ORIGINAL ARTICLE

Outcome at school age following antenatal detection of absent or reversed end diastolic flow velocity in the umbilical artery

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Aim: To determine whether fetal compromise, manifested by abnormalities of Doppler recordings of umbilical artery velocity waveforms in utero, is associated with neurodevelopmental or educational abnormalities at school age.

Methods: A cohort of neonates born following high risk pregnancies had been previously identified for a study of the perinatal sequelae of absent (AEDFV) and reversed (REDFV) end diastolic flow velocities. Seventy six children were assessed at 5–12 years of age by a developmental paediatrician who was blinded to perinatal course and Doppler assessments. Forty children born following pregnancies with forward end diastolic flow velocities (FEDFV), were compared with 27 with AEDFV and nine with REDFV. Tests of cognitive, neurological, and sensory function were performed, and reports of behavioural and educational progress were obtained from parents and teachers.

Results: There were no significant differences between FEDFV and AEDFV groups, but on tests of mental ability and neuromotor function the REDFV group had worse scores than either FEDFV or AEDFV. Comparing REDFV and FEDFV groups, the British Ability Scales general conceptual ability mean scores were 87.7 versus 101, and the Quick Neurological Screening Test mean scores were 32.8 versus 21.5.

Conclusions: Absence of EDFV is well recognised as a marker of fetal compromise which is associated with acute perinatal sequelae. This study suggests it is not associated with adverse neurodevelopmental outcome. However, we found reversal of EDFV on antenatal assessment to be associated with a wide range of problems at school age, suggesting that REDFV represents intrauterine decompensation which may have adverse effects on the developing brain.

D oppler studies of umbilical artery velocity waveforms are widely used in clinical perinatal management to assess fetal wellbeing. In some high risk pregnancies, especially those complicated by pre-eclampsia and intrauterine growth restriction, increased placental vascular resistance may lead to absent or reversed end diastolic flow velocities (AREDFV). This sequence of wave forms is assumed to reflect increasing severity of fetal compromise—reversed being the more severe. It is known that fetuses of high risk pregnancies with AREDFV have an increased risk of intrauterine or early neonatal death compared to fetuses with forward end diastolic flow velocity (FEDFV) in the cord umbilical artery or aorta.[1–3] They are more likely to be born preterm,[3 4] and small for gestational age (SGA).[5 6] Associations have been reported between AREDFV and fetal hypoxia and acidosis,[7] neonatal acidosis,[8–11] cerebral haemorrhage,[3 12–14] hypotension,[3] respiratory distress syndrome,[9] bronchopulmonary dysplasia,[13] necrotising enterocolitis,[1 13 14] and prolonged hospitalisation.[5 12] Weiss *et al* reported an increased risk of neurological signs at discharge.[15]

Less information is available about the later outcome of babies born after pregnancies complicated by AREDFV. Follow up in the early years reported increased neurological compromise at 6 months,[15] 18 months,[2] and 2 years of age.[8] One study reported a five year follow up with six of 42 (14%) survivors of AREDFV having severe learning difficulties.[16] Moreover, Ley *et al* found that abnormal fetal aortic velocity wave forms were related with lower verbal and global IQ[17] and minor neurological dysfunction at age 7.[18] However, although abnormal fetal Doppler studies indicating redistribution of fetal blood flow preference to the brain predicted fetal death and growth retardation,[19] it was not independently associated with adverse neurological outcome at age 3 in a cohort born between 26 and 33 weeks of gestation.[20] Wilson *et al* showed that neurological outcome at 5 years of age in 40 children born following high risk pregnancies was not predicted by antenatal Doppler ultrasonography.[21]

Previously, we reported the neonatal outcome of 122 high risk infants, 61 with AREDFV and 61 with forward flow who were matched for gestational age and sex.[16] These babies were born between 1985 and 1992, so there is now an opportunity to assess outcome at school age. We have traced this cohort and compared the outcome of groups of children defined by type of fetal umbilical artery flow pattern. We have tested the following hypotheses:

(1) Children born after pregnancies complicated by AREDFV have an increased frequency of neurological impairment, cognitive deficit, and school difficulties compared with those with forward flow.

