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Fetal umbilical artery Doppler pulsatility index and childhood neurocognitive outcome at 12 years

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ABSTRACT

Objective: To determine whether an elevated fetal umbilical artery Doppler (UAD) pulsatility index (PI) at 28 weeks' gestation, in the absence of fetal growth restriction (FGR) and prematurity, is associated with adverse neurocognitive outcome in children aged 12 years.

Methods: Prospective cohort study, comparing children with a normal fetal UAD PI (<90th centile) (n=110) and those with an elevated PI (≥90th centile) (n=40). UAD was performed at 28, 32 and 34 weeks gestation. At 12 years of age, all children were assessed under standardised conditions at Queen's University, Belfast, UK to determine cognitive and behavioural outcomes using the British Ability Score-II and Achenbach Child Behavioural Checklist Parent Rated Version under standardised conditions. Regression analysis was performed, controlling for confounders such as gender, socioeconomic status and age at assessment.

Results: The mean age of follow-up was 12.4 years (±0.5 SD) with 44% of children male (n=63). When UAD was assessed at 28 weeks, the elevated fetal UAD group had lower scores in cognitive assessments of information processing and memory. Parameters included (1) recall of objects immediate verbal (p=0.002), (2) delayed verbal (p=0.008) and (3) recall of objects immediate spatial (p=0.0016). There were no significant differences between the Doppler groups at 32 or 34 weeks' gestation.

Conclusions: An elevated UAD PI at 28 weeks' gestation in the absence of FGR or prematurity is associated with lower scores of declarative memory in children aged 12 years. A potential explanation for this is an element of placental insufficiency in the presence of the appropriately grown fetus, which affects the development of the fetal hippocampus and information processing and memory long-term. These findings, however, had no impact on overall academic ability, mental processing and reasoning or overall behavioural function.

Strengths and limitations of this study

- Novel in concept/design.
- Longest follow-up in a group of children with abnormal in utero UAD measurements.
- Validity of methodology—standard investigation/same investigator that is blinded
- Two rounds of recruitment in order to obtain adequate numbers led to uneven numbers in both groups.
- Lack of placental and estimated fetal weight data.

INTRODUCTION

The association between fetal growth in utero and disease in later life was first proposed by Barker in the 1990s and is supported by further studies over past decades.[1–4] The fetal umbilical artery Doppler (UAD) pulsatility index (PI) measurement serves as a surrogate marker for the well-being of the fetus in utero through assessing impedance within the feto-placental circulation and is an indirect measure of resistance to flow within the placental vasculature. Typically, the PI is assessed using insonation of the fetal umbilical artery using pulsed-wave colour Doppler ultrasonography and subsequent analysis can be performed to obtain gestation-dependent centiles for the PI, with a PI of greater than the 90th or 95th centile signalling increased level of impedance in the majority of cases.[5]

While an abnormal UAD measurement is associated with perinatal death, its relationship with neurodevelopmental outcome is less clear. A recent Cochrane review of the application of the UAD concluded that there was no available evidence to assess the ability to predict substantive long-term outcomes, including neurodevelopment.[6] In the presence of fetal growth restriction (FGR), an abnormal Doppler has an association with abnormal childhood neurodevelopment.[7] An association between an abnormal UAD and neurological outcome in the apparently normally grown fetus has not been described to date.

The primary objective of this study was to compare childhood neurodevelopmental

outcome in terms of (1) cognitive and (2) behavioural performance in children at the age of 11–12 years who had elevated fetal UAD PI at 28 weeks' gestation compared to a control group with normal measurements, in the absence of FGR and preterm delivery.

PATIENTS AND METHODS

In 1988, a prospective cohort study of 2097 consecutive non-growth-restricted singleton pregnancies underwent serial UAD PI testing at 28, 34 and 38 weeks' gestation to assess whether the UAD PI could predict peri-natal outcome data (RB Beattie. Evaluation of umbilical artery Doppler ultrasound in human pregnancy. [Unpublished Thesis]. [Belfast (UK)]: Queen's University, Belfast; 1988).

