The Relationship between arterial and venous Doppler pulsatility index, fetal abdominal circumference and growth and in severe early onset fetal growth restriction

Key words: fetal growth restriction; Doppler ultrasound; umbilical artery; middle cerebral artery; abdominal circumference; z-score; FLDA

Talmor A

Daemen A

Murdoch E

Missfelder-Lobos H

Timmerman D

Bourne T

Lees C

[1]Division of Fetal Maternal Medicine, Cambridge University Hospitals NHS Trust; [2] Department of Electrical Engineering, Katholieke Universiteit Leuven, Leuven, Belgium; [3]Department of Obstetrics and Gynecology, University Hospitals Leuven, Campus Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium.; [4] Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0HS, UK

Introduction: That there is an association between abnormal fetal and venous Doppler measurements and fetal growth restriction is well known. However the nature of this relationship remains undefined. We sought to establish the relationship between umbilical artery, middle cerebral artery (MCA) and ductus venosus (DV) Doppler with abdominal circumference (AC) in babies with severe early onset fetal growth restriction with an estimated fetal weight <500g at 24 weeks gestation using FLDA, a statistical technique recently applied to biomedicine.

Methods: Women with AC<10th centile and abnormal umbilical artery Doppler delivered between 2003-2007 were included in this prospective audit. Serial arterial and venous Doppler and AC measurements were recorded, expressed as z-scores and longitudinally analyzed using FLDA. The longitudinal curves were converted into a correlation coefficient expressing the relationship between the Doppler with both absolute AC measurements and the rate of AC growth with time.

Results: 16 women were studied, comprising 70 scans. There was a negative correlation between umbilical artery PI z-score and AC z-score (Spearman correlation coefficient=-0.367; p=0.0008) and a positive correlation between MCA PI z-score and both z score AC and rate of AC growth. No relationship was observed between z score DV PI and either z-score AC or z-score AC growth.

Conclusions: We report the mathematical relationship between fetal arterial and venous Doppler PI and the degree of fetal growth restriction and fetal growth rate as assessed by z-scores, using a new technique for longitudinal analysis. Though this model requires external validation, it may enable a clearer understanding of fetal physiological changes in response to progressive hypoxia and growth restriction and a more rational basis for follow up of these babies.

Introduction

Fetal growth restriction is defined as a failure to attain optimal intrauterine growth. Most cases are secondary to utero-placental insufficiency, which leads in a stepwise though not predictable way to fetal hypoxia, acidaemia and-if delivery does not take place-intra uterine demise.

Doppler provides a means of directly assessing the increases in vascular impedance in the fetal circulation, and thus indirectly inferring the degree of fetal hypoxia (3,4) often as a result of placental insufficiency. Pregnancies exhibiting absent or reversed end-diastolic frequencies within the umbilical artery have reduced placental weights, vascularisation and cross sectional diameter of the terminal villi as compared to unaffected pregnancies (ref). . Meta-analysis of Doppler ultrasonography of the umbilical artery in high-risk pregnancies demonstrated a significant reduction in the number of antenatal admissions, induction of labour, Caesarean sections for fetal distress and perinatal deaths in the Doppler group (19). For this reason high risk pregnancies complicated by fetal growth restriction are frequently monitored by umbilical artery waveforms studies.

Placental insufficiency results in compensatory haemodynamic changes in the fetus (6) with shunting of blood flow to essential vital organs such as the brain, myocardium and adrenal glands (12,13). These changes are seen by Doppler studies within the fetal circulation, such that in the brain, reduced resistance and increased blood flow velocity is observed in the internal carotid and middle cerebral artery and a decreased flow in the descending thoracic aorta (16, 17). One such response is the "brain sparing effect", resulting in increased blood flow to the brain, at the expense of the fetal liver (and its glycogen stores), and deposition of fat. The net result is of growth restriction, with diminished fetal ability to cope in a potentially acidotic, hostile intrauterine milieu, and the demanding challenges of labour. Portal blood flow is primarily shunted to the right lobe of the liver whilst the left lobe receives blood from the umbilical vein. Oxygenated blood from the left hepatic vein flows into the ductus venosus across the foramen ovale and the left atrium (18).

Timely detection of such fetuses is aided by the recognised pattern that Doppler velocimetry abnormalities generally affects different vessels in a sequential fashion. Early Doppler abnormalities are first noted in the middle cerebral Artery PI followed by umbilical artery absent-end diastolic flow; later changes include reverse umbilical Artery flow and ductus venosus reverse flow (8). Efforts have been made to describe the temporal changes in fetal Doppler as a progressive stepwise deterioration (11). Stage I comprising of abnormal umbilical artery or middle cerebral artery PI; stage II, abnormal middle cerebral artery peak systolic velocity, umbilical artery absent/reversed diastolic flow, umbilical vein pulsation and an abnormal ductus venosus pulsatility index; and stage III, reversed flow at

the ductus venosus or reversed flow at the umbilical vein, an abnormal tricuspid E wave and tricuspid regurgitation.

To date, the correlation between the degree of fetal arterial and venous Doppler abnormality (umbilical, middle cerebral artery and ductus venosus Doppler PI) and growth restriction, remains undefined. The difficulty with this type of analysis, probably contributing to why it has not been performed before, is that severe fetal growth restriction is relatively uncommon-therefore few cases will have multiple Doppler and growth points, and all will be at different gestations. No one case can easily be compared to another. Few statistical techniques allow robust analysis of this type of data, as measurements from the same case are clearly not independent.

