

The impact of fetal umbilical artery Doppler pulsatility index on childhood respiratory function and atopy – A prospective case-control study

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Title: The impact of fetal umbilical artery Doppler pulsatility index on childhood respiratory function and atopy – A prospective case-control study

Short title: Fetal Doppler and respiratory outcome

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ABSTRACT

OBJECTIVE: To determine if an elevated fetal umbilical artery Doppler pulsatility index is associated with abnormal respiratory function and atopy in children aged 12 years.

METHODS: This prospective case-control study compared children that had an elevated fetal umbilical artery Doppler pulsatility index (>90th centile) to those with a normal pulsatility index (<90th centile). All subjects were delivered at full-term and with appropriate growth for gestational age. Outcome measures included; (i) presence of asthma and/or atopy; (ii) spirometry measurements and (iii) serum C-reactive protein and leptin. Multiple regression was used to account for parental smoking, childhood age, gender and socioeconomic status.

RESULTS: 174 children with an average age of 12.1 (+/- 0.6 SD), 48% of who were male were included in the analysis. Of the 174, 99 (57%) were in the normal umbilical artery Doppler pulsatility index group and 75 (43%) elevated umbilical artery Doppler pulsatility index groups. The overall proportion of subjects with asthma was 28% (48/174) and atopy 56% (98/174). No association was found between elevated fetal umbilical artery Doppler pulsatility index and asthma ($p=0.47$) or atopy ($p=0.75$) at age 12 years. Similarly there was no association between FEV1(%) ($p=0.96$), FVC(%) ($p=0.98$), elevated serum C-reactive protein ($p=0.69$) or leptin ($p=0.20$) and an elevated fetal umbilical artery Doppler pulsatility index.

CONCLUSION: An elevated umbilical artery Doppler at 28 weeks gestation in the absence of prematurity or fetal growth restriction is not associated with altered respiratory function or presence of atopy in children aged 12 years. These findings support the theory that such disease has a multifactorial pathophysiology.

INTRODUCTION

Fetal growth and well-being serve as predictors of childhood and adult health [1]. To assess fetal well-being one can assess the impedance within the fetal placental circulation, as measured by the umbilical artery Doppler (UAD) pulsatility index (PI),

which, from the second trimester is associated with adverse long term cardiovascular and neurodevelopmental outcome in children [2-4].

There is conflicting evidence as to whether being a growth restricted fetus, with a birth weight below the 10th centile for gestational age (FGR) impacts on respiratory function and atopy in later life, with the confounding factor of pre-maturity appearing to carry a greater weight in terms of a positive association [5-9]. In addition to clinical history and pulmonary function tests, elevated serum leptin and C-reactive protein (CRP) serve as markers of severity of asthma and allergic airways disease [10-11]. In an attempt to understand the pathophysiology behind the origins of childhood respiratory disease in appropriately grown foetuses delivered at full-term, the objectives of this study were to determine the impact of an elevated in-utero UAD PI and: (i) clinical asthma and/or atopy, (ii) altered pulmonary function and (iii) elevated serum leptin and CRP at twelve years of age.

MATERIALS AND METHODS

This longitudinal case-control study assessed a cohort of patients after 12-years whom had been initially assessed in 1988 when 2097 unselected singleton non-growth restricted pregnancies underwent UAD assessment at 28-weeks gestation with the aim of determining the impact of Doppler findings on perinatal outcome (RB Beattie. Evaluation of umbilical artery Doppler ultrasound in human pregnancy. [Unpublished Thesis]. [Belfast (UK): Queen's University Belfast; 1988).

Patient selection

A case-control subset of patients from the aforementioned cohort were selected at random at 11 to 12 years of age to formulate two groups including subjects that had an in-utero UAD PI greater than (elevated) and below (normal) the 90th centile for gestational age as per pre-defined criteria [12]. For a statistical power of 0.85 and significance level of 0.05, it was estimated that 80 subjects per group would be required to detect a mean difference of 10% FEV1 (% predicted) between groups. Patient selection was similar to that used to obtain the cohorts of subjects assessed in previously published studies from the same group [2-3]. Patient tracing was performed via the Central Services Agency for Northern Ireland and the General Practitioner records and initially targeted 300 subjects due to the anticipated challenges with recruitment. Following two rounds of recruitment, the final cohort excluded subjects delivered pre-term (<37 weeks), with a congenital anomaly or genetic syndrome and birth weight <10th centile for gestational age. The final cohort with completed data on respiratory and allergy status included 174 children; 99 (57%) normal UAD PI (<90th centile) and 75 (43%) elevated UAD PI (>90th centile). Written parental consent and child assent were obtained for the study stating that they consented to inclusion of material pertaining to themselves in subsequent publication

and that were aware that their data was fully anonymized. This study was prospectively approved by the Northern Ireland Research Ethics Committee, Queen's University, Belfast.