Patient selection

The present study population included a nested case–control subset of patients from the aforementioned study aged 11–12 years (RB Beattie, Unpublished Thesis, 1988) that had had an in utero UAD PI, randomly selected either above (abnormal) or below (normal) the 90th centile for gestational age at 28 weeks' gestation as per the pre-defined criteria,[8] and alternatively defined as abnormal or normal on the PI centile at 34 and 38 weeks of gestation.[9] A power calculation estimated that 100 subjects per group should be tested to detect a mean difference of 7.5 (SD of 15) in the scores for components of the British Ability Score-II (BAS-II) assessments of cognitive function at 28 weeks, with a power of 94% at a significance level of 0.05. In the course of the study, low response rates limited the sample to 180 with a 1:3.5 imbalance; however, a post hoc calculation indicated power was maintained at 79%. Results and assessments centred around UAD PI at 28 weeks due to the known association between Doppler status from 27 weeks and neurodevelopmental delay in pregnancies affected by FGR, high-lighting the significance of assessing at this gestation.[10] Anticipating the difficulties in locating and recruiting participants for follow-up research, 724 names were initially selected and traced through the Central Services Agency. Following two rounds of recruitment, 204 subjects underwent psychological assessment. Subjects delivered pre-term (<37 weeks), with a small-for-gestational-age birth weight (<10th centile) or identifiable genetic syndromes, were subsequently omitted, leaving an overall sample of 180 subjects. Following ethical approval from the Northern

Table 1 Demographic characteristics of study cohort at 28 weeks' gestation in the normal (<90th centile) and elevated (>90th centile) umbilical artery Doppler (UAD) pulsatility index (PI) reported as mean with SDs (SD) or percentages, respectively

	UAD PI<90th centile N=140	UAD PI>90th centile N=40	All individuals N=180
Gender (male)	36 (54%)	27 (44%)	63 (49%)
Age of child (years)	12.4 (0.5)	12.4 (0.4)	12.4 (0.5)
Age of mother (years)	40.5 (5.3)	39.9 (5.8)	40.2 (5.6)
Weight (kg)	44.1 (10.3)	45.5 (11.7)	44.9 (11.1)
Height (cm)	151.6 (7.7)	151.0 (7.6)	151.3 (7.6)
Townsend score	1.66 (3.44)	1.66 (3.45)	1.66 (3.4)
Tanner public hair staging			
1	32 (49%)	29 (48%)	61 (48%)
2	15 (23%)	15 (25%)	30 (24%)
3	5 (8%)	8 (13%)	13 (10%)
4	13 (20%)	7 (12%)	20 (16%)
5	1 (2%)	1 (2%)	2 (2%)
11+ grade=pass	39 (59%)	42 (69%)	81 (64%)
Maternal smoking	44 (33%)	15 (37%)	59 (34%)
Mode of delivery			
Normal (SVD)	112 (81%)	31 (76%)	143 (79%)
Assisted breech	1 (1%)	1 (2%)	2 (1%)
Instrumental	15 (11%)	3 (7%)	18 (10%)
Caesarean section	11 (8%)	6 (15%)	17 (9%)
Birth weight (g)	3679 (586)	3429 (426)	3532 (511)
Gestation (weeks+days)	40+3 (1+0)	40+1 (1+0)	40+2 (1+0)
APGAR 1 min	8 (7, 9)	8 (7, 9)	8 (7, 9)
APGAR 5 min	9 (9, 9)	9 (9, 9)	9 (9, 9)
Cord pH	7.29 (0.14)	7.30 (0.09)	7.29 (0.11)
PI 28 weeks	0.95 (0.06)	1.69 (0.29)	1.34 (0.43)
PI 34 weeks	0.96 (0.19)	1.06 (0.20)	1.02 (0.20)
PI 38 weeks	0.90 (0.20)	1.03 (0.15)	0.97 (0.18)

Ireland Research and Ethics committee, Queen's University Belfast, informed consent was obtained from parents and children for this study.