Functional linear discriminant analysis (FLDA), is a new statistical technique recently applied to biomedical statistical analysis (Bottomley,Habayeb) appropriate to longitudinal data of this sort. FLDA is an extension of classical linear discriminant analysis (LDA) to longitudinal data (James and Hastie, 2001). LDA aims to predict membership of two or more mutually exclusive groups from a set of predictor variables. It is used to determine which variables discriminate between these naturally occurring groups, with maximum separability aimed for between the two groups. FLDA uses curves (instead of one-dimensional variables) as predictor variables, distinguishing between classes by maximizing the ratio of the between-class variation to the within-class variation. FLDA is particularly useful where only fragments of the curves are observed. Individuals, parameterized with a four- or five-dimensional coefficient vector (corresponding to spline curves), are used to estimate the mean coefficient vector of each class. The dimension chosen depends on the complexity of the relational curve.

A more precise knowledge of the sequence of these Doppler changes would enable a more informed guidance as to the timescale of deterioration of these babies. It would also assist clinical management and ultrasound surveillance in these pregnancies. The aim of this study is therefore to establish whether a relationship exists between commonly measured arterial and venous Doppler parameters, fetal growth and growth rate in babies with severe early onset fetal growth restriction undergoing routine monitoring and follow up.

Patients:

Between 2003-2007 patients with severe early onset Fetal Growth Restriction were examined at the time of tertiary level referral to a specialist fetal medicine unit and data collected prospectively. Inclusion criteria were those with an estimated fetal weight below 500g at 24 weeks gestation, and umbilical artery PI >95th centile. In none was there proven or suspected genetic, chromosomal or infective aetiology.

Sixteen cases comprising 70 scans were included in the study, which was registered as an ongoing clinical audit with the Hospital Trust. The data were recorded on a separate database with restricted access on the hospital server, and all anonymised prior to analysis. Serial umbilical artery, MCA and ductus venosus Doppler and abdominal circumference measurements were performed and recorded on a fetal medicine database (Astraia GMBH, Munich, Germany) as part of routine clinical analysis.

Data from X subjects undergoing ultrasound scans after 24 weeks whose pregnancies were otherwise considered as healthy, where the fetal AC was >10th percentile for gestation and where umbilical artery Doppler was recorded were recorded.

Materials and Methods

In this study, abdominal circumference (AC) and the change of AC within the first trimester (dAC/dt) were considered with respect to the Doppler indices umbilical artery pulsatility index (UA PI), ductus venosus pulsatility index (DV PI) and middle cerebral artery pulsatility index (MCA PI). We did not work on the raw data itself, but used z-scores, defined as the difference between the observed and expected quantity, expressed in standard deviations.

Statistical Analysis:

The following steps were followed:

1. Scatter plots

Initially, scatter plots of our data were constructed, superimposed on the normal charts of Chitty AC ( ) and of Parra-Cordero ( ) for the Doppler indices, all shown as mean, 5^{th} and 95^{th} centile.

2. Conversion of fetal Doppler PI indices to gestation normalized 'z' scores.

For the Doppler indices, the z-scores were calculated with respect to the expected Doppler values in normal pregnancies after log- or square-transformation of the indices (Parra-Cordero ref).

3. Conversion of abdominal circumference values to gestation normalised 'z' scores

The change in AC over time (dAC/dt) was calculated as the difference in AC between two consecutive scans divided by the number of days between these two scans. This means that a linear growth between two scans was assumed due to lack of any other growth evidence. In the analyzes the calculated dAC/dt values were used as data points available at the gestational age in the middle between the two time points at which the two consecutive scans were performed. For both AC and dAC/dt, z-scores were calculated with respect to expected size in normal pregnancies according to Chitty et al.

4. Scatter plots z-scores UA PI, MCA PI and DV PI

To derive the relationships between size and the Doppler indices in severe growth restricted fetuses, we first applied a cross-sectional approach on the corresponding z-scores. The Pearson correlation coefficient (requiring a normal distribution for both variables that are compared) and the Spearman correlation

coefficient (a non-parametric correlation coefficient, assuming no specific distribution) were calculated for all relationships we wanted to investigate. However, for the majority of women, data from multiple scans were available. We included all data, neglecting possible co-dependencies between data obtained from the same woman at multiple time points during pregnancy.

5. FLDA curves and coefficients for the relationships

To correct for this co-dependency, a similar cross-sectional approach can be followed in which data from only one randomly chosen scan per woman is included for the calculation of the correlation coefficients, and repeating this procedure a sufficient number of times, each time with a different combination of data points randomly selected from the subjects. The disadvantage of this approach is data-loss, especially for DV PI as this Doppler index was not measured in all women. Due to the limited number of data points able to include in this method, it can be expected that the correlation coefficients found to be significant with the previous approach are not significant anymore with this method.

To be able to include all available data points for not diminishing the strength of our data set, and to take the co-dependency between scans of the same subject into account, we applied FLDA on our data set of severe growth restricted fetuses to obtain a mean coefficient vector or curve for each considered relationship between size and Doppler Pulsatility index.

As the FLDA technique is sensitive to the most extreme points according to the x-axis (i.e., z-score AC or z-score dAC/dt), the portion of the FLDA curves that is reliable was defined using the concept of robust bivariate boxplots (Zani et al, 1998). First, the 50% convex hull was determined, which is defined as the biggest hull containing not more than 50% of the data and which can be considered as a two-dimensional extension of the interquartile range of the univariate boxplot. Subsequently, a robust bivariate centroid was derived from the inner 50% of the data. Finally, a cut-off at each end of the FLDA curves was determined, encompassing 95% of the data points, except for DV PI for which we chose the 90% range due to the low number of data points available.

