Automated quantitative evaluation of fetal atrioventricular annular plane systolic excursion

L. HERLING1,2, J. JOHNSON1,2, K. FERM-WIDLUND2, A. ZAMPRAKOU1,3, M. WESTGREN1,2# and G. ACHARYA1,2,4#

1Department of Clinical Science, Intervention and Technology - CLINTEC, Karolinska Institutet, Stockholm, Sweden; 2Center for Fetal Medicine, Department of Obstetrics and Gynecology, Karolinska University Hospital, Stockholm, Sweden; 3Pregnancy and Delivery Medical Unit, Department of Obstetrics and Gynecology, Karolinska University Hospital, Stockholm, Sweden; 4Women’s Health and Perinatology Research Group, Department of Clinical Medicine, UiT-The Arctic University of Norway, Tromso, Norway

KEYWORDS: annular plane systolic excursion; atrioventricular plane displacement; automated analysis; fetal cardiac function; fetal echocardiography; M-mode; tissue Doppler imaging

CONTRIBUTION
What are the novel findings of this work?
Fetal atrioventricular plane displacement in the left and right ventricular walls and interventricular septum of the fetal heart (i.e. mitral, tricuspid and septal annular plane systolic excursion, respectively) can be analyzed automatically over several cardiac cycles using myocardial velocity traces obtained by color tissue Doppler imaging (cTDI).

What are the clinical implications of this work?
Automated analysis of cTDI cineloops of the four-chamber view of the fetal heart has the potential to simplify assessment of fetal atrioventricular plane displacement, enabling gathering of larger amounts of data. Such data could potentially be used in machine-learning models to facilitate prenatal assessment of different fetal disease states and evaluation of fetal risk at an individual level.

ABSTRACT
Objectives The primary aim of this study was to evaluate the feasibility of automated measurement of fetal atrioventricular (AV) plane displacement (AVPD) over several cardiac cycles using myocardial velocity traces obtained by color tissue Doppler imaging (cTDI). The secondary objectives were to establish reference ranges for AVPD during the second half of normal pregnancy, to assess fetal AVPD in prolonged pregnancy in relation to adverse perinatal outcome and to evaluate AVPD in fetuses with a suspicion of intrauterine growth restriction (IUGR).

Methods The population used to develop the reference ranges consisted of women with an uncomplicated singleton pregnancy at 18–42 weeks of gestation (n = 201). The prolonged-pregnancy group comprised women with an uncomplicated singleton pregnancy at ≥ 41 + 0 weeks of gestation (n = 107). The third study cohort comprised women with a singleton pregnancy and suspicion of IUGR, defined as an estimated fetal weight < 2.5th centile or an estimated fetal weight < 10th centile and umbilical artery pulsatility index > 97.5th centile (n = 35). Cineloops of the four-chamber view of the fetal heart were recorded using cTDI. Regions of interest were placed at the AV plane in the left and right ventricular walls and the interventricular septum, and myocardial velocity traces were integrated and analyzed using an automated algorithm developed in-house to obtain mitral (MAPSE), tricuspid (TAPSE) and septal (SAPSE) annular plane systolic excursion. Gestational-age specific reference ranges were constructed and normalized for cardiac size. The correlation between AVPD measurements obtained using cTDI and those obtained by anatomic M-mode were evaluated, and agreement between these two methods was assessed using Bland–Altman analysis. The mean Z-scores of fetal AVPD in the cohort of prolonged pregnancies were compared between cases with normal and those with adverse outcome using Mann–Whitney U-test. The mean Z-scores of fetal AVPD in IUGR fetuses were compared with those in the normal reference population using Mann–Whitney U-test. Inter- and intraobserver
variability for acquisition of cTDI recordings and offline analysis was assessed by calculating coefficients of variation (CV) using the root mean square method.

