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Umbilical artery pulsatility index and fetal abdominal circumference in isolated gastroschisis

U. HUSSAIN*, A. DAEMEN†, H. MISSFELDER-LOBOS*, B. DE MOOR†, D. TIMMERMAN‡, T. BOURNE‡§ and C. LEES*‡

*Division of Fetal Medicine, Addenbrooke's Hospital, Cambridge, UK; †Department of Electrical Engineering (ESAT), Katholieke Universiteit, Leuven, Belgium; ‡Department of Obstetrics and Gynecology, University Hospitals, KU Leuven, Leuven, Belgium; §Institute of Development and Reproductive Biology (IRDB), Imperial College London, Hammersmith Campus, London, UK

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ABSTRACT

Objectives *To investigate changes in abdominal circumference (AC) and umbilical artery pulsatility index (UA-PI) with gestation in fetuses with isolated gastroschisis, and to determine whether a relationship exists between UA-PI and fetal AC.*

Methods *Data from 58 pregnancies with isolated gastroschisis diagnosed at between 24 and 36 weeks' gestation were included in the study. Z-scores were calculated with respect to expected UA-PI values in normal pregnancies after log-transformation. AC-Z-scores were calculated with respect to expected size in normal pregnancies according to a standard chart. Functional linear discriminant analysis (FLDA) was applied to generate 50th, 5th and 95th percentile curves for changes in both AC and UA-PI with gestational age in fetuses with gastroschisis. These curves were compared with the standard curves, as were the means. UA-PI was also plotted against AC. For this relationship, a robust Spearman correlation coefficient was obtained with FLDA.*

Results *In fetuses with gastroschisis, there was a highly significant negative correlation between UA-PI and AC, normalized for gestation using Z-scores (median correlation coefficient, −0.289; median* $P = 0.000023$*). Moreover, compared with standard curves AC was lower and UA-PI higher in the gestational-age range studied. Both the AC and UA-PI curves showed a significantly different rate of change with gestation compared with the normal ranges. The mean values for fetuses with gastroschisis compared with the standard AC and UA-PI range curves were significantly different for AC throughout gestation, and for UA-PI from 32 weeks' gestation.*

Conclusions *In fetal gastroschisis, it is well known that AC tends to be smaller, though UA-PI has not been reported to be abnormal in any consistent way. There is a clear relationship between the fetus's AC for gestation and UA-PI, which is not the case for normally grown fetuses. The data suggest that the growth restriction seen in gastroschisis may be explained by hypoxia, and not simply by the classical explanation of extra-abdominal displacement of the abdominal viscera. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Gastroschisis is an uncommon condition, although its prevalence is rising and it is now thought to affect 1 in 3000 pregnancies[1]. The condition is characterized by failure of the anterior abdominal wall to close; the intestine and, occasionally, other abdominal viscera are situated outside the fetal abdomen, exposed to amniotic fluid. The condition is not normally associated with other congenital defects or aneuploidy, and the outlook after surgical repair is generally good.

It has been known for many years that gastroschisis affects fetal growth, many publications reporting an association of gastroschisis with small-for-gestational-age infants. A recent study reported that 38% of affected babies were born weighing less than the 10th percentile for gestation[2]. The smallness of these babies has generally been attributed to the abdomen growing poorly on account of the lack of distension by extra-abdominal contents. More recently, the growth parameters biparietal diameter and head circumference have been shown to be symmetrically small by derivation of growth charts for babies with gastroschisis[3].

In our clinical practice, we routinely record umbilical artery (UA) Doppler parameters for babies with gastroschisis, and noticed that the UA pulsatility index (UA-PI) was frequently high in these babies. We therefore

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Correspondence to: Dr C. Lees, Division of Fetal Medicine, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK (e-mail: christoph.lees@addenbrookes.nhs.uk)

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undertook to investigate the relationship between UA-PI and change in fetal abdominal circumference (AC) in pregnant women referred for ongoing care for apparently isolated fetal gastroschisis. To do this, we normalized AC and UA-PI data for gestational age. In order to correct for codependency of repeat measurements in the same subject, we used functional linear discriminant analysis (FLDA), a statistical technique that has recently been applied to biomedicine in the context of first-trimester fetal growth[4,5].

METHODS

All women in the study had a viable ongoing pregnancy affected by fetal gastroschisis with no other prenatally identified abnormality, and were referred for ongoing care and delivery at Addenbrooke's Hospital at a variety of gestational ages. The data were recorded prospectively as part of an ongoing trust-registered clinical audit relating to fetal growth and outcome in antenatally diagnosed abdominal-wall abnormalities, and were anonymized before analysis.