We converted each relational curve within the 95%-range into the 'FLDA coefficient', defined as a correlation coefficient based on all the individual curves of the subjects. First, applying FLDA results in spline curves fitted through all data points belonging to each individual subject. The median number of data points per subject was calculated (x) and subsequently, x data points were randomly selected from each individual curve, resulting in x times N data points with N the number of subjects in the data set. Finally, the Spearman correlation coefficient was calculated for these data points. The random selection of x data points from each curve was repeated 1000 times due to the variance on the

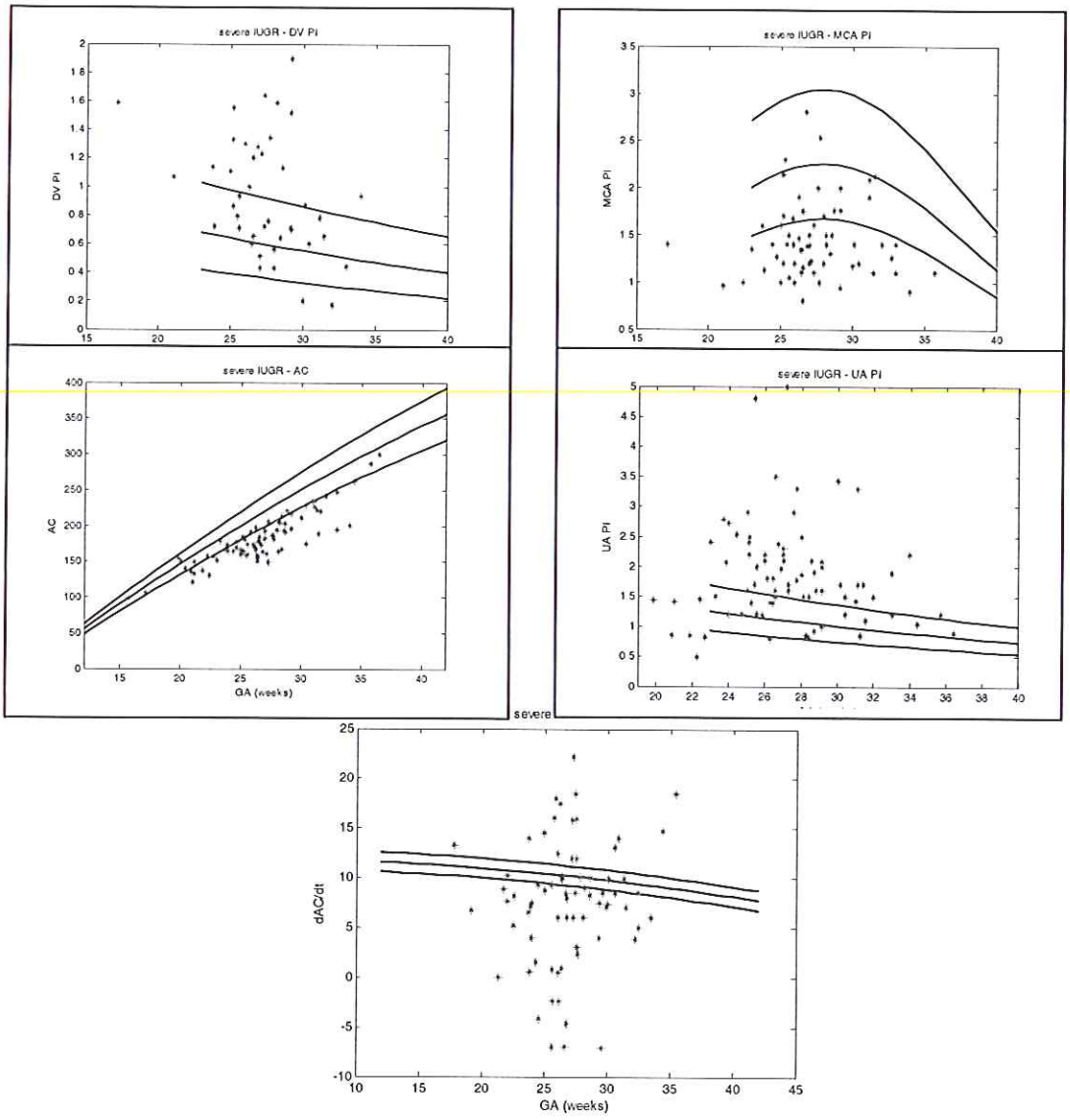
correlation coefficient when different data points along the curves are chosen. The median correlation coefficients and p-values are reported.

6. Threshold

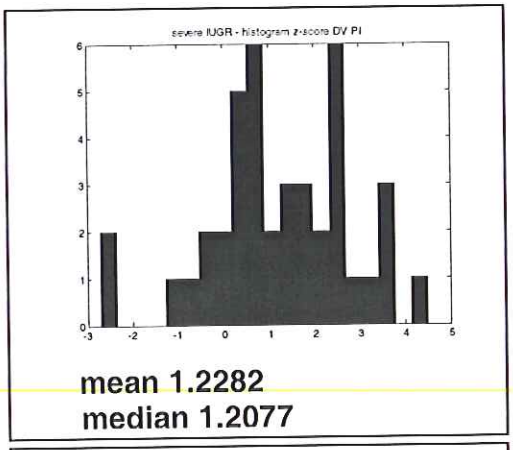
For the variables for which a significant relation was identified, we determined the threshold below which this relation was most significant. At different z-score threshold values, the FLDA correlation coefficient was calculated as the median correlation coefficient across 1000 samplings of data points below the threshold z-score.