(2) Within the group with abnormal umbilical flow velocity wave forms, those born following reversed EDFV (REDFV) have a worse outcome than those born following absent EDFV (AEDFV).

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Table 1 Comparison of children assessed and those not assessed

| | Not assessed | Assessed | | | |
| | | Umbilical artery EDFV pattern | | | |
		Forward	Absent	Reversed	Total
Number of children	33†	40	27	9	76
Sex (no. males)	17	22	9	5	36
Gestational age (wk)					
Mean	31.7	31.6	32.3	30*	31.6
SD	2.7	2.9	2.8	2	2.8
Range	26–36	26–38	27–37	27–32	26–38
Birth weight (g)					
Mean	1355	1535	1123	950	1319
SD	491	537	375	206	508
Range	594–2466	642–3206	532–2191	585–1262	585–3206
SGA <10th centile					
No.	22	19	24	8	51
(%)	(67)	(48)	(89)	(89)	(66)
SGA <3rd centile					
No.	14	9	23	7	39
(%)	(42)	(23)	(85)	(78)	(51)

†18 with absent and 15 with forward EDFV.
*p=0.03, absent versus reversed.

METHODS

Subjects

All subjects were admitted to the high risk pregnancy unit for either maternal or fetal reasons, or both. Fetal umbilical Doppler assessment was included in a routine check up of fetal growth and wellbeing on admission and was regularly repeated during admission. Classification into three groups—forward, absent, and reversed EDFV (FEDFV, AEDFV, and REDFV)—was made according to the last Doppler assessment before delivery. Timing of delivery was not based on Doppler assessment but on the usual parameters of fetal and maternal wellbeing. Of the 122 infants in the original cohort, 13 were excluded from this follow up study. Three children with Down's syndrome, one early neonatal death, and their four matched controls were excluded, as were five other babies who died (two cases and three controls). Of the remaining 109 children, 82 were traced. Six parents declined to participate. Of the 76 children assessed, 40 had FEDFV, 27 AEDFV, and nine REDFV. There were no significant differences in birth weight, gestation, or the proportion who were SGA between those assessed and those who were not assessed (table 1).

All children were assessed by the same developmental paediatrician who was blind to the antenatal Doppler findings and neonatal course. Seventy two assessments were done at home and four at school. Seventy four parents consented to us contacting the school, and 55 questionnaires (76%) were returned by teachers.

Study procedure

Approval was obtained from the local research ethics committee. A letter was sent to the general practitioner enquiring if the family was still registered with the practice and living at the same address. The general practitioner was also asked whether there was any reason why the family should not be approached. Once located, a letter was sent to the family explaining the aims of the study and enclosing a questionnaire asking for information on the child's health, behaviour, and school progress. Permission to contact the school was also sought. The family was asked whether they would prefer to have an assessment of the child at home or at school. When the parents had given permission, a questionnaire was sent to the child's teacher, asking for information on progress at school and behaviour.

Outcome measures

Sociodemographic information from parents included educational level and occupation of both parents, language spoken at home, and family structure.

Cognitive ability was described using the revised British Ability Scales (BAS II), in which the total score is made up as the calculated mean of three clusters: verbal ability, non-verbal reasoning, and spatial ability. Each cluster consists of two subtests.[23] The BAS has an ability score (general conceptual ability, GCA) standardised to a mean of 100 and an SD of 15.