Assessments

In addition to physical assessment of cardiovascular and respiratory status,[4] cognition and behaviour were tested under standardised conditions using validated questionnaires by a single child psychologist who was blinded to UAD PI category. Cognitive function was assessed using the BAS-II questionnaire,[11] which is inclusive of (1) diagnostic scales; assessing information processing and memory, (2) achievement scales; assessing academic performance and (3) core scales which formulate the global conceptual ability score (GCA); assessing mental processing and reasoning. Behavioural function was assessed by a parent questionnaire through the Achenbach Child Behavioural Checklist Parent Rated Version (CBCL),[12] which rates the presence of specific behaviours on a 3-point rating scale.

Statistical analysis

Number and percentages were derived for categorical characteristics, and means, SDs and medians and first and third quartiles (IQR) were calculated for continuous characteristics. Categorical characteristics were compared between the UAD PI groups using Student's t-test after weighting for non-response. Several of the demographic and psychometric measures had a skew or other non-normal distribution, and therefore the non-parametric Mann-Whitney tests were performed to compare the normal and elevated UAD PI groups. Outcomes of interest were carried forward to compare the normal and elevated UAD PI groups while adjusting for potential confounders including gender, age at assessment and Townsend score as a proxy for socioeconomic status. These outcomes included all variables, which showed statistical significance at an α of 0.1 from the Mann-Whitney tests. Linear regression analyses were performed to adjust for confounders, and residuals closely inspected to verify assumptions were met. No correction for multiple testing was performed, and a p value threshold of 0.05 was considered statistically significant in the final adjusted analyses. Psychometric scores with extreme non-normal distributions were modelled using binary logistic regression after dichotomisation at the median and adjusted for the same confounders. All analyses were performed using IBM SPSS V.20, and weighted by the non-response rates in the respective recruitment cohorts and high/normal PI strata.

RESULTS

This study included 180 subjects; 40 with a UAD PI of ≥90th centile (elevated) and 140 with a UAD PI of <90th centile (normal). This accounts for 19.0% (40/210) and 7.4% (140/1887) of the original 2087 cohort,

Table 2 Adjusted linear or logistic regression analysis for elevated (>90th centile) and normal (<90th centile) umbilical artery Doppler (UAD) pulsatility index (PI) for validated British Ability Scales II diagnostic scale parameters at 28, 34 and 38 weeks expressed as mean and SDs (SD).

	Week 28 (1.73 threshold)			Week 34 (1.28 threshold)			Week 38 (1.17 threshold)		
Diagnostic scale	**Normal**	**Elevated**	**p Value**	**Normal**	**Elevated**	**p Value**	**Normal**	**Elevated**	**p Value**
Recall of objects immediate verbal, mean (SD)	142.9 (1.9)	130.7 (3.3)	0.002	140.5 (1.8)	136.1 (5.3)	0.438	139.7 (2.0)	130.3 (6.2)	0.151
Recall of objects immediate spatial,* mean (SD)	0.48 (0.07)	0.69 (0.05)	0.016	0.53 (0.04)	0.58 (0.12)	0.731	0.59 (0.05)	0.46 (0.13)	0.380
Recall of objects delayed verbal, mean (SD)	15.6 (0.25)	14.3 (0.43)	0.008	15.3 (0.2)	14.6 (0.7)	0.298	15.1 (0.2)	14.1 (0.8)	0.206
Recall of objects delayed spatial,* mean (SD)	0.52 (0.05)	0.67 (0.07)	0.108	0.55 (0.04)	0.64 (0.12)	0.530	0.62 (0.04)	0.55 (0.13)	0.604
Speed of information processing—ability score, mean (SD)	163.2 (3.1)	157.9 (5.2)	0.389	163.0 (2.7)	154.6 (8.0)	0.323	160.0 (3.0)	163.1 (9.3)	0.750
Recall of digits forward—ability score, mean (SD)	151.5 (1.8)	150.4 (3.0)	0.761	150.9 (1.6)	150.1 (4.7)	0.872	150.7 (1.8)	150.2 (5.7)	0.941
Recall of pictures—ability score, mean (SD)	123.8 (1.2)	120.7 (2.1)	0.209	122.8 (1.1)	123.9 (3.3)	0.752	121.3 (1.3)	130.3 (3.9)	0.030
Recall of digits backwards—ability score, mean (SD)	129.8 (1.7)	124.1 (2.8)	0.087	128.6 (1.5)	126.4 (4.4)	0.634	128.6 (1.7)	125.4 (5.3)	0.564