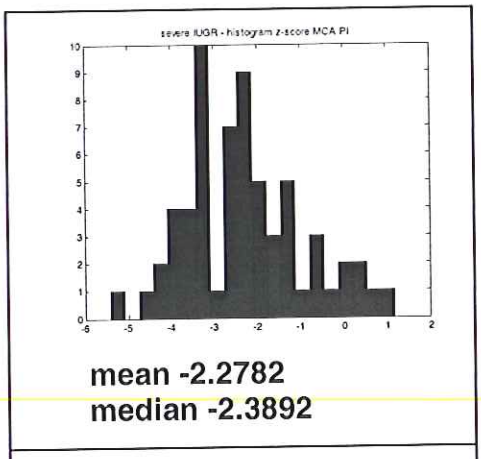
Results

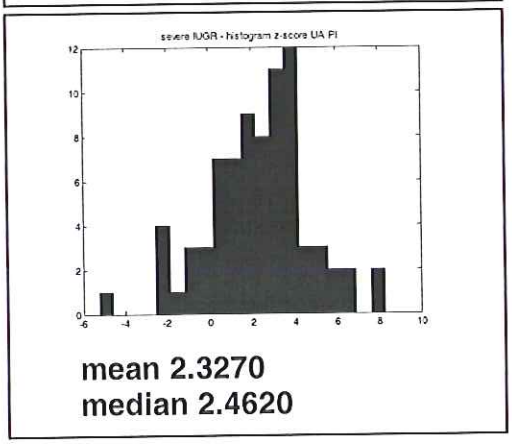
1. Scatter plots

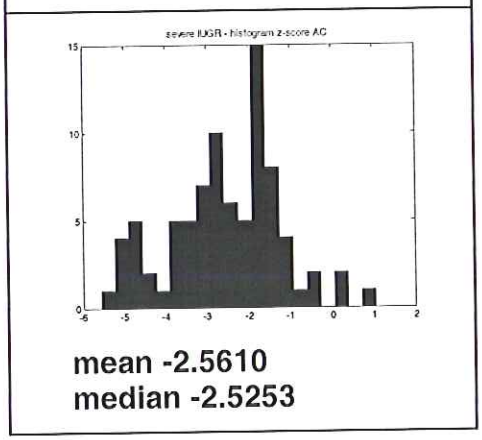


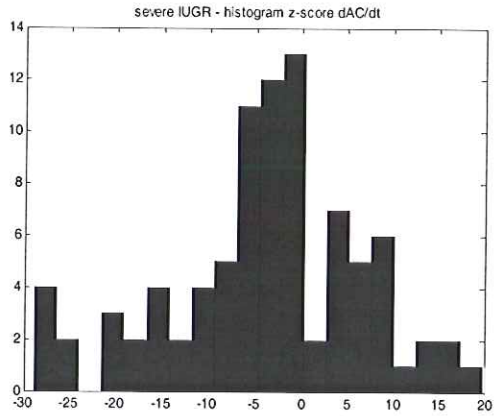
2 & 3. Conversion of fetal Doppler PI indices to gestation normalized 'z' scores, and conversion of abdominal circumference values to gestation normalised 'z' scores







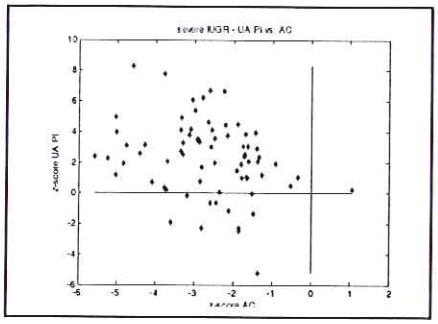




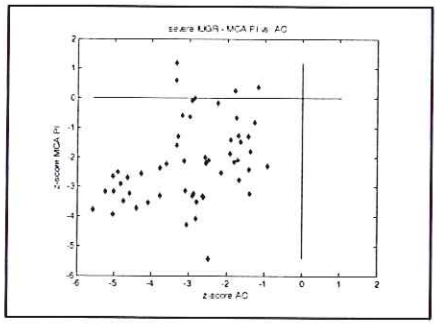
mean -3.9948; median -3.1042

4. Scatter plots z-scores UA PI, MCA PI and DV PI

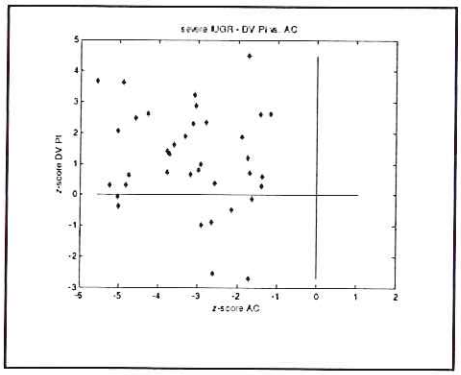
For absolute size (AC), a significant correlation was obtained for MCA PI and UA PI. We confirmed that this correlation is specific to severe early onset fetal growth restriction, as correlation was not present in the data from our normal subjects. Concerning growth (dAC/dt), DV PI was significantly correlated.



