**Is cardiomegaly an indication of ‘heart-sparing effect’ in small fetuses?**

**Running Title:** Cardiomegaly in Fetal Growth Restriction

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**ABSTRACT**

**Introduction**: To test the hypothesis that cardiac size is maintained in small fetuses presenting with cardiomegaly.

**Material and Methods**: We identified singleton fetuses with estimated fetal weight less than 10th centile and with cardiomegaly without another more likely cardiac or extra-cardiac cause. We used Z-scores for cardiac and thoracic circumferences normalized for gestational age (GA), biparietal diameter (BPD), head circumference (HC) and femur length (FL), obtained from 188 normally grown fetuses.

**Results**: When comparing chest size, small fetuses had significantly lower thoracic circumferences median Z-scores (IQR) for GA= -4.82 (-6.15 to -3.51), BPD= -2.42 (-4.04 to -1.48), HC=-2.72 (-4.53 to -1.90) and FL= -1.60 (-2.87 to -0.71); *P*< 0.001 for all. When comparing heart size, small fetuses showed lower cardiac circumferences median Z-scores (IQR) for GA= -1.59 (-2.79 to -0.16); *P* =<0.001; but similar cardiac circumferences Z-scores for BPD =0.29 (-0.65 to 1.28); *P*=0.284 and HC=0.11 (-1.13 to 0.96); *P*=0.953; and higher cardiac circumferences Z-scores for FL= 0.94 (-0.05 to 2.13); *P*<0.001.

**Conclusions:** Our results show that in small fetuses with cardiomegaly, the heart maintains normal dimensions when normalized to cranial diameters and higher dimensions when normalized to long bones. This provides insight on cardiac adaptation to adverse intrauterine environment.

**INTRODUCTION**

Fetal cardiomegaly has a distinctive sonographic appearance that easily draws the attention of examiners during screening obstetric scans as subjectively, cardiac size is compared to thoracic size. Cardiomegaly has been defined by a cardio-thoracic circumference ratio (CTR = heart /chest circumference at the four-chamber level >95th centile for gestational age (GA)) [1]. Cardiomegaly has various etiologies carrying a diversity of fetal outcomes, but is predominantly cardiac in origin, either structural or rhythm abnormalities [2]. However, several extra-cardiac anomalies can be associated with cardiomegaly, which in turn can be the first sign of an extra-cardiac fetal abnormality [3]. Non-cardiac causes include fetal anemia, extra-cardiac malformations (lung abnormalities, kidney malformations and skeletal dysplasia), placental and fetal vascular tumors, arterio-venous malformations, twin-twin transfusion syndrome, twin anemia-polycythemia sequence and congenital infection.

Cardiomegaly is also a common ultrasound finding in growth-restricted fetuses and recently, has been associated with adverse outcomes in children at primary school age as well as other haemodynamic parameters (absent or reverse end-diastolic flow in the umbilical artery, reverse A-wave in the ductus venosus, hydrops and low cardiovascular profile score) [4]. However, the effects of fetal growth restriction on thoracic and cardiac biometry remain largely undetermined. Miyague et al. [5] observed that after controlling for fetal weight, there are no significant differences between appropriate and small for gestational age (SGA) fetuses. Veille et al. [6] documented significantly larger heart sizes among growth-restricted fetuses compared with normally grown ones after correcting for fetal weight. Similarly, radiographic evidence of abnormally elevated CTR indices has been reported in growth-restricted neonates [7].

The aim of this study is to evaluate the significance of cardiomegaly in a population of small fetuses with no other underlying reason for cardiomegaly. We hypothesized that in small fetuses with increased CTR, heart dimensions are maintained as part of the mechanisms to preserve vital organs.

**MATERIALS AND METHODS**

*Study population*

This is a retrospective study conducted in a single tertiary referral centre for fetal medicine and fetal cardiology, between January 1997 and July 2014. Cases were identified by searching the departmental database (Viewpoint 5.6.8.428, Viewpoint Bildverarbeitung GmbH, Webling, Germany) in the Fetal Medicine and Fetal Cardiology Unit, St George’s Hospital, London.

