relative sparing of perfusion, both cerebellar weight and myelination are decreased (Rees *et al.*, 1988; Chase *et al.*, 1969; Bourre *et al.*, 1981), and children who were growth-retarded at birth have cerebellar dysfunction and poor fine coordination at the age of 4–5 years (Fitzhardinge and Steven, 1972; Fancourt *et al.*, 1976).

This study establishes that in IUGR the growth of the fetal cerebellum is reduced in proportion to the severity of the disease. Therefore, the TCD cannot be used to obtain reliable information on the gestational age of small fetuses. In women with uncertain dates who first present to the obstetrician in late pregnancy, the differential diagnosis does not reside in further measurements of various fetal parts or their ratios, but requires a series of investigations directed at the diagnosis of fetal abnormalities, and assessment of placental perfusion and fetal oxygenation.

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