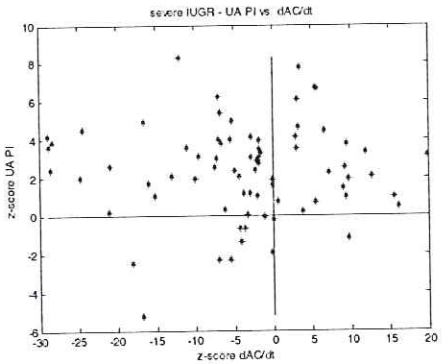
n=72	corr. coeff.	p-value
Pearson	-0.2789	**0.0177**
Spearman	-0.2927	**0.0129**



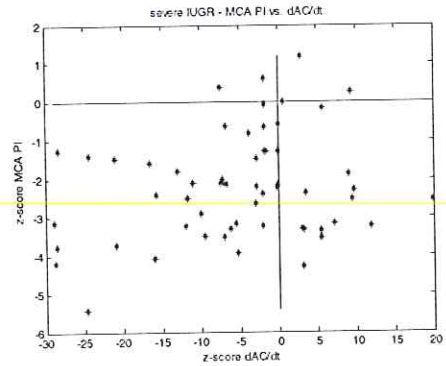
n=55	corr. coeff.	p-value
Pearson	0.3751	**0.0048**
Spearman	0.3937	**0.0031**



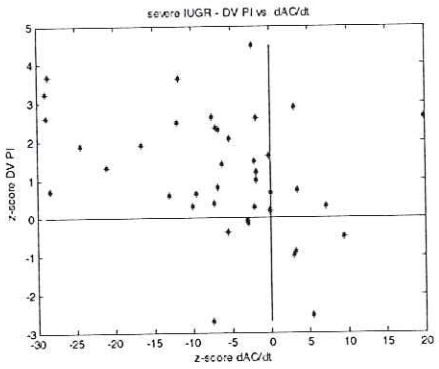
n=37	corr. coeff.	p-value
Pearson	-0.1511	**0.3720**
Spearman	-0.1491	**0.3770**



n=77	corr. coeff.	p-value
Pearson	0.0261	**0.8218**
Spearman	-0.0196	**0.8655**



n=58	corr. coeff.	p-value
Pearson	0.2353	**0.0754**
Spearman	0.1540	**0.2478**



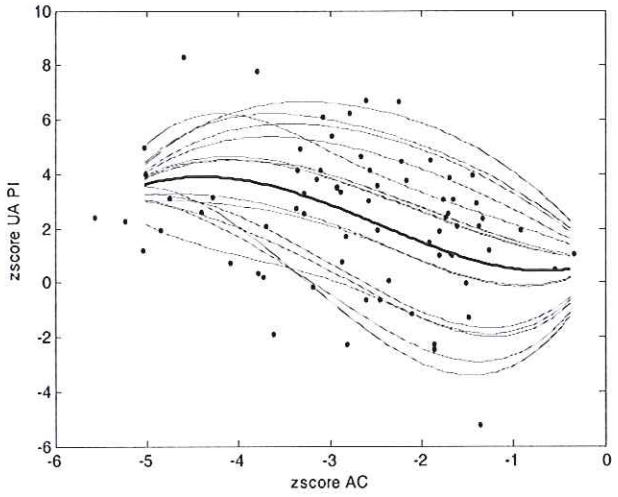
n=40	corr. coeff.	p-value
Pearson	-0.3375	**0.0332**
Spearman	-0.3531	**0.0260**

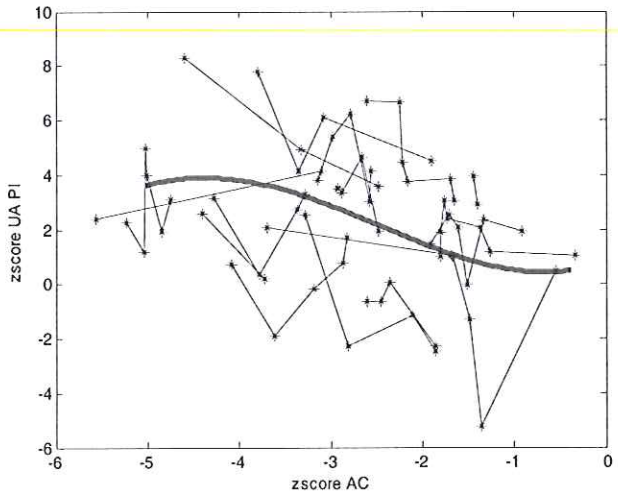
40

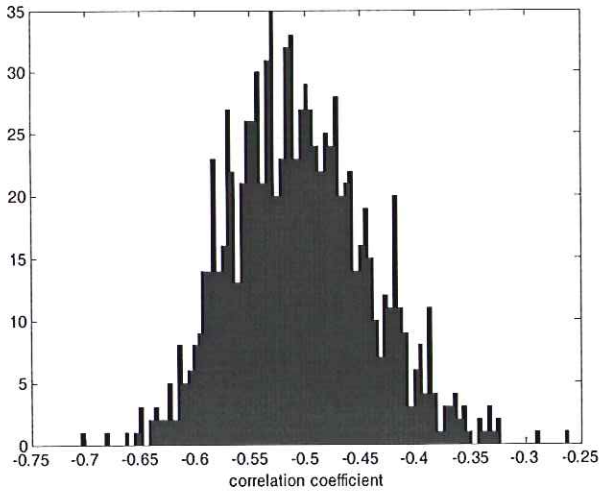
5. FLDA curves and coefficients for the above relationships