Neuromotor function, balance, and coordination were described with the Quick Neurological Screening Test (QNST-II).[24] The QNST was constructed to identify persons as young as 5 years old who have minor neurological signs that are frequently associated with learning disabilities. The QNST consists of a series of 15 observed tasks. To accommodate younger subjects, age sensitive modifications have been made in administering the test (for two tasks) and for scoring (for five tasks). Typically, neuromotor function tasks that are age dependent and merely reflect development are scored 1 point, but tasks that reflect a clear neuromotor dysfunction are scored 3 points. A score of 25 or less on the QNST is considered in the normal range, 26–49 is considered a moderate discrepancy, and 50 or more is considered a severe discrepancy.

Visual function was tested by acuity testing of each eye separately at 6 metres and at 30 cm using the Snellen chart, and by testing depth perception (TNO test). Visual abnormalities were defined as an acuity of 6/9 or worse for near or far in one or both eyes, impaired depth perception, or a combination of both. Severe acuity loss was defined as 6/12 vision or worse, for far or near.

Hearing was tested with a handheld pure tone diagnostic audiometer at 500, 1000, 2000, and 4000 Hz. Each threshold was determined by crossing it three times. The average loss for those four frequencies was calculated. Significant hearing loss was defined as a loss in one or both ears of >25 dB.

Table 2 Comparison between groups assessed—age at assessment, availability of questionnaires, and family information

	Umbilical artery EDFV pattern			
	Forward	Absent	Reversed	Total
Number of children	40	27	9	76
Age assessed (months)				
Mean	94	92.9	79.8*	91.9
SD	22.5	0.3	9.1	22.3
Range	63–151	63–142	67–93	63–151
Parent questionnaire returned				
No.	36	22	8	66
(%)	(90)	(81)	(89)	(87)
Teacher questionnaire returned				
No.	28	19	8	55
(%)	(70)	(70)	(89)	(72)
Mother's age leaving full time education				
Mean	17.2	17.6	16.7	17.3
SD	2.1	2.9	0.8	2.3
Father's age leaving full time education				
Mean	17.5	17.8	17.9	17.7
SD	2.7	3.2	3	2.9
English not first language				
No.	2	0	1	3
(%)	(5)		(11)	(4)
Single parent family				
No.	7	3	2	12
(%)	(18)	(11)	(22)	(16)

*p=0.03, reversed versus absent; p=0.005, reversed versus forward.

Growth measurements included measurement of height, weight, head circumference, and mid upper arm circumference. These were expressed as proportions below the 50th, 10th, and 3rd centile to compare between the subgroups.[25 26]

Behaviour was rated using the Strengths and Difficulties Questionnaire (SDQ).[27] This was completed by both parents and teachers. The questionnaire consists of 25 items. The total behaviour deviance score is calculated as the sum of four of the five subscales: emotional symptoms, conduct problems, hyperactivity, and peer problems. For questionnaires completed by parents, a total of 0–13 was considered a low score, a total score of 14–16 was considered borderline, and a score of 17–40 as high. For questionnaires completed by teachers, 0–12 was considered a low score, 13–15 a borderline score, and 16–40 a high score.[28]

Educational achievement was rated by teachers using a five point scale (1 = very good, 5 = very poor). Teachers were asked to compare the index children with other children of the same age in the following areas: speaking/listening, writing (composition), writing (fine motor skills), arithmetic/mathematics, reading, and PE/games. Poor school performance in any area was defined as a score of 4 or 5 (when children were described by their teachers as performing "poorly" or "very poorly"). In addition, information was requested from teachers on type of schooling and the provision of special help at school.

Statistical analysis

Three sets of comparisons were made. Firstly, all children with AREDFV (both absent and reversed EDFV) were compared with those in the group with forward EDFV. Secondly, the two subgroups of children with absent and reversed EDFV were compared separately with those with forward EDFV. Thirdly, children with absent EDFV were compared with those with reversed EDFV.

The BAS is standardised for age, and the QNST makes an adjustment for age in several tasks. The use of age sensitive scales allowed comparisons between groups of children assessed at different ages.