*Logistic regression, mean in these cases refers to the odds of an abnormal (low) recall score for a child at the mean age (12.1 years) with a mean Townsend score (1.79).

respectively. The demographics of the study population at the time of assessment, delivery and during gestation are demonstrated in table 1.

Following adjustment for potential confounders including gender, age at assessment and Townsend score, the findings between UAD PI groups (normal and elevated) were compared (tables 2–5). These findings are demonstrated for the variable aforementioned psychometric parameters assessed inclusive of the BAS II diagnostic scales (table 2), achievement scales (table 3), core scales (table 4) and Achenbach CBCL (table 5) for UAD performed at 28, 34 and 38 weeks, respectively, with associated p values. The unadjusted version of this analysis is provided in online supplementary file 1.

Scores of processing and memory; notably recall of objects immediate verbal, immediate spatial and delayed verbal in the diagnostic scale group were significantly lower in the elevated UAD PI group (p=0.002, 0.016 and 0.008, respectively). This did not appear to be the case when UAD was measured in groups at later gestations. There were no significant differences between UAD PI groups in the achievement scales group, and in the GCA group, the overall GCA score was not significantly different between groups. In terms of the Achenbach child behaviour checklist parent-rated version (CBLC), internalising and externalising parameters were not overall significantly different.

DISCUSSION

This study demonstrates that at 12 years of age, in the absence of FGR and prematurity, an elevated fetal UAD PI at 28 weeks' gestation is associated with significantly lower scores in parameters of cognitive function in the form of information processing and memory. There is no association between abnormal fetal UAD PI and overall academic ability, mental processing and reasoning or overall behavioural function of children at this age.

Existing research suggests that in FGR, the degree of neurodevelopmental abnormality in childhood is proportionally related to the impedance within the UAD.[7] Early-onset FGR is associated with impaired placental perfusion due to a reduction in the overall cross-sectional villous vascular area, which appears to affect UAD resistance when villous damage is >30%.[13] Our study agrees with existing research which demonstrates that there is an effect of abnormal UAD measurement in the coexistence of FGR in terms of impaired childhood neurodevelopment,[7 14] yet our study is unique in assessing neurodevelopmental outcomes in children with abnormal UAD, but no associated FGR or prematurity. One explanation may lie in the definition of FGR; a topic much debated within the literature. Traditional definitions of FGR, that is, birth weights <10th and <3rd centile for gestational age which were used at the time of the original study, are being replaced by histological placental evidence of impaired perfusion or 'placental disease'. Emerging studies demonstrate abnormal cerebral and placental blood flow distributions within appropriately grown fetuses as a marker of placental insufficiency and call for a revision of the diagnosis of fetuses 'failing to reach their growth potential'.[15]

The strength of this study is that the cohort is that it is the first of its' kind to assess the impact of an abnormal fetal UAD PI in a non-growth restricted population on long-term neurodevelopmental outcome. In addition, this study represents the longest follow-up in a group of children with abnormal in utero UAD measurements.[7] A recent study, which is the longest cohort study to date of extreme low-birth weight survivors, demonstrated that cases of babies born with a birth weight under 1000 g were more likely to exhibit a psychiatric problem than their normal birth weight counterparts.[16] However, Doppler status was not formally assessed within the methodology, probably because its routine use predated the starting date of the study.