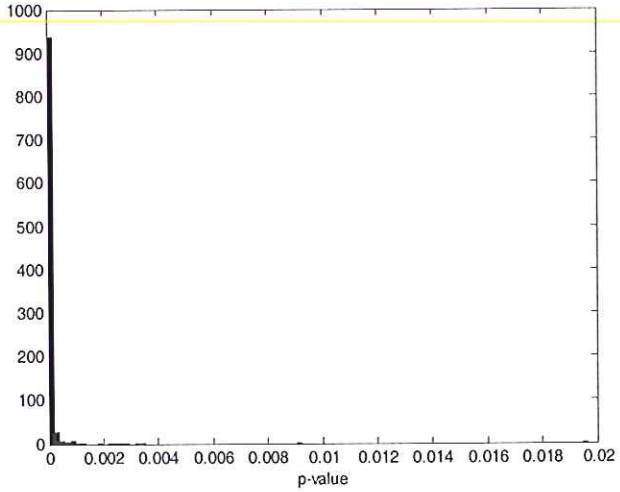
The relationships between Doppler indices and size or change in size over time expressed as z-scores were analysed using Functional Linear Discriminant Analysis (FLDA). For each relationship, the individual FLDA curves were converted to an FLDA coefficient as explained in the methods and histograms of the correlation coefficients obtained in the 1000 samplings is shown together with the mean p-value. A significant relationship was found between UA PI and AC (correlation coefficient -0.5080; p-value 1.51e-6), between MCA PI and AC (correlation coefficient 0.9865; p-value 2.44e-47) and between MCA PI and dAC/dt (correlation coefficient 0.7758; p-value 7e-10).

UA PI: **z-score PI vs z score AC and z-score d(AC)/dt**

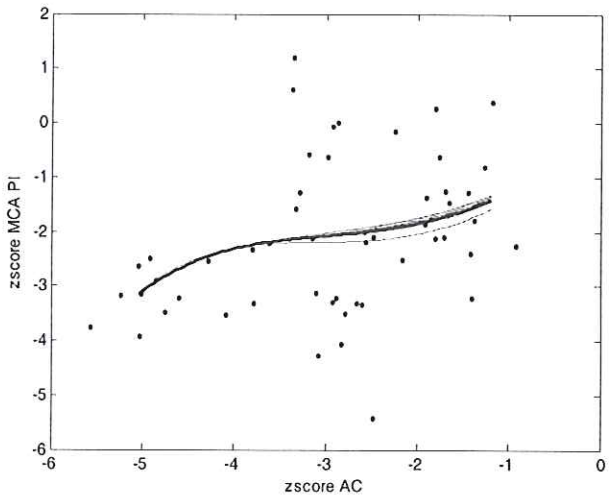

zscore UA PI
zscore AC
10
8
6
4
2
0
-2
-4
-6
-6
-5
-4
-3
-2
-1
0

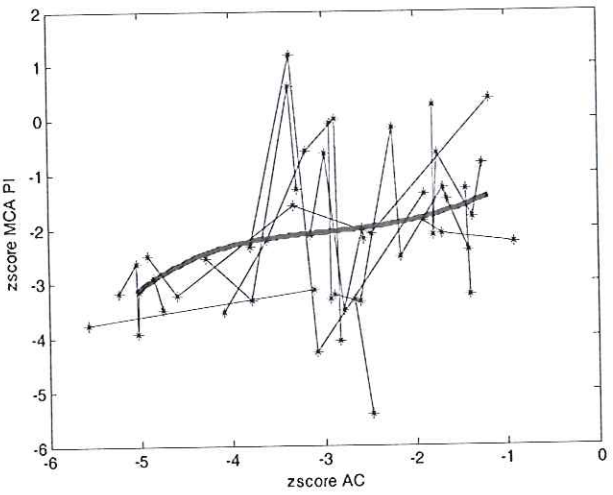

zscore UA PI
zscore AC
10
8
6
4
2
0
-2
-4
-6
-6
-5
-4
-3
-2
-1
0

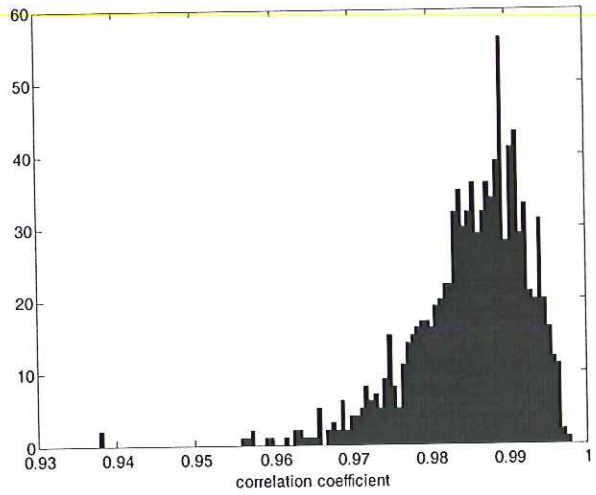

35
30
25
20
15
10
5
0
-0.75 -0.7 -0.65 -0.6 -0.55 -0.5 -0.45 -0.4 -0.35 -0.3 -0.25
correlation coefficient