Fifty-eight women were included in the study, of whom 52 had two or more scans with complete AC and UA-PI data: 10 had 2 scans, 9 had 3, 17 had 4, 10 had 5, 4 had 6, 1 had 7 and 1 had 8.

Change of AC or UA-PI with gestation

Firstly, and taking no account of data dependency, we derived scatterplots to show the relationship between AC and UA-PI and gestational age. These plots included all data points. To take the codependency between scans of the same subject into account without diminishing the strength of our data set and without having to exclude dependent data points, we subsequently applied FLDA[4]. With this technique a mean coefficient vector or curve is obtained for the considered relationship between size and Doppler index. The reliable portion of the FLDA curves was defined using the concept of robust bivariate boxplots[6].

To compare these FLDA curves with the AC and UA-PI changes in normal pregnancies, 1000 data points were randomly sampled from each FLDA curve based on its mean and SD. This means that a gestational-age value within the range 154–266 days was randomly selected, repeated 1000 times. At each gestational-age value a corresponding AC or UA-PI value was then selected from a normal distribution with mean and SD specific for the current gestational age. These data points were used for the construction of the regression curve:

$$y = a_1 + a_2\, GA + a_3\, group + a_4\, group \times GA,$$

where *group* is a binary variable equal to 0 for the normal curve and 1 for the gastroschisis curve, and *group* × *GA* an interaction term between group and gestational age to test for a difference in slope between both groups.

To confirm the results obtained by comparing the curves, a second approach was used for comparison. For the normal curve and the FLDA gastroschisis curve, a normal distribution with known mean and SD was constructed at four gestational ages (24, 28, 32 and 36 weeks), followed by a random sampling of 100 points from each distribution. The two-sample *t*-test was performed at each gestational age to verify whether the normal distribution and the distribution for gastroschisis had equal mean. The construction of the distributions, data sampling and *t*-test were repeated 1000 times.

Relationship between AC and UA-PI

The Spearman correlation coefficient was calculated for the relationship between AC and UA-PI. However, for the majority of women, data from multiple scans were available. In the first instance we included all data, neglecting possible codependencies between data obtained from the same woman at multiple time points during her pregnancy. A correlation coefficient between AC and UA-PI was calculated after transformation of the data to Z-scores. For the Doppler indices, the Z-scores were calculated with respect to the expected Doppler values in normal pregnancies after log-transformation of the indices[7]. For AC, Z-scores were calculated with respect to expected size in normal pregnancies according to the method of Chitty *et al.*[8].

We then converted the relational curve between AC and UA-PI within the 95%-range into the 'FLDA coefficient', defined as a correlation coefficient based on all the individual curves of the subjects. First we applied 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, where *n* is 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 of the correlation coefficient when different data points along the curves are chosen. Median correlation coefficients and *P* are reported.

RESULTS

Fifty-eight women were included in the study, though the FLDA dataset totalled 52 with repeat scans, in whom 204 scans were carried out. There was one intrauterine death and one termination of pregnancy; for the live births ($n = 49$) the mean birth weight was 2477 g and mean gestational age at delivery was 36 + 3 weeks.

Scatterplots of AC and UA-PI in relation to gestational age are shown in Figures 1 and 2, superimposed on the normal charts of Chitty *et al.*[8] for AC and of Parra-Cordero *et al.*[7] for the Doppler indices, all shown as mean, 5th and 95th percentiles.

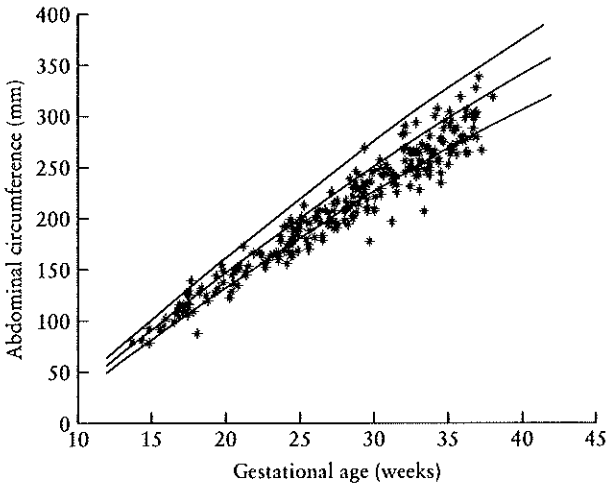

Figure 1 Scatterplot of abdominal circumference (AC) against gestational age in fetuses with gastroschisis, superimposed on the normal AC chart (5th, 50th and 95th centiles) of Chitty *et al.*[8].