Results Fetal MAPSE, SAPSE and TAPSE increased with gestational age but did not change significantly when normalized for cardiac size. The fitted mean was highest for TAPSE throughout the second half of gestation, followed by SAPSE and MAPSE. There was a significant correlation between MAPSE ($r = 0.64$; $P < 0.001$), SAPSE ($r = 0.72$; $P < 0.001$) and TAPSE ($r = 0.84$; $P < 0.001$) measurements obtained by M-mode and those obtained by cTDI. The geometric means of ratios between AVPD measured by cTDI and by M-mode were 1.38 (95% limits of agreement (LoA), 0.84–2.25) for MAPSE, 1.00 (95% LoA, 0.72–1.40) for SAPSE and 1.20 (95% LoA, 0.92–1.57) for TAPSE. In the prolonged-pregnancy group, the mean ± SD Z-scores for MAPSE (0.14 ± 0.97), SAPSE (0.09 ± 1.02) and TAPSE (0.15 ± 0.90) did not show any significant difference compared to the reference ranges. Twenty-one of the 107 (19.6%) prolonged pregnancies had adverse perinatal outcome. The AVPD Z-scores were not significantly different between pregnancies with normal and those with adverse outcome in the prolonged-pregnancy cohort. The mean ± SD Z-scores for SAPSE ($–0.62 ± 1.07$; $P = 0.006$) and TAPSE ($–0.60 ± 0.89$; $P = 0.002$) were significantly lower in the IUGR group compared to those in the normal reference population, but the differences were not significant when the values were corrected for cardiac size. The interobserver CVs for the automated measurement of MAPSE, SAPSE and TAPSE were 38.1%, 17.7% and 15.3%, respectively, and the respective intraobserver CVs were 33.5%, 15.0% and 17.9%.

Conclusions This study showed that fetal AVPD can be measured automatically by integrating cTDI velocities over several cardiac cycles. Automated analysis of AVPD could potentially help gather larger datasets to facilitate use of machine-learning models to study fetal cardiac function. The gestational-age associated increase in AVPD is most likely a result of increasing cardiac size, as the AVPD normalized for cardiac size did not change significantly between 18 and 42 weeks. A decrease was seen in TAPSE and SAPSE in IUGR fetuses, but not after correction for cardiac size. © 2021 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Atrioventricular (AV) plane displacement (AVPD), often expressed as mitral annular plane systolic excursion (MAPSE), septal annular plane systolic excursion (SAPSE) and tricuspid annular plane systolic excursion (TAPSE), is a major contributor to cardiac pumping and a measure of longitudinal cardiac function. AVPD is defined as the distance between the two positions where the AV plane is the farthest from the apex and closest to the apex during a cardiac cycle. In healthy adults, examined using magnetic resonance imaging, AVPD accounts for 80% of the right-ventricular (RV) and 60% of the left-ventricular (LV) stroke volume. Even in situations in which the absolute AVPD is decreased, the longitudinal contribution remains the main component of LV stroke volume. Longitudinal cardiac function, which is executed by longitudinal myocardial fibers, is considered to be the first affected in the event of hypoxia.

In fetuses, AVPD can be evaluated using ultrasound techniques, such as M-mode, tissue Doppler imaging (TDI) and speckle tracking. AVPD depends on body size and cardiac size, and absolute values increase with gestational age.

METHODS

This was a cross-sectional study conducted at the Center for Fetal Medicine, Karolinska University Hospital, Stockholm, Sweden, between September 2009 and February 2017. Ethical approval was obtained from the Stockholm Regional Ethics Committee (DNr 2009/1617-31/2, 2012/895-31/4 and 2017/539-32). All women gave written informed consent to participate.

The first cohort, used for the development of reference ranges for AVPD in the second half of pregnancy, consisted of women with an uncomplicated singleton pregnancy between 18 and 42 weeks of gestation ($n = 201$). Exclusion criteria were conception after in-vitro fertilization/intracytoplasmic sperm injection treatment, maternal complications at inclusion, such as pre-eclampsia, chronic hypertension or diabetes, and fetal chromosomal or major structural abnormalities discovered during pregnancy or postnatally. Pregnancies were dated by measuring the biparietal diameter in the second trimester. Each fetus was included only once. Reference ranges for myocardial velocities and cardiac...
cycle time intervals based on the same population have been published previously\textsuperscript{14}.