Limitations of our study include the method of recruitment, which required two rounds of recruitment in order to obtain adequate numbers and led to uneven numbers either side (elevated UAD PI n=40, normal UAD PI n=140), which may have accounted for a skew in the demographic characteristics. Nevertheless, non-response was corrected for within the statistical analysis. Correction for confounders was included in multiple

Table 3 Adjusted linear and or logistic regression analysis for elevated (>90th centile) and normal (<90th centile) umbilical artery Doppler (UAD) pulsatility index (PI) for validated British Ability Scales II achievement scale parameters at 28, 34 and 38 weeks, respectively, expressed as mean and SDs

	Week 28 (1.73 threshold)			Week 34 (1.28 threshold)			Week 38 (1.17 threshold)		
Achievement scale	Normal	Elevated	p Value	Normal	Elevated	p Value	Normal	Elevated	p Value
Number standard score, mean (SD)	111.6 (1.2)	108.1 (2.0)	0.143	110.8 (1.1)	108.5 (3.1)	0.484	110.1 (1.2)	104.9 (3.7)	0.188
Spelling standard score, mean (SD)	102.5 (1.3)	100.1 (2.2)	0.340	102.0 (1.2)	102.2 (3.4)	0.947	102.0 (1.3)	95.6 (3.9)	0.124
Reading standard score, mean (SD)	98.0 (1.2)	98.9 (2.0)	0.690	98.2 (1.1)	99.4 (3.3)	0.742	98.9 (1.2)	95.2 (3.7)	0.349

Table 4 Adjusted linear regression analysis for elevated (>90th centile) and normal (<90th centile) umbilical artery Doppler (UAD) pulsatility index (PI) for validated British Ability Scales II General Conceptual Ability Score (GCA) scale parameters at 28, 34 and 38 weeks, respectively, expressed as mean and SD

	Week 28 (1.73 threshold)			Week 34 (1.28 threshold)			Week 38 (1.17 threshold)		
GCA scale	Normal	Elevated	p Value	Normal	Elevated	p Value	Normal	Elevated	p Value
Verbal sums of scores, mean (SD)	103.5 (1.6)	99.3 (2.6)	0.186	102.6 (1.5)	101.5 (4.3)	0.810	102.2 (1.6)	102.1 (5.0)	0.985
Non-verbal reasoning sums of scores, mean (SD)	97.5 (1.5)	93.9 (2.5)	0.230	96.0 (1.4)	99.9 (4.1)	0.363	96.0 (1.5)	94.5 (4.8)	0.766
Spatial sums of scores, mean (SD)	100.1 (1.4)	97.7 (2.4)	0.417	99.5 (1.4)	100.3 (4.0)	0.846	97.9 (1.4)	110.3 (4.4)	0.008
Standard verbal ability scores, mean (SD)	102.7 (1.2)	99.5 (2.1)	0.193	102.0 (1.2)	101.1 (3.4)	0.803	101.7 (1.3)	101.8 (4.0)	0.978
Standard non-verbal reasoning ability, mean (SD)	97.7 (1.3)	94.7 (2.1)	0.238	96.4 (1.2)	99.6 (3.4)	0.370	96.4 (1.3)	95.2 (4.0)	0.768
Standard spatial ability, mean (SD)	99.5 (1.3)	97.4 (2.1)	0.409	98.9 (1.2)	99.6 (3.5)	0.845	97.6 (1.2)	108.6 (3.9)	0.008
Standard GCA, mean (SD)	99.9 (1.3)	96.4 (2.1)	0.175	98.8 (1.2)	100.1 (3.5)	0.737	98.2 (1.3)	101.9 (4.0)	0.385

regression. In addition, an attempt to limit bias in the methodology was limited through blinding of the assessors to PI category. One must also note that significant findings were among a large number of outcome measures and hence results must be interpreted with caution.