We searched for the term ‘cardiomegaly’ in all fetal echocardiography, anomaly and growth scan reports. We also searched for all cases where the thoracic (TC) and cardiac circumferences (CC) had been measured within the same time period. Among these, we excluded all cases with structural heart disease or rhythm abnormalities. For the remaining, all available images and digital records were reviewed. When the diagnosis of cardiomegaly was based on the subjective ultrasound appearance, we measured the CC and TC by the ellipse method in a transverse section of the chest at the level of the four-chamber view. Reference points for the heart were cardiac apex and the upper edge of the atrial septum, and for the chest, the anterior thoracic wall and the posterior edge of the vertebra including the ribs and the skin [8].

We excluded all fetuses with measured CTR ≤ 95th centile for the GA (Viewpoint reference graph, Allan personal communication based on previously described data[1]) and those in whom CTR could not be measured retrospectively. Our final cohort included fetuses affected by cardiomegaly (CTR >95th centile) not explained by any other extra-cardiac aetiology, with an estimated fetal weight (EFW) <10th centile according to the locally used growth curves and for whom all necessary data could be retrieved (Figure 1).

In all cases, we recorded maternal age, gravidity, maternal height and weight and the body mass index (BMI) at booking. Data on pregnancy outcomes (date of birth, GA at delivery, method of delivery, birthweight, birthweight centile, Apgar scores at five minutes) were collected from hospital obstetric and neonatal records. GA was established by ultrasound dating by crown rump length (CRL) prior to 14 weeks of gestation. Routine fetal biometry was performed according to a standard protocol and the EFW calculated using the Hadlock IV model [9]. From the scan performed at the time of diagnosis of cardiomegaly and from the last examination before delivery or fetal demise, we recorded biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), HC/AC ratio and their corresponding centiles [10] as well as EFW and the EFW centile [11].

Pulsed wave Doppler signals of the umbilical artery (UA) and middle cerebral artery (MCA) were used to calculate pulsatility index (PI), guided by colour flow mapping according to a standard protocol, which is in keeping with current International Doppler guidelines [12]. The UA PI was considered abnormal when > 95th centile based on the reference range by Harrington et al [13].

*Reference population*

We developed Z-scores for CC, TC and CTR based on GA, FL, BPD and HC from a population of fetuses seen in our unit, whose data on CC, TC and CTR was previously published [14]. Briefly, indications for the scans included routine 20 to 23-weeks anomaly scans, growth scans and examinations for placenta localisation in the third trimester. GA was established by CRL. Inclusion criteria were singleton pregnancies with normal fetal anatomy and growth. Exclusion criteria were increased nuchal translucency in the first trimester, abnormal karyotype, congenital malformations at the initial scan or subsequent development of fetal abnormalities (structural or abnormal growth), reduced or increased amniotic fluid and maternal diabetes. A single observer performed all ultrasound examinations. Measurements were made prospectively by the ellipse method, using the aforementioned landmark points. From this dataset, complete data were available for 188 normally grown fetuses. The median GA at the examination was 22+0 weeks (range 19+2 to 41+4).

*Statistical Analysis*

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the data in the study population. Continuous data were presented as mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) if not. Normally distributed data were compared using the two sample t-test. A nonparametric analysis (Mann-Whitney U test) was used to compare skewed data. Z-scores for each fetal biometry (BPD, HC and FL) and for UA PI and MCA PI were calculated according to the previously published reference ranges [10-13].

For developing Z-scores for CTR, CC and TC, linear regression analysis was used to test the associations of CC, TC and CTR with GA, BPD, HC and FL in the normally grown fetuses. The assumptions underpinning the linear regression analysis were checked by inspection of regression diagnostic plots, and suitable transformations of the variables were made. Z-scores were calculated in a two-stage process:

1. Predicted cardiac or thoracic measurement: = m\* biological measurement or GA + c;

2. Z-score: (observed - predicted cardiac or thoracic measurements)/root MSE,

where c is the intercept, m is a multiplier and MSE is mean squared error from the appropriate regression equation. All variables had very strong correlations to CC and TC with R-squared values greater than 0.9 for all associations (p<0.001 in all cases). The CTR showed a statistically significant relationship with all measurements, but the associations were much weaker than when measuring heart and chest sizes separately, with all R-squared values less than 0.1 (*P*<0.001 in all cases). By using the same linear regression analysis, CC, TC and CTR Z-scores for GA and for BPD, HC and FL were calculated in our cohort of small fetuses. In the supplementary material the equations for CC, TC and CTR Z-scores calculations are reported.

SPSS version 20 was used for statistical analysis.