The χ^2 test with continuity correction was used for dichotomous outcome variables, Fisher's exact test when there were less than five individuals per cell. Continuous outcome variables were tested for normal distribution using the Kolmogorov–Smirnov test for normality. In variables with a normal distribution, means were compared using Student's *t* test; in variables where distribution was not normal, the Mann–Whitney U test was used. Associations between continuous variables were assessed using analysis of variance and linear regression. All analyses were conducted using SPSS.

RESULTS

Seventy six children were neurodevelopmentally assessed at a mean age of 92 months (range 63–151). Table 2 shows that children in the REDFV group were assessed at a significantly younger mean age than the 40 children in the FEDFV and the 27 children in the AEDFV subgroups.

Sociodemographic factors

There were no differences between the subgroups in mother's age and parity, mother's and father's age leaving full time education, the proportion of single parent families, or families where first language was other than English (table 2).

Cognitive ability

For the whole group under study, cognitive ability, as measured by the mean GCA score, was 99.5 (95% CI: 96–103%). Cognitive ability was <85 (< −1 SD) in 11 infants

Table 3 Results of mental development testing using the British Ability Scales (BAS-II)

	Umbilical artery EDFV pattern		
	Forward (n=39)	Absent (n=27)	Reversed (n=9)
General conceptual ability			
Mean score	101	101.1	87.7*
(95% CI of mean)	(97–105)	(95–107)	(71–105)
Distribution of GCA scores			
<70	2	1	2
70–84	2	3	1
85–115	31	18	6
115+	4	5	
Verbal ability			
Mean score	102.5	103.8	90.2
(95% CI of mean)	(98–107)	(97–111)	(70–111)
Non-verbal reasoning			
Mean score	104.4	104.2	92.6
(95% CI of mean)	(99–110)	(97–111)	(75–110)
Spatial/pictorial ability			
Mean score	96.3	96.2	80.7†
(95% CI of mean)	(91–102)	(90–102)	(64–97)

*p=0.049, reversed versus forward; p=0.048, reversed versus absent.
†p=0.023, reversed versus forward; p=0.025, reversed versus absent.

(14%), and <70 (< −2 SD) in five (7%). There was no difference in GCA between the infants that had AREDFV and FEDFV. However, mean GCA was lower for the REDFV group when compared to the FEDFV group and also when compared with the AEDFV group (table 3). On the cluster of visuospatial or pictorial ability, those with REDFV scored worse than those with FEDFV and worse than those with AEDFV (table 3).

Neurological screening
In the whole group, we found a mean total risk score on QNST of 23.5. There was no difference in mean total risk score between the group with AREDFV and the group with forward flow. However, the subgroup with REDFV had significantly worse mean scores than FEDFV or AEDFV subgroups (table 4).

As the children in the REDFV group were assessed at a significantly younger age than the FEDFV children, the QNST scores were adjusted for age at assessment.

After adjustment, the mean QNST score for the REDFV group was 30.3. This was significantly higher than the mean score for the FEDFV group, which was 21.9. The difference between mean scores for the REDFV and the FEDFV was 8.4 (p =0.033).

Vision
Forty three per cent of infants (32/74) had one or more visual abnormalities. Fifteen of these (47%) had minor acuity problems, 15 (47%) had severe acuity problems, and two had no depth perception with normal acuity. There was no significant difference between the AREDFV and FEDFV groups with respect to the proportion of children with any visual abnormality (42% (15/36) versus 45% (17/38)), or in the proportion that wore glasses/lenses (17% (6/36) versus 18% (7/38)). There were more children with severe acuity loss in the REDFV group (5/9, 56%) than in the AEDFV group (3/27, 11%; p = 0.014) or the FEDFV group (7/37, 19%; p = 0.047).

Hearing
Data on hearing threshold were only available for 48 children. Mean hearing threshold was almost identical, between 17 and 18 decibels, for all groups. There were three children (6%) with a significant hearing loss, 0/6 in the REDFV group, 1/16 in the AEDFV group, and 2/26 in the FEDFV group.