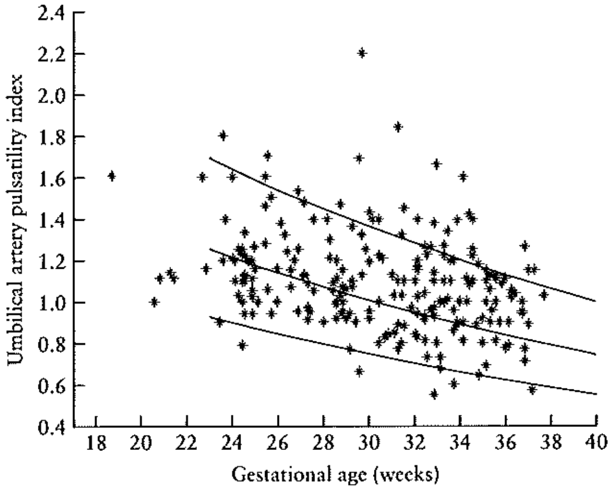

Figure 2 Scatterplot of umbilical artery pulsatility index (UA-PI) against gestational age in fetuses with gastroschisis, superimposed on the normal UA-PI chart (5th, 50th and 95th centiles) of Parra-Cordero *et al.*[7].

The 5th, 50th and 95th percentile curves obtained with FLDA are shown in Figures 3 and 4 and are superimposed on standard graphs in normal usage. As statistically proven below, the percentile lines in all cases fall significantly below those for the corresponding normal population for AC, and significantly above for UA-PI from 32 weeks onwards.

Abdominal circumference

For AC, the interaction term between group and GA was significant ($P = 0.0006$), indicating a significantly slower growth in the gastroschisis group. Significance remained with a decrease in the number of sampled data points to 100. For a direct comparison of AC in normal pregnancies and gastroschisis at the four gestational age points 24, 28, 32 and 36 weeks, the median P-values and their interquartile range after Bonferroni correction for multiple testing remained significant when at least 20 points were sampled at each gestational age.

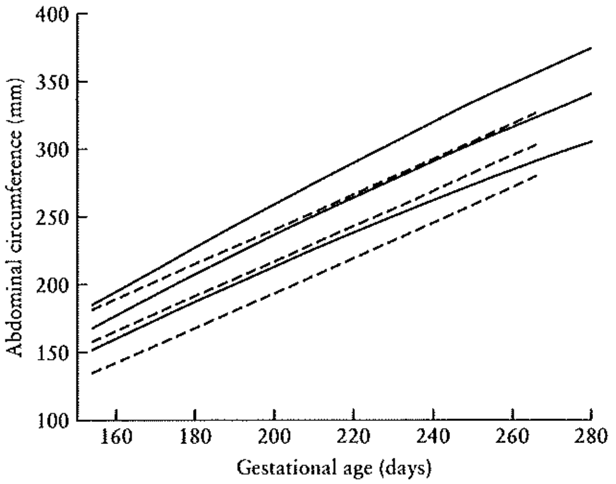

Figure 3 Functional linear discriminant analysis curve for abdominal circumference (AC) against gestational age with 5th, 50th and 95th centiles (- - -) in fetuses with gastroschisis and normal AC chart of Chitty *et al.*[8] with 5th, 50th and 95th centiles (——) (SE, 14.27 mm).

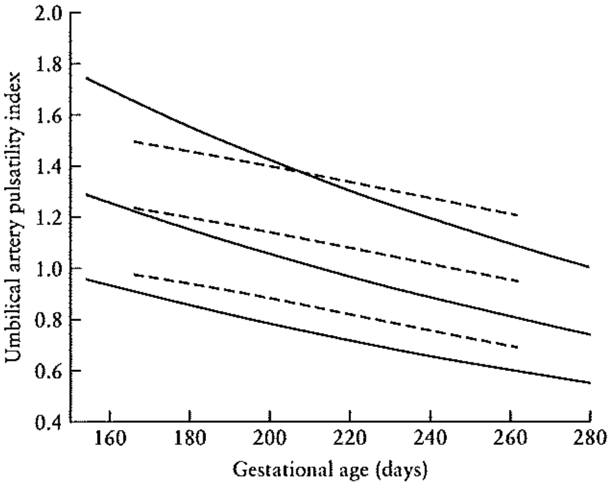

Figure 4 Functional linear discriminant analysis curve for umbilical artery pulsatility index (UA-PI) against gestational age with 5th, 50th and 95th centiles (- - -) in fetuses with gastroschisis and normal UA-PI chart of Parra-Cordero *et al.*[7] with 5th, 50th and 95th centiles (——) (SE, 0.157).