The second cohort, used to assess AVPD in prolonged pregnancy in relation to adverse perinatal outcome, comprised women with an uncomplicated pregnancy who attended a routine appointment at $\geq 41 + 0$ weeks of gestation ($n = 107$) and underwent an ultrasound examination between $41 + 0$ and $41 + 5$ weeks. A composite adverse perinatal outcome was defined as the presence of at least one of the following: intrapartum fetal scalp blood lactate $> 4.8$ mmol/L, umbilical cord arterial pH $< 7.15$, 5-min Apgar score $< 7$ or 5-min Apgar score for muscle tone $< 2$. Data regarding the feasibility of automated analysis of fetal myocardial velocity measurements obtained by cTDI have been published previously using this cohort\textsuperscript{16}.

The third cohort included, as part of a pilot study, women with a singleton fetus with a suspicion of IUGR, defined as an estimated fetal weight (EFW) $< 2.5$\textsuperscript{th} centile or an EFW $< 10$\textsuperscript{th} centile and umbilical artery pulsatility index $> 97.5$\textsuperscript{th} centile. The definition used is based on Swedish reference ranges for estimation of fetal weight and umbilical artery cut-off values\textsuperscript{17,18}.

Fetal echocardiography using cTDI was performed by an experienced ultrasonographer (K.F.-W.) using a GE Vivid-i ultrasound imaging system, equipped with a 3S-RS 1.9–3.8-MHz phased-array transducer (GE Vingmed, Horten, Norway) or a Vivid S6 ultrasound imaging system with a M4S-RS 1.9–4.1-MHz phased-array transducer (GE CV Ultrasound, Haifa, Israel). An apical or basal four-chamber view of the fetal heart was acquired and cineloops of consecutive cardiac cycles were recorded using cTDI. The insonation angle was kept as close as possible to the long axis of the heart (and always $< 30^\circ$) and the image was adjusted to obtain as high a frame rate as possible. Offline analysis was performed using EchoPAC version 201 (GE Vingmed). The region of interest (ROI) was adjusted in height and width according to GA, as in previous research\textsuperscript{13}, and placed at the AV plane in the LV and RV walls and the interventricular septum (IVS). All ROIs were placed by one operator (L.H.). Myocardial velocity traces were subsequently exported from EchoPAC to MATLAB (R2019b; MathWorks, Natick, MA, USA) and then analyzed using an automated software tool developed in-house. Cardiac cycle time intervals were defined by the software. The program in MATLAB, i.e. the automated analysis described, has several user-defined functions and some MATLAB built-in functions\textsuperscript{2,19}. The myocardial velocity data were integrated and AVPD was obtained automatically and defined as the maximum distance covered by the AV plane during the cardiac cycle (Figure 1). AVPD in the LV, IVS and RV were called MAPSE, SAPSE and TAPSE, respectively, and according to nomenclature used previously in fetuses. The analysis is a fully automated procedure and no manual marking of the traces is needed once the velocity traces are exported to MATLAB. The average of all available cardiac cycles was also calculated.

The fetal cardiac size was measured as the longitudinal diameter (apex to base) in early systole, right after the closure of the AV valves in diastole. Calipers were placed from the midpoint of the atria at the outer border to the outer border of the apex. The cardiac size, i.e. the longitudinal diameter of the heart\textsuperscript{20}, was used to normalize AVPD measurements.

In a subset of 30 fetuses from the first cohort (i.e. the cohort used for development of the reference ranges), AVPD was measured additionally using anatomic M-mode echocardiography for comparison with the cTDI-derived AVPD measurements obtained using the automated technique. The M-mode cursor was placed through the lateral leaflets of the AV valves and the IVS to obtain an alignment with the IVS $< 30^\circ$. The total AVPD was measured according to previously described

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Automated analysis of a myocardial velocity trace from the right ventricular wall (a) and a trace showing the tricuspid annular peak systolic excursion (TAPSE) (b), obtained by color tissue Doppler imaging in a normal 34-week fetus. The colors indicate the different phases in the cardiac cycle, as defined by the automated algorithm: atrial contraction (■), pre-ejection (◼), ventricular ejection (◆), post-ejection (□), rapid ventricular filling (▲), slow ventricular filling (●). The blue and red asterisks in (b) indicate the maximum amplitude of TAPSE.}
\end{figure}
techniques\textsuperscript{21,22}. The average of three measurements was calculated.

The inter- and intraobserver variability of the acquisition of cTDI recordings and offline analysis was evaluated using a Vivid S6 ultrasound imaging system with a M4S-RS 1.9–4.1-MHz phased-array transducer (GE CV Ultrasound). The interobserver variability was evaluated by two ultrasonographers (K.F.-W. and L.H.) who examined 25 fetuses, between 19 and 41 weeks of gestation, between December 2016 and February 2017. Subsequently, 22 of these fetuses were examined again by the first ultrasonographer (K.F.-W.) approximately 10 min later, and the intraobserver variability for the entire procedure was evaluated by comparing the two recordings. This means that the calculated coefficients of variation (CV) also reflect the variability associated with the change in fetal physiological state and position, as well as the resulting technical challenges during the examination period, not just the operator-related measurement variability. ROIs were placed by one operator (L.H.) and all generated myocardial velocity traces were analyzed by the automated algorithm.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) and MATLAB (MathWorks). Continuous variables are presented as mean ± SD or median (interquartile range), as appropriate. Categorical variables are presented as n (%)\. The statistical approach described by Royston and Wright\textsuperscript{23} was used to create reference intervals for MAPSE, SAPSE and TAPSE. Box–Cox power transformation was used to decide the appropriate type of transformation. The best-fitting fractional polynomials were chosen from a list of 44 regression models based on $R^2$ value, using NCSS 2020 Statistical Software (NCSS LLC, Kaysville, UT, USA) to construct mean curves of each dependent variable in relation to GA, expressed in exact weeks (decimal days). The normality of the distribution of the Z-scores was checked using the Shapiro–Wilk test. Mean, SD and CI curves as a function of GA were calculated and plotted. The equations of the polynomial regression were used to calculate the estimated mean, 5\textsuperscript{th} and 95\textsuperscript{th} centiles for the corresponding GA were calculated and plotted. The equations of the Z-scores was plotted on the graphs of the reference ranges and the mean -scores of AVPD in the cohort of prolonged pregnancies with an adverse neonatal outcome using Mann–Whitney U-test.

The correlation between AVPD measurements obtained using cTDI and those obtained by anatomic M-mode was evaluated using Spearman’s correlation, and agreement between the two measurement methods was tested for bias and precision using Bland–Altman analysis of log-transformed data\textsuperscript{24–26}. We defined precision by the 95\% limits of agreement (LoA) (±1.96SD) and bias as the difference between the geometric mean of all individual ratios between pairs of values obtained using the two methods and the line of equality. The statistical significance level was set to $P < 0.05$. To assess intra- and interobserver variability, CVs were calculated using the root mean square method\textsuperscript{27}.

RESULTS

Baseline characteristics, ultrasound data and pregnancy outcomes of the normal group (n = 201), prolonged pregnancies (n = 107) and fetuses with a suspicion of IUGR (n = 35) are presented in Table 1.

Normal reference ranges for cTDI-derived AVPD

Initially, 202 pregnant women were enrolled in this cohort. After the exclusion of one woman whose fetus was diagnosed with muscular ventricular septal defect and bicuspid aortic valve, the cohort consisted of 201 women. In total, 603 fetal myocardial velocity traces (201 each from LV, IVS and RV) were available for analysis and subsequent integration to obtain AVPD data. One RV trace was excluded due to severe artifacts and two IVS traces could not be analyzed. The mean ± SD number of cardiac cycles analyzed were 10.2 ± 2.6 in the LV, 10.3 ± 2.7 in the IVS and 10.3 ± 2.6 in the RV.

The interobserver CVs for the automated measurement of AVPD on cTDI cineloop recordings of the four-chamber view of the fetal heart obtained consecutively by two sonographers in 25 fetuses were 28.1%, 17.7% and 15.3% for MAPSE, SAPSE and TAPSE, respectively. The intraobserver CVs for the automated measurement of AVPD on cineloop recordings obtained by a single sonographer approximately 10 min apart in 22 fetuses were 33.5%, 15.0% and 17.9% for MAPSE, SAPSE and TAPSE, respectively. The measurement variability of automated analysis on the same cineoop recording was zero on repeated evaluation.

The best model for all variables was a quadratic polynomial fit. MAPSE was transformed logarithmically, whereas SAPSE and TAPSE did not require any transformation. MAPSE, SAPSE and TAPSE all increased with GA (Figure 2 and Tables 2–4). The regression equations are displayed in Table 5. The fitted mean was highest in TAPSE throughout the second half of gestation, followed by SAPSE and MAPSE. Reference ranges with the corresponding 95\% CIs calculated for the fitted mean and 5\textsuperscript{th} and 95\textsuperscript{th} centiles are displayed in Figure 2. A Z-score and centile calculator for MAPSE, SAPSE and
TAPSE obtained by cTDI and analyzed automatically is provided in Appendix S1.

When corrected for cardiac size, all three variables showed a weak non-significant trend to decline from 18 weeks of gestation onwards. Reference ranges corrected for cardiac size with the corresponding 95% CIs calculated for the fitted mean, 5th and 95th centiles are displayed in Figure 3.

Comparison between AVPD measurements obtained in the same fetus by cTDI and anatomic M-mode was performed in 30 pregnancies from the reference population. The fetuses evaluated by anatomic M-mode were distributed evenly across gestation, with five fetuses included in each of the following GA windows: 18 + 0 to 21 + 6, 22 + 0 to 25 + 6, 26 + 0 to 29 + 6, 30 + 0 to 33 + 6, 34 + 0 to 37 + 6 and 38 + 0 to 42 + 6 weeks. We observed a statistically significant correlation between MAPSE \( (r = 0.84; P < 0.001) \), SAPSE \( (r = 0.72; P < 0.001) \) and TAPSE \( (r = 0.84; P < 0.001) \) measurements obtained by M-mode and those obtained by cTDI (Figure 4). When 30 pairs of log-transformed AVPD measurements were compared using Bland–Altman analysis, the geometric means of ratios between AVPD measured by cTDI and M-mode were 1.38 (95% LoA, 0.84–2.25) for MAPSE, 1.00 (95% LoA, 0.72–1.40) for SAPSE and 1.20 (95% LoA, 0.84–1.57) for TAPSE (Figure 5).

Prolonged pregnancy and adverse outcome

A total of 107 women were included in this cohort and 321 myocardial velocity traces were analyzed. The mean ± SD number of cardiac cycles analyzed were 8.5 ± 1.3 in the LV, 8.9 ± 0.9 in the IVS and 8.6 ± 0.7 in the RV. The mean ± SD Z-scores for MAPSE (0.14 ± 0.97), SAPSE (0.09 ± 1.02) and TAPSE (0.15 ± 0.90) in this cohort did not show any significant difference compared to the reference ranges of the normal population \( (P > 0.05) \) (Figure 2). No significant differences were found when the measurements were corrected for cardiac size. Twenty-one of the 107 (19.6%) neonates had an adverse perinatal outcome. No significant differences in AVPD Z-scores were found between the pregnancies with normal and those with adverse outcome within the prolonged-pregnancy cohort.

Fetuses with suspicion of IUGR

A total of 35 fetuses with a suspicion of IUGR were included and 105 velocity traces were analyzed and integrated to obtain AVPD data. The mean ± SD number of cardiac cycles analyzed were 9.0 ± 2.8 in the LV, 9.4 ± 2.5 in the IVS and 10.3 ± 1.6 in the RV. The mean ± SD Z-scores for SAPSE \( (-0.62 ± 1.07; \) Table 1 Maternal baseline characteristics, ultrasound data and pregnancy outcome in 201 normal pregnancies between 18 and 42 weeks’ gestation, 107 pregnancies at ≥ 41 weeks’ gestation and 35 