Interestingly, the findings of this study also add information on the time point where the UAD PI assessment is critical in determining long-term impact on neurodevelopment. Assessments performed at 28 weeks appeared to have the most significant impact on cognitive outcome, notably on information processing and memory. However, this was not the case when UAD PI was assessed at later gestations. It is known that fetuses with FGR are more likely to exhibit long-term cognitive impairment and memory deficit, as has been demonstrated within this study.[17] The statistically significant results from our study were found in assessments of cognitive function focusing on recall of objects verbal and spatial; the area of the brain controlling this function being the hippocampal region which controls declarative memory, with children with elevated UAD PI in utero having poorer scores in these assessments. There were no cases of abnormal development within the study cohort as such cases were excluded at the selection process. What can be extrapolated clinically from this study is that the cohort of patients with an elevated UAD PI were more likely to have lower but not abnormal scores in assessments of short-term and declarative memory function than their normal UAD PI peers, which may express itself as a child having executive-attention deficit and/or mild learning difficulties, somewhat similar to that of children who had FGR in utero.[17] It is important to note, however, that despite these changes they did not affect the overall academic ability, mental processing and reasoning or overall behavioural function. The latter supports the theory that reduced placental blood flow, notably during the second half of pregnancy, correlates with a reduction in the number of neurons within this area of the fetal brain; as correlated with the histological brains of primates and humans at this stage in addition to vulnerability of hippocampus to injury in the prenatal period.[18 19] This would certainly go some way to explaining why the earlier abnormal UAD assessment has a stronger association with the abnormal parameters. It is unclear as to why there was no significant difference in parameters at later gestations between groups.

Potential explanations are twofold, primarily as fewer Doppler assessments were performed at these gestations and second, perhaps fetuses at 28 weeks have an altered vulnerability in terms of brain pathophysiology as a result of elevated UAD PI compared to later gestations.[10] The latter suggestion is supported by existing research which suggests that neurodevelopment is affected by increased impedance in the UAD and aortic indices in early FGR and by cerebral blood flow in late onset IUGR.[10]

Table 5 Adjusted linear or logistic regression analysis for elevated (>90th centile) and normal (<90th centile) umbilical artery Doppler (UAD) pulsatility index (PI) for Achenbach child behaviour checklist parent rated version (CBLC) parameters at 28, 34 and 38 weeks, respectively, as expressed as mean with associated SD