Growth
Of the total group, 63% had a height below the 50th centile and 19% had a height less than the 10th centile accounting for

Table 4 Findings on Quick Neurological Screening Test (QNST-II)

	Umbilical artery EDFV pattern		
	Forward (n=39)	Absent (n=27)	Reversed (n=9)
QNST raw total risk score			
Mean	21.5	23.2	32.8*
(95% CI of mean)	(18.1–24.9)	(18.3–28.1)	(24.9–40.6)
QNST moderate or severe discrepancy; score >25			
No.	17	12	7
(%)	(44)	(44)	(78)
QNST total risk score after correction for age at assessment			
Mean	21.9	23.4	30.3
(95% CI of mean)	(18.7–25.2)	(19.5–27.3)	(23.4–37.2)

*p=0.006, reversed versus forward; p=0.045, reversed versus absent.

Table 5 Behaviour from parent and from teacher completed questionnaires (Strengths and Difficulties Questionnaire)

SDQ	Umbilical artery EDFV pattern*		
	Forward (n=36)	Absent (n=22)	Reversed (n=8)
Parent's total score			
Mean	10.5	11.8	15.4
(95% CI)	(7.9–13.6)	(9.2–14.4)	(10.7–20.6)
Parent's total score; high ≥17			
No.	5	5	4
(%)	(14)	(23)	(50)
	Forward (n=28)	Absent (n=19)	Reversed (n=8)
Teacher's total score			
Mean	9.5	6†	12.6
(95% CI)	(6.9–12.1)	(3.8–8.1)	(5.4–19.9)
Teacher's total score; high ≥16			
No.	5	0	4‡
(%)	(18)		(50)

*A total of 66 questionnaires were returned by parents and 55 by teachers.
†p=0.035, absent versus forward; ‡p=0.008, reversed versus absent.

mid-parental height.[25] There were no differences between the forward, absent, or reversed EDFV groups in the proportion of children with weight, height, height corrected for mid-parental height,[25] or mid upper arm circumference[26] below the 10th centile for age and sex.

Of the 10 children who had a head circumference below the 10th centile for age and sex, eight (24%) were in the group with AREDFV and two (5%) in the forward flow group (p = 0.041).

Blood pressure
Blood pressure (BP) was within normal limits for age in all children that were assessed.[29] Mean systolic BP was 99 mm Hg (range 93–105) and mean diastolic BP was 54 mm Hg (range 49–62). There were no significant differences in BP between subgroups.

Behaviour
Questionnaires were returned by 66/76 parents and 55/74 teachers. The parents of two children did not agree to us contacting the school. For the whole group, the means of the total behavioural deviance scores rated by parents and teachers were 11.6 and 8.7 respectively. Overall, 14 of 66 children (21%) had an abnormally high total behavioural deviance score as rated by parents, and nine of 55 (16%) as rated by teachers (table 5). The group with REDFV scored higher on the subscales indicating hyperactivity (median 5.5 (range 4.4–8.3) versus 3.0 (1.0–5.0), p = 0.015) and peer problems (median 4.5 (2.2–6.0) versus 2.0 (1.4–2.8), p = 0.028) when compared with the group with forward flow.

Education
In total, 20/55 children (36%) required additional educational help or were in a class lower than expected for their age. Fifteen children were receiving non-teaching help (three in the REDFV, five in the AEDFV, and seven in the FEDFV groups). One child in the FEDFV and one in the REDFV group were in a class lower than appropriate for their age. Three children were in mainstream education but had required statements of special educational needs, two were in the group with REDFV, and one was in the group with AEDFV. Four were not in mainstream education (one in the REDFV and three in the AEDFV groups). Some children receive a combination of different types of extra help.

Table 6 shows that 26/55 (47%) of the whole group scored "poorly or very poorly" on two or more subjects according to their teachers. Poor or very poor performance was reported in 22% for speaking/listening, 35% for writing (composition), 27% for writing (fine motor skills), 31% for arithmetic/mathematics, 22% for reading, and 25% for PE/games. We did not find significant differences between REDFV, AEDFV, and FEDFV groups with respect to the mean of the teachers' ratings on any of these scales.