S. Salvi and J.S. Carvalho had full access to all the data in the study and takes responsibility for its integrity and the data analysis

**RESULTS**

The analysis comprised 54 fetuses with cardiomegaly not explained nor by cardiac structural or rhythmic abnormality or by extra-cardiac etiology and with EFW <10th centile. As reference population, 188 fetuses from singleton pregnancies with normal fetal anatomy and growth were used.

Regarding the study population, the median maternal age was of 31.0 years (27.3-36.8), median gravidity of 2.0 (1.0-3.0) and the BMI at booking was of 25.6 (22.9-27.7).

The median GA at the time of diagnosis of cardiomegaly was 28.0 weeks (23.3-32.0). Fetal ultrasound data including biometry and Doppler findings expressed as Z-scores, at the time of diagnosis of cardiomegaly and at the last scan before delivery or fetal demise are summarized in Table 1. The 87% at the time of diagnosis and 89% at the last scan of these small fetuses have to be classified as intrauterine growth restricted fetuses since they exhibited an EFW less than 3rd centile [15]. Looking to the hemodynamic findings, the UA PI was considered abnormal in 63% of these fetuses at the time of the diagnosis of cardiomegaly and 60% at the last scan [13].

The HC/AC ratio was > 50th centile in 52 fetuses (96%) and > 95th centile in 28 (52%). Data on pregnancy outcomes available for 43 of the 54 fetuses are shown in Table 2.

Tables 3 shows comparisons of Z-scores for TC and CC respectively between the study and the reference population. When comparing chest size, small fetuses with cardiomegaly had significantly lower TC median Z-scores for GA, BPD, HC and FL (*P*< 0.001 for all). When comparing heart size, small fetuses with cardiomegaly showed significantly lower CC median Z-scores for GA (*P* <0.001), but CC Z-scores were similar to normally grown fetuses when normalised for BPD (*P*=0.284) and HC (*P*=0.953) and higher in relation to FL (*P*<0.001).

Figure 2 is a graphic representation of the CC and TC Z-scores for the 54 small fetuses with cardiomegaly related to GA, BPD, HC and FL.

**DISCUSSION**

In this study, we introduced the use of the Z-scores for the CC and TC in the assessment of cardiomegaly in small fetuses and provided evidence for asymmetrical growth between the thorax and the heart. Different to the thorax, which is strongly restricted in size, the heart maintains its size. In particular cardiac dimensions are comparable and similarly preserved to the cranial ones. These observations which result in cardiomegaly judged by the increased CTR may be indicative of a ‘heart-sparing’ effect.

In 2005 Schneider et al. [14] firstly produced rules and nomograms that allow computation of Z-scores for fetal cardiac dimensions from knowledge of FL, BPD or GA using fetal echocardiography. Since then, other studies reported similar and additional Z-scores references for cardiac structures based on 2D[16-18] and M-mode echocardiography [19]. Z-scores references are also available for cardiac blood flow velocities [19] and pulsed wave myocardial tissue Doppler velocities [20] in the fetus. More recently, Z-scores for cardiac size related to gestational age and standard fetal biometry have also become available [17, 21-24]. Their potential utility in antenatal screening of alpha-thalassemia was highlighted [25], but their value as a screening tool for congenital heart disease was thought to be limited [22]. We are not aware of any previous publication on Z-scores for chest dimension and no previous work addressed the significance of cardiac size in a population of fetuses compromised by growth restriction.

The use of CC and TC Z-scores could be useful in clinical practice, especially for the longitudinal assessment of the cardiac and thoracic size in all conditions that may involve cardiomegaly. Importantly, calculating Z-scores not only for the GA, but also for the standard fetal biometry (BPD, HC and FL), provides further insight about the finding of cardiomegaly in this population. In clinical practice, cardiac dimension, often assessed by CTR is usually compared to GA as a surrogate for fetal size. Whilst it may be reasonable to normalize for the GA in the second trimester, in the third trimester there is significant variability between GA and size of the fetus. In normally grown fetuses, the FL had the highest correlation to the dimensions of various fetal cardiac structures [14]. In growth-restricted fetuses, the shift of the cardiac output in favour of the left ventricle is able to maintain the growth of vital organs at the expense of other non-vital structures like long bones[26]. Starting from these observations, we calculated the CC and the TC Z-scores not only for the GA and for the FL, but also for BPD and HC.