	Week 28 (1.73 threshold)			Week 34 (1.28 threshold)			Week 38 (1.17 threshold)		
CBLC parameters	**Normal**	**Elevated**	**p Value**	**Normal**	**Elevated**	**p Value**	**Normal**	**Elevated**	**p Value**
CBLC withdrawn,* mean (SD)	0.40 (0.05)	0.38 (0.08)	0.889	0.40 (0.04)	0.36 (0.13)	0.770	0.41 (0.05)	0.27 (0.13)	0.310
CBLC somatic problems,* mean (SD)	0.53 (0.05)	0.66 (0.08)	0.150	0.58 (0.04)	0.33 (0.12)	0.056	0.60 (0.05)	0.40 (0.14)	0.165
CBLC anxious/depressed,* mean (SD)	0.52 (0.05)	0.59 (0.08)	0.444	0.54 (0.04)	0.43 (0.13)	0.412	0.53 (0.05)	0.63 (0.13)	0.506
CBLC social problems,* mean (SD)	0.52 (0.05)	0.54 (0.08)	0.803	0.52 (0.04)	0.39 (0.12)	0.317	0.50 (0.05)	0.40 (0.14)	0.484
CBLC thought/behaviour,* mean (SD)	0.57 (0.05)	0.57 (0.08)	0.930	0.59 (0.04)	0.34 (0.11)	0.063	0.56 (0.05)	0.49 (0.14)	0.659
CBLC attention problems,* mean (SD)	0.50 (0.05)	0.58 (0.09)	0.466	0.54 (0.05)	0.34 (0.13)	0.169	0.56 (0.05)	0.26 (0.12)	0.056
CBLC delinquent behaviour,* mean (SD)	0.70 (0.05)	0.88 (0.05)	0.021	0.76 (0.04)	0.57 (0.14)	0.139	0.73 (0.05)	0.75 (0.13)	0.884
CBLC aggressive behaviour,* mean (SD)	0.49 (0.05)	0.56 (0.08)	0.517	0.49 (0.05)	0.41 (0.14)	0.597	0.46 (0.05)	0.66 (0.15)	0.179
CBLC other problems,* mean (SD)	0.52 (0.05)	0.64 (0.08)	0.215	0.55 (0.04)	0.44 (0.13)	0.404	0.54 (0.05)	0.48 (0.15)	0.683
CBLC internalising,* mean (SD)	0.52 (0.05)	0.64 (0.08)	0.193	0.56 (0.04)	0.45 (0.13)	0.399	0.57 (0.05)	0.57 (0.14)	0.983
CBLC externalising,* mean (SD)	0.49 (0.05)	0.57 (0.08)	0.412	0.50 (0.05)	0.41 (0.14)	0.566	0.47 (0.05)	0.66 (0.15)	0.207
CBLC internalising standard score, mean (SD)	52.0 (0.9)	51.4 (1.5)	0.759	51.7 (0.8)	54.2 (2.5)	0.331	51.7 (1.0)	53.6 (2.8)	0.523
CBLC externalising standard score, mean (SD)	49.8 (0.9)	48.0 (1.5)	0.290	49.4 (0.8)	53.7 (2.3)	0.079	50.2 (0.9)	50.7 (2.7)	0.860
CBLC total standard score, mean (SD)	45.2 (0.8)	44.0 (1.4)	0.464	44.8 (0.8)	49.0 (2.2)	0.074	45.3 (0.9)	46.6 (2.5)	0.642

*Logistic regression, mean in these cases refers to the odds of an abnormal (high) psychometric score for a child at the mean age (12.1 years) with a mean Townsend score (1.79).

It is a challenge to determine the clinical implications of this study as one refers to a test which is not indicated for the general unselected pregnant population. Certainly, if the definition of FGR was revised and the fetuses with elevated UAD PI were truly growth restricted and all of their placentae were retrospectively histopathologically examined, then perhaps this would support re-exploring the definition of FGR. Additionally, due to the demonstrated apparent deficit in short-term memory at childhood follow-up, a focus should be made on those children who had FGR to facilitate orientation, and direct attention and reiteration of material to optimise learning performance.[17]

CONCLUSION

An elevated UAD PI at 28 weeks' gestation in the absence of FGR or prematurity is associated with some adverse cognitive findings in children aged 12 years. A potential explanation for this phenomenon is an element of placental insufficiency in the presence of the appropriately grown fetus which affects the development of the fetal hippocampus, and this information processing and memory long-term further studies should be performed before firm conclusions or guidance can be drawn from the findings of this study.

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Contributors FM analysed and interpreted the data, drafted, reviewed and revised the manuscript and approved the final version as submitted. BMcC and AT conceptualised and designed the study, acquired the data, carried out the initial analysis and revised the article critically for intellectual content and approved the final manuscript as submitted. RS, SO and FMMcA performed the final analysis and interpretation of the data, revised the article critically for intellectual content and approved the final manuscript as submitted. PH, MCS, JCD and MDS conceptualised and designed the study and data collection instruments, and coordinated and supervised data collection in addition to critically reviewing the manuscript and approving the final manuscript as submitted.

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