Perinatal risk factors
In this selected high risk population we did not find a statistically significant difference in mean BAS score nor in total QNST score between the children born below the 3rd centile for birth weight or those born between the 3rd and 10th centile, or those who had a birth weight appropriate for gestational age. The REDFV group had significantly lower

Table 6 School performance as reported by teachers: number (%)

School performance*	Umbilical artery EDFV pattern		
	Forward (n=28)	Absent (n=19)	Reversed (n=8)
All six subjects average or above	14 (50)	8 (42)	3 (38)
Below average in two or more subjects	14 (50)	7 (37)	5 (62)
Any extra educational provision	8 (29)	8 (42)	4 (50)
Not in mainstream education		3 (16)	1 (13)

A total of 55 questionnaires returned by teachers.
*Subjects may appear in one or more columns.

gestational ages than the AEDFV group and this difference in gestation could clearly have confounded our findings. When BAS and QNST scores were corrected for gestation, the poorer performance of the REDFV group persisted: BAS GCA mean scores, REDFV 89.7 versus FEDFV 101.2 (p = 0.043); QNST mean scores, REDFV 33.3 versus FEDFV 21.6 (p = 0.007).

DISCUSSION

The mean scores for cognitive ability, neuromotor development, and behaviour in this particular group of high risk infants are within the range as considered normal for age. However, in common with many other follow up studies of low birth weight infants, we found a high proportion of children who scored at the low end of the spectrum.[30–33] For example, 7% of children scored below 85 (−2 SD) on the BAS, almost half of all children had a moderate discrepancy of the QNST score, and roughly one in five were reported by the parents to have a high total behaviour deviance score. Although cognitive ability, neuromotor development, and behavioural problems were not different between the forward and absent flow groups, the REDFV children scored worse in all areas.

There are only a few follow up studies looking at the neurodevelopmental outcome of children who were born following pregnancies complicated by AREDFV. None report school performance, and only very few differentiate between the effects of absent and reversed EDFV.[2 10 16] Our study reports outcome at school age of children who were born after high risk pregnancies, comparing those who had forward EDFV with those with abnormal Doppler studies (AREDFV), but also compared AEDFV and REDFV groups. We were interested to determine whether AEDFV and REDFV represented a gradient of fetal insult which may lead to differential effects on later neurological development. High risk pregnancy is obviously not a homogeneous condition and we need to stress that these children are from an "abnormal" population; we cannot easily compare them with the same age children from the population at large, who are predominantly born after a non-risk pregnancy at term, with a birth weight appropriate for gestational age. Comparison of the AREDFV group with a group with FEDFV is open to the criticism that the groups may contain pregnancies with different pathologies, which themselves will have a major impact on outcome. However, it is generally accepted that AEDFV and REDFV represent different grades of severity of the same pathological process. Comparison of outcome between AEDFV and REDFV groups may therefore be a better indicator of the long term sequelae of placental vascular compromise than comparison between either group and the FEDFV group.

Our study population included all pregnancies with fully documented Doppler studies admitted to a busy high risk pregnancy service over a long period. Nevertheless, the number of children available for this follow up study was small, especially in the subgroup with REDFV. In addition, a relatively large number of children could not be traced despite attempts through the NHS Central Register. Some children were presumed to have returned to the USA following the closure of US air bases in Oxfordshire. Only 6% of parents declined to participate when contacted. There was no difference between those assessed and those not assessed with regard to gestational age, birth weight, and sex, and it is unlikely that the missing data introduced sufficient bias to explain the differences we found.