Assessments

Assessments were performed in a standardized fashion by one of two researchers that were blinded to group status. At baseline demographic details, perinatal data and parental smoking status were obtained on all subjects. Blood testing included assessment of (i) serum leptins - quantitatively determined by radioimmunoassay (Quantikine, R & D Systems), (ii) serum IgE - assessed using double antibody radioimmunoassay (Pharmacia IgE RIA, Pharmacia) and (iii) CRP - measured using a latex-enhanced immunoturbidimetric assay (Randox Ultrasensitive CRP assay. Additional tests on children included rapid gas-liquid chromatographic quantification of salivary cotinine levels [13], which served as an objective measure of active smoking and/or exposure to passive smoking. Atopy was defined as a prior clinical diagnosis of eczema or hay fever with a co-existing elevated IgE level >200 IU/ml. Subjects underwent pulmonary function tests using a Microlab 3300 spirometer (Micro Medical Limited) to determine peak expiratory flow rate (PEF), forced vital capacity (FVC) and maximal expiratory flow rate (MEF) with standardisation of measurements as percentage predicted based upon age, height and gender. All mandatory laboratory health and safety procedures were complied with in the course of conducting the aforementioned experimental work.

Statistical analysis

This was performed by a biostatistician (RS), using IBM SPSS V.20. Risk factors and outcomes were summarised using N and percentages, mean and standard deviation, where appropriate. Several variables showed some degree of skew, and were summarised using medians and the interquartile range. At baseline, outcome measures were compared

statistically using Pearson chi-square tests, independent samples t-tests and Mann-Whitney tests where appropriate. A p-value of <0.05 was taken to be statistically significant. The effect of an elevated UAD PI on risk for asthma or atopy was examined using logistic regression. Linear regression was used to assess the relationship between pulmonary function measures and quantile regression was used to assess for association between CRP and leptin with UAD PI group to account for the outliers in serum levels. All regressions were run unadjusted (crude) and adjusted for smoking exposure (parental smoking or elevated salivary cotinine levels), age of the child at assessment, gender, and Townsend score (a validated measure of deprivation based on four variables (unemployment, overcrowding, non-car ownership and non-home ownership) [14]. The study dataset is available on request from the corresponding author.

RESULTS

The study included 174 children: 99 (57%) normal UAD PI (<90th centile) and 75 (43%) elevated UAD PI (>90th centile). Demographics for both study groups are presented in Table 1. There was a significant difference in relation to the elevated UAD PI group where there were a greater proportion of female children and children that had a lower birth-weight. These confounders were controlled for in the multiple regression analysis.

<Insert Table 1>

There were no differences in outcome measures between subjects in the elevated UAD PI and normal PI groups as demonstrated in Table S1.

Following adjustment for smoking exposure, age, gender, birth-weight and Townsend score there was no difference between Doppler groups in relation to presence of asthma or atopy (OR 0.77 (95% CI 0.37-1.58) and OR 0.90 (95% CI) (0.48-1.71) respectively) [Table S2]. There was also no difference in spirometry measures or serum CRP and leptin [Table 2]. Although there was a trend for higher serum CRP and leptin in the elevated PI group, this was attenuated when controlling for other factors.

<Insert Table 2>

DISCUSSION

This study has found no association between an elevated fetal umbilical artery Doppler pulsatility index in a cohort of appropriately grown for gestational age term infants and the presence of asthma, atopy or altered respiratory function in children aged twelve. There was a trend toward elevated levels of serum C-reactive protein and leptin levels prior to adjustment.

This is one of the first studies of its kind to assess the relationship between in-utero Doppler and long-term respiratory function and allergy status in the absence of co-existing prematurity and FGR. With no similar study cohort examined elsewhere, one looks towards evidence from low birth-weight fetuses, where it is proposed that hypoxaemia and under-nutrition manifesting as FGR are associated with abnormal pulmonary development, perinatal respiratory distress syndrome, infection and abnormal spirometry measures and atopy in later life [15]. The novel term of 'failure to reach growth potential' of the 'appropriately grown for gestation fetus', whereby a fetus may be of a normal birth weight centile, although have a fall-off in growth and does not reach its genetically pre-defined growth potential, also reflects utero-placental insufficiency and has been shown to present with abnormal Doppler pathology, likely presenting as a subtype of FGR [16]. Existing studies appear to give more weight to the association of prematurity and such proposed outcomes, rather than FGR or low birth weight primarily [17]. It has also been proposed that the impact of FGR, if any, is greatest in relation to poorer lung function at eight to nine years, and less so at 14-17 years which may in part explain an attenuated association in our own cohort [18].

In relation to atopy and allergy, although less investigated than the effect of fetal programming in development of childhood asthma, increased 'stress' in-utero has been associated with elevated levels of cord blood IgE [19] and a fall off in fetal growth trajectory has been linked to later development of childhood eczema [20]. Asthma and atopy share a common pathophysiology and the common theme of a multifactorial origin of disease may offer some explanation for our study findings. One could hypothesise that early exposure of fetal hypoxic stress as indicated by an elevated UAD PI at 28-weeks in a fetus which manages to avoid FGR or prematurity could accelerate lung maturation and pulmonary surfactant secretion, thus balancing out any potential prior insult to lung development [15].