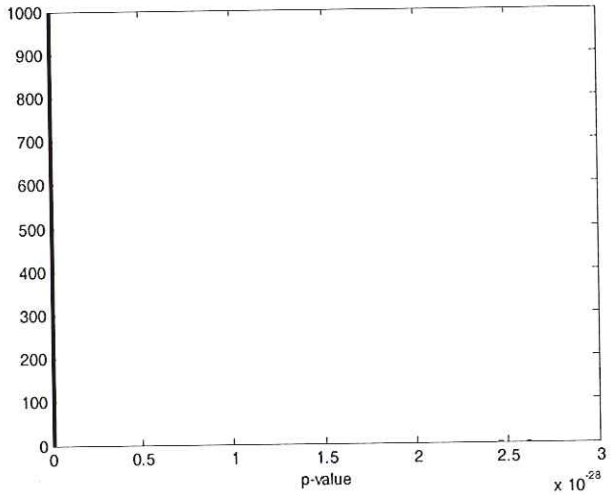

1000
900
800
700
600
500
400
300
200
100
0
0 0.002 0.004 0.006 0.008 0.01 0.012 0.014 0.016 0.018 0.02
p-value

MCA PI: z-score PI vs z score AC

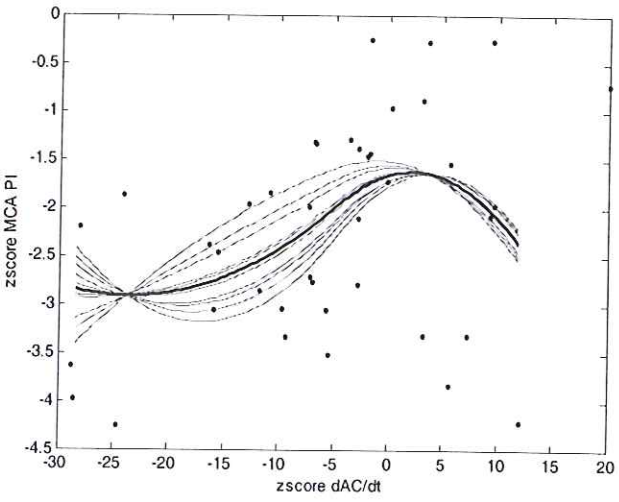


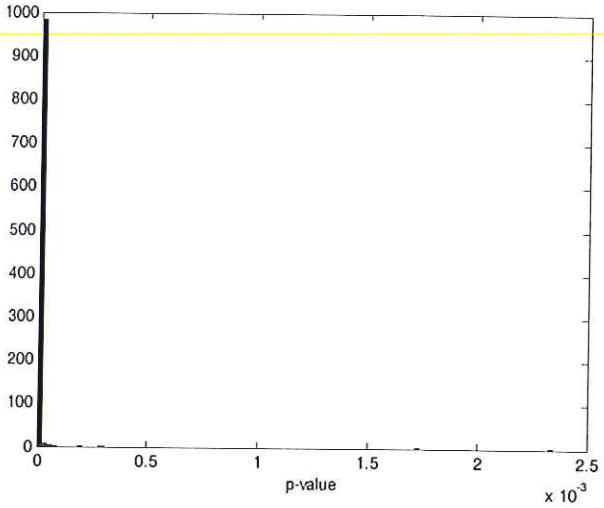




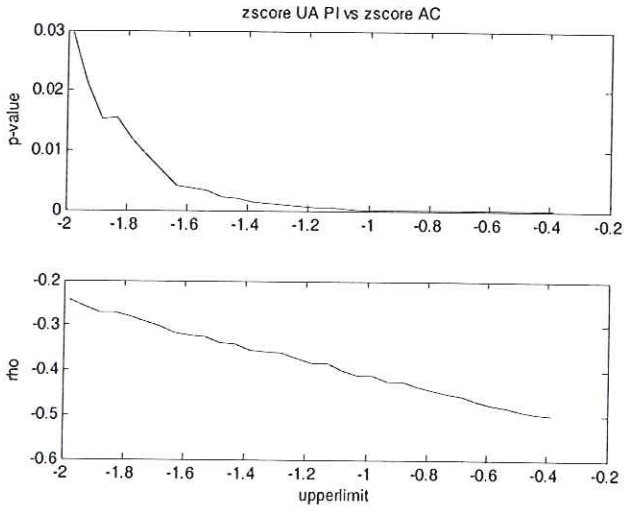


MCA PI: z-score PI vs z-score d(AC)/dt


zscore MCA PI
zscore dAC/dt

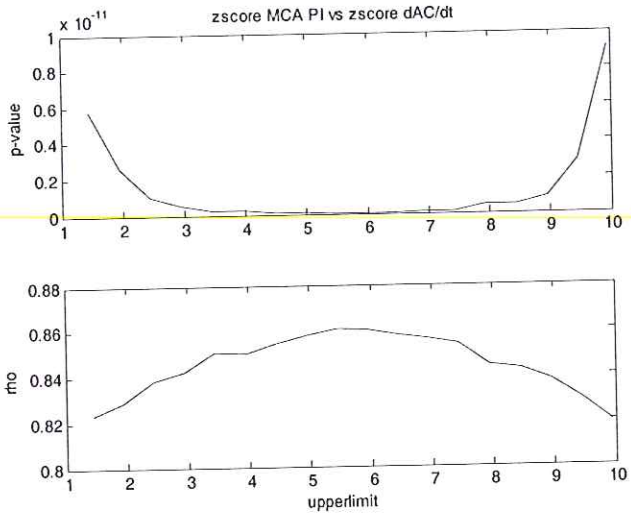

p-value
x 10^-3

6. Threshold


zscore UA PI vs zscore AC
p-value
rho
upperlimit

For z-score UA PI versus z-score AC, the most significant relation is obtained with an upper limit on z-score AC of -1 (-1 or higher). Below -1, the correlation coefficient increases towards zero and becomes less significant, due to a reduction in the length of the piece of the curve with the highest correlation coefficient (in absolute value), in the interval from -1 to -4.5.