There were no significant differences in gestation between the AREDFV and FEDFV groups followed up in this study (the original FEDFV cohort was selected to be matched for gestation with the AREDFV group). However, neonates born following AREDFV were much more likely to be SGA, and were on average 475 g lighter at birth. Gestational age is known to be a more important predictor of outcome than birth weight; this presumably explains why so few differences were seen in follow up status between FEDFV and AEDFV groups, despite the mean birth weight difference and the higher proportion of SGA babies in the latter group. The shorter gestation and lower birth weight of the REDFV group could certainly have been a significant confounder in our finding of a worse outcome. Hall et al reported the follow up of the total Scottish very low birthweight population at 8 years.[32] Their data showed a 3 point difference on the BAS GCA score and a 7% difference in QNST between groups of <1000 g and 1000–1499 g birth weight. The comparable figures in our study comparing REDFV with AEDFV were 13 points on the BAS GCA score and a 30% difference in proportion of children with a QNST score >25. This suggests that birth weight was very unlikely to have been completely responsible for the differences elicited in our study. In addition there were no significant differences in cognitive or neurological outcome between SGA and appropriate for gestational age babies in our study. The group with REDFV were assessed at a younger age, but after correction for age at assessment there was still a significant difference in QNST between the group with FEDFV and the group with REDFV. The subset of the AREDFV group with REDFV were significantly more preterm than the AEDFV group, but multiple regression suggested that the adverse effect of REDFV on neurological outcome was more significant than the effect of gestation.

Our data show an apparent threshold effect rather than a gradient of fetal cerebral compromise associated with increasingly abnormal fetoplacental circulation. Assessments of cognitive and neurological function, behaviour, educational performance, and visual acuity all showed a remarkably consistent pattern of relative impairment in the REDFV group, but no significant difference between the AEDFV and FEDFV groups. Neither was there a consistent trend towards a worse outcome in the AEDFV group compared to the FEDFV group. Previous studies have shown that neonates born following pregnancies complicated by AEDFV are more liable to a variety of problems in the perinatal period. It appears, though, that if they survive to school age they show no evidence of long term neurodevelopmental sequelae. In contrast, reversal of EDFV in pregnancy is not only associated with immediate risk during pregnancy and the perinatal period but also with evidence of long term cerebral sequelae. The data from this study and others suggest that the fetal vascular adaptations that occur in utero in response to maternal and placental disease are effective in sparing the brain from permanent damage, even when growth, intestinal circulation, and marrow function may be compromised. Progression from absent to reversed EDFV is, however, a marker of decompensation of these protective mechanisms.

Our study included only a small number of survivors following REDFV, and any clinical implications drawn from our data would be more robust if similar or larger studies confirm our finding at school age follow up. Even then it would not be straightforward to derive simple lessons from our data to improve clinical management. The fact that pregnancies complicated by AEDFV produce children who do not have an excess of neurodevelopmental problems is of course reassuring. These data may be interpreted as evidence to support usual obstetric practice, which is to adopt a conservative and watchful approach to such pregnancies, unless there is additional evidence of acute fetal compromise from cardiotocography or other fetal assessments, or progression to REDFV. However, the detection of REDFV may be considered "too late", and our results could also be used to advocate a policy of intervention in the AEDFV period, before decompensation leads to permanent neurological damage. Delivery of the preterm fetus with AEDFV may well be appropriate if there is ancillary evidence of fetal compromise, or if the fetus is sufficiently mature that serious complications of prematurity are unlikely.

Timing the delivery of the fetus with REDFV can also be difficult, in the situation where severe growth retardation or

extreme prematurity carry their own risks of mortality, and the chance of surviving preterm birth is improving at about 2% per day, as it does at 25–26 weeks gestation.[34] Although neurodevelopmental problems were more frequent in the REDFV group in our study, it is also important to consider that 50% of the children in this group were doing well in a normal school without special help. These data should therefore not be taken to indicate that immediate delivery on the basis of REDFV is always appropriate. Reversal of EDFV may be a marker of severe fetal compromise or even decompensation, but timing of delivery remains a complex decision based on many other factors including gestation, estimated fetal weight, and the results of other techniques of fetal assessment.

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