Umbilical artery pulsatility index

For UA-PI, the interaction term was significant ($P < 0.0001$), indicating a significantly slower decrease in the gastroschisis group. The group term was also significant ($P < 0.0001$). Significance remained with a decrease in the number of sampled data points to 100. For direct comparisons at 24, 28, 32 and 36 weeks, the median P-values and their interquartile range after Bonferroni correction were significant from 32 weeks on when at least 50 points were sampled at each GA.

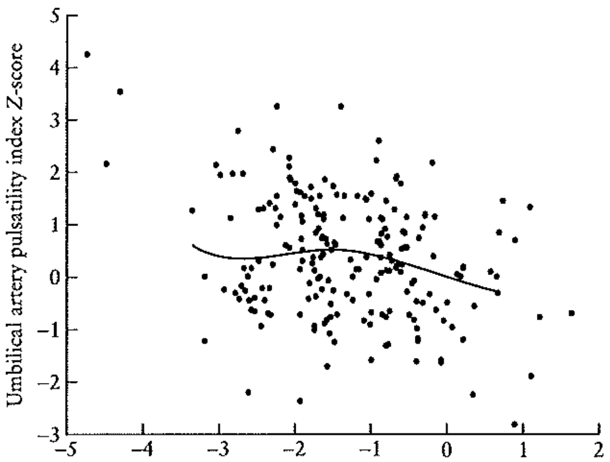

Figure 5 Scatterplot of the relationship between umbilical artery pulsatility index and abdominal circumference Z-scores with functional linear discriminant analysis curve (line).

Following conversion of UA-PI and AC data to Z-scores, mean UA-PI Z-score was 0.410 and median Z-score was 0.363; mean AC Z-score was −1.172 and median Z-score was −1.173. For the relationship between UA-PI and AC, the Spearman correlation coefficient was −0.241 ($P = 0.00049$). Applying the FLDA technique to 95% of the AC Z-score range on the other hand resulted in a median correlation coefficient for the relationship between UA-PI and AC of −0.289, with a median P of 0.000023 (Figure 5).

DISCUSSION

This study, in common with other studies – most notably that of Netta *et al.*[3] – shows that AC is systematically smaller in babies with gastroschisis. Those authors concluded, however, that fetal growth in gastroschisis was of a symmetrically small pattern. We do not concur: it is evident from closer examination of the AC chart and those for biparietal diameter, head circumference and femur length that they report that all these measurements are already small for gestational age at 18–20 weeks. However, fetal growth by AC deviates progressively away from the 10th percentile. It is important to note that the charts generated in the study of Netta *et al.*[3] appear to have been developed from 'raw data', not taking into account codependency. The charts that we derived using FLDA – to correct for codependency – do in fact show a similar pattern, though not as extreme.

UA-PI was consistently significantly higher in babies with gastroschisis than the normal range. This was unexpected and has not previously been reported, though abnormal appearance of the UA waveform has[9]. It has previously been hypothesized that fetal death seen in the third trimester of pregnancy may be associated with bowel dilatation leading to UA compression[10]. This is unlikely to be the mechanism underlying the persistently increased UA-PI seen in this study, as only a small proportion of the pregnancies were affected by extra-abdominal bowel dilatation.

Raised UA-PI implies fetal hypoxia, and it may be that babies with gastroschisis are chronically hypoxic. This would explain both the raised UA-PI seen, and the fetal growth restriction reported[3,11]. Moreover, this would be consistent with one theory of the development of gastroschisis, namely vascular disruption[12,13], though this theory is thought to only partially explain its etiology[14]. Furthermore, there is a strong association between low maternal body mass index, young maternal age and the risk of gastroschisis, and the same characteristics are also associated with fetal growth restriction[15].

Although this study cannot do more than raise theories as to the etiology of the condition, the strong and highly significant negative correlation between UA-PI Z-score and AC Z-score does indicate the possibility of underlying fetal hypoxia. UA-PI would always be expected to be normal in an otherwise normal, normoxic baby. These data suggest that this is frequently not the case in gastroschisis. Furthermore, there is a correlation between small fetal AC and high UA-PI.

Given these findings, we believe that gastroschisis constitutes a separate phenotypic entity, especially since these pregnancies have a high rate of intrauterine demise. The temporal relationship between UA-PI and fetal growth restriction is undoubtedly more complex than can be inferred from this study, as by comparing Z-scores, time is removed from the comparison. Whether the results of ultrasound examinations undertaken for monitoring according to several published protocols[3,16] should be compared to population 'normal' ranges for growth and Doppler indices is a moot point, but these fetuses perhaps should not be considered as variants according to a 'normal' curve for AC and UA-PI.

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