Contrary to chest size, when we calculated the heart circumference Z-score normalized for FL, the CC was found to be statistically significantly bigger in small fetuses compared to the CC in the normally grown ones. As seen in Figure 2, the heart size in small fetuses is mainly in the upper range (Z-scores mostly >0), if compared to FL. Considering the FL as a good surrogate of the effective fetal size, this finding is in keeping with other reports that documented significantly larger heart sizes among small fetuses compared with normally grown fetuses [6, 27, 28]. We could hypothesize that these data may be explained not exclusively in relation to the smallness of the FL, but also to a different ability of maintaining the dimensions of the heart in comparison to the thorax and the rest of the body in small fetuses.

The evidence of a mantained heart size is further described by the CC and TC Z-scores for BPD and HC. If the TC measurement was significantly smaller in growth restricted fetuses in comparison to the normally grown ones based on GA or any fetal biometry (Table 3), no significant difference for the CC Z-score was found between the two groups when normalised for head size (Table 3). Thus, in our cohort of small fetuses, heart and head being symmetrical in size and less affected by the restriction of growth in comparison to the long bones.

The preferential growth of the head is well known in these fetuses and completely clarified also from a hemodynamic point of view[26,29]. Our data regarding cardiac dimension provide new insights into the phenomenon called “heart-sparing effect”. This phenomenon was firstly described by Gembruch and Baschat [30, 31] who demonstrated differences in coronary blood flow visualization between normally grown and growth-restricted fetuses. Several years before, animal studies demonstrated that growth-retarded foetuses with severely impaired utero-placental perfusion showed a redistribution of ventricular output which increased blood flow to the brain, heart and adrenal glands[26, 32-34]. Significantly in the study from Baschat et al.[35] the coronary blood flow visualization coincides with deteriorating venous flow, indicating that growth restricted fetuses which display coronary blood flow have clear hemodynamic deterioration compared with intrauterine growth restricted (IUGR) fetuses which do not show this, and are at high risk of adverse perinatal outcome.

It is plausible to assume that cardiomegaly in growth-restricted fetuses is an ultrasound feature of impaired placental perfusion where preferential growth of vital organs like the heart and the brain is actively maintained[6, 27, 28]. On the other hand, we could hypothesize that in constitutionally small fetuses as well as in the mild cases of fetal growth restriction, the heart grows in proportion with the chest measurements, as observed in the study by Miyague et al. [5].

Despite our data are related to SGA fetuses since defined on EFW<10th centile, the vast majority of these fetuses exhibited an EFW<3rd centile and so they have to be properly classified as intrauterine growth restricted. Moreover, both Pérez-Cruz M et al. [27] and Hobbins JC et al.[28] showed larger hearts in populations of SGA fetuses in comparison to normally grown ones independently from the doppler findings, supporting the concept that an overlap may exist between IUGR and SGA and differences are not always so clinically obvious.

We are aware that the main limitation of this study was in its retrospective nature. A longitudinal assessment of the CC and CTR in this population may provide further insight into clinical management of small fetuses by documenting the correlation between the appearance and progression of cardiomegaly and the perinatal outcome.

**CONCLUSIONS**

In conclusion, our results on cardiac dimensions provide evidence for the asymmetry in the cardiac size as part of the same mechanism preferentially devoted to preserve fetal vital organs including the brain and the heart itself.

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**STATEMENT OF ETHICS**: The study is registered with the R&D department at St George's University Hospital (Ref: 14.0249). Due to its retrospective nature using pre-collected anonymised data, REC approval and consent were not required, in compliance with NHS Health Research Authority.

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**AUTHOR CONTRIBUTIONS:**

SS - Acquisition, analysis or interpretation of data for the work, drafting the manuscript.

LDE - Revising the manuscript critically for important intellectual content.

MR - Analysis and interpretation of data for the work.

AL - Acquisition, analysis or interpretation of data for the work, revising the manuscript critically for important intellectual content.

SDC - Acquisition, analysis or interpretation of data for the work, revising the manuscript critically for important intellectual content.

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• All the authors approved the final version of the manuscript.

• All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed

**DATA AVAILABILITY STATEMENT:** All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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**LEGENDS OF FIGURES**

**Fig. 1**: Flow chart presenting the selected study population

**Fig. 2**: Box-and-whisker plots comparing Z-score values for cardiac (red boxes) and thoracic (blue boxes) circumferences in relation to the gestational age, biparietal diameter, head circumference and femur length in small fetuses. Boxes show median and interquartile range and the whiskers represent the minimum and maximum values. Dotted horizontal lines indicate normal Z-score range (-2 to +2). Note that cardiac dimensions are within normal range compared to head size