The relation between z-score MCA and z-score AC was not investigated because it is clear from the graph that no real cut-off exists for this relationship. There is a monotone decrease in z-score MCA with decreasing z-score AC.



For z-score MCA versus z-score dAC/dt, the threshold as upperlimit on z-score dAC/dt was found to be between 5 and 6, at which the correlation coefficient was largest with the most significant p-value. The exact threshold value slightly varied across different runs of 1000 samplings.

Discussion

These data show a strong and highly significant negative correlation between the z-score of umbilical artery pulsatility index and positive correlation between z-score of the middle cerebral artery pulsatility index with z-score abdominal circumference (AC). Further, by examining growth rate (z-score d(AC)/dt), there is a correlation with slowing fetal abdominal growth being associated with a reduction in the MCA Pulsatility index. These relationships are biologically plausible in that one would expect an increase in umbilical PI as a baby becomes progressively more growth restricted and the converse for middle cerebral artery PI. Importantly in normal babies (AC>5th percentile), no relationship between z-score umbilical artery PI and z-score d(AC)/dt exists; biologically plausible as Doppler indices show the strongest relationship with fetal hypoxia-very unlikely in babies that are normally grown. Further analyses of these data suggest that there is, as one might expect, a 'threshold effect for these relationships to hold. The FLDA curve appears to reliably delineate the relationships between two thresholds-one presumably relating to the onset of hypoxia in the fetus at which an association between the Doppler and size/growth rate variables appears to start, and a second threshold at which the curve becomes unreliable because of too few data points. The latter problem is partially overcome with by using robust bivariate boxplots, defining the 'reliable' data range within which the FLDA curve is constructed

That no relationship is seen for ductus venosus z-score PI with either z score abdominal circumference or its rate of growth, or umbilical artery z-score PI and z score abdominal circumference growth rate does not mean that a relationship does not exist. The FLDA curves are derived from a relatively small number of cases, and more robust relationships would be likely to be generated from more subject data particularly as the error from multiple Doppler and abdominal circumference measurements would be likely to become less important.

Previous studies have however attempted to classify babies exhibiting abnormal Doppler patterns in relation to growth cut-offs (Mari, Gudmundssen).The mathematical relationship between Doppler arterial and venous impedance changes with fetal size and growth rate in IUGR has not previously been characterized. A difficulty in doing this was that these changes occur at different gestations, and the Doppler ranges differ with gestation; By normalizing all data for gestation using z-scores, this problem is overcome. There is a further problem which is that of not assuming data points from multiple examinations of the same fetus are independent, without losing statistical power. This is overcome by using FLDA-recently applied to biomedicine-which treats each subject's measurements as a separate curve-and it is these curves that are then combined-preventing bias from single cases, for example, with multiple observed points. Interestingly,

however, the results with FLDA confirm what we found with the cross-sectional approach based on correlation coefficients taking no account of co-dependency.

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Once fetal growth restriction is diagnosed, obstetric management is pivoted between preterm delivery, with its known sequelae; or allowing fetal intrauterine maturation and risk of demise in a potential harmful environment (15). Whilst it is recognised that the severe growth restricted fetus below 30 weeks of gestation has a significant decrease in perinatal mortality for each week it remains in utero, striking the balance between delivery and surveillance poses a critical obstetric challenge (5). Early diagnostic markers of incipient fetal growth restriction and potential compromise may allow for pre-emptive timely management of such cases and potential stratification of the risks involved. The timing of delivery is primarily driven by abnormal fetal heart rate (cardiotocography) recordings in combination with fetal Doppler abnormalities and fetal biometric parameters. By the time the cascade of events lead to such abnormalities, approximately 75% of fetuses are compromised by hypoxia and acidosis(9,10).Iatrogenic preterm delivery is associated with neurodevelopmental delay and cerebral palsy (14). Despite the fact that umbilical artery reversed end-diastolic flow is in independent contributor to poor neurodevelopment; quantitating the risk versus benefit of delivery and increased surveillance has yet to be elucidated.

In summary, we demonstrate a negative relationship between umbilical artery PI and a positive relationship between middle cerebral artery Doppler PI measurements with increasing growth restriction and middle cerebral artery PI with reduced fetal growth rate. Previously, birth weight z-scores examined prospectively have been shown to be the strongest predictor of adverse neonatal outcomes in pregnancies complicated by severe placental insufficiency (7). We have not attempted to correlate outcome with Doppler findings in this study. What is clear however, is that at a certain point on the curves, the relationship between umbilical and MCA PI and abdominal circumference starts; this is at a z-score of -1, and the mid point of both curves is around -3. For umbilical PI, threshold modelling suggests that the relationship is strongest between AC z-score -1 and -4.5 This information is potentially useful in understanding at what point Doppler ultrasound of these vessels is likely to start to become informative. Conversely, the data suggest that if the fetal AC z-score is >-1, there is perhaps little information that is likely to be obtained by repeated fetal arterial Doppler investigation.

We would urge caution in applying these results to clinical practice in the assessment of the growth restricted fetus. The data are best interpreted as establishing that a relationship between fetal arterial Dopplers and growth restriction does indeed exist. These findings may be a starting point for further investigation to determine as to when and how to offer clinical follow up to these particularly vulnerable fetuses.

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