Interestingly, we noted a trend toward higher leptin and CRP levels in the elevated UAD PI group, which was not significant following adjusted analysis. Leptin and C-reactive protein are adipocytokines; a peptide hormone produced by the adipocytes [20]. Elevated serum leptin levels are suggestive of leptin resistance, associated with increased visceral body fat. At a physiological level, leptin resistance has been suggested to increase parasympathetic tone and increased bronchoconstriction in addition to increasing alpha-1 antitrypsin levels, increasing the likelihood of childhood asthma [21]. C-reactive protein is an acute phase reactant, involved in host defence and inflammation. Although its precise mechanism is unknown, CRP serves as a systemic marker of local airway inflammation and bronchial asthma [22]. Failure to reach growth potential is known to be associated with leptin resistance and an increased centralisation of body fat. This supports the 'fetal programming' theory, in that the in-utero environment and fetal nutrition, affect the physiology and metabolism beyond fetal life, as reflected by a trend toward increased leptin and CRP levels with an elevated UAD PI [21].

Study strengths include the application of a robust study design with use of researcher blinding to minimise bias in addition to the incorporation of objective measures of salivary cotinine and serum IgE to confirm passive smoking status and atopy, thus optimising validity. Use of regression analysis allowed for controlling of confounding variables, which are known to influence respiratory function and allergy status. Study limitations included the need for two rounds of recruitment to obtain a sufficient number of subjects and the difference in numbers between groups (57% vs. 43%), which led to some skewing of the data.

In conclusion, this prospective case-control study does not display a link between an elevated fetal umbilical artery Doppler pulsatility index and altered respiratory function or atopy in children aged 12-years in the absence of prematurity and FGR. This supports the theory that the pathophysiology for such disease is multifactorial. Future research

should consider the interaction of variables in the development of disease encompassing genetic, epigenetic and environmental factors.

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DECLARATION OF INTEREST: Authors report no conflict of interest

DATA AVAILABILITY STATEMENT: The complete data set is available from the corresponding author on request

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		All subjects N=174	Normal N=99	Elevated N=75
Gender*	Male (1)	84 (48%)	55 (56%)	29 (39%)
	Female (2)	90 (52%)	44 (44%)	46 (61%)
Age at assessment (years)		12.1 ± 0.55	12.1 ± 0.57	12.2 ± 0.51
Gestational age at birth (weeks)		40.1 ± 1.17	40.1 ± 1.22	40.2 ± 1.11
Townsend score		1.62 ± 3.51	1.24 ± 3.63	2.14 ± 3.32
Birth weight (g)*		3507 ± 458	3586 ± 482	3404 ± 404
BMI at assessment (kg/m ²)		19.3 ± 3.57	19.2 ± 3.22	19.4 ± 4.01
Delivery mode	Normal	142 (82%)	80 (81%)	62 (83%)
	Assisted/Instrumental	18 (10%)	11 (11%)	7 (9%)
	CS	14 (8%)	8 (8%)	6 (8%)
Parental smoking (either/both)		87 (52%)	44 (46%)	43 (57%)

Table 1: Demographic measures of the study cohort in the normal (<90th centile) and elevated (>90th centile) umbilical artery Doppler (UAD) pulsatility index (PI) [Reported as N (%), or Mean $\pm$ Standard deviation]. * p<0.05

	Crude			Adjusted*		
	B	95% CI	p	B	95% CI	p
FEV1 (%)	0.60	-2.9, 4.2	0.74	-0.1	-3.5, 3.2	0.96
FVC (%)	0.20	-3.7, 4.1	0.92	0.0	-3.6, 3.7	0.98
FEV1: FVC ratio (%)	0.01	-0.01, 0.03	0.49	-0.001	-0.02, 0.02	0.88
MEF (%)	3.0	-3.4, 9.4	0.36	1.8	-4.5, 8.2	0.57
CRP - median	0.00	0.00, 0.00	1.00	0.00	0.00, 1.00	1.00
CRP -75 th centile	0.10	-0.49, 0.50	0.62	0.09	-0.25, 0.43	0.61
CRP – 90 th centile	0.6	-1.82, 1.80	0.60	-0.31	-1.85, 1.22	0.69
Leptin -median	779	-1931, 3940	0.66	1077	-1519, 3672	0.42
Leptin – 75 th centile	3777	-1254, 9664	0.29	1581	-5305, 8468	0.65
Leptin – 90 th centile	6281	-4754, 18344	0.33	7187	-3597, 17971	0.20

Table 2: Association of percentage predicted spirometry measure and serum CRP and leptin centiles with the presence of an elevated umbilical artery Doppler pulsatility index >90% pre- and *post- adjustment for smoking exposure, age, gender, birth-weight and Townsend score [CI=confidence interval]

JUST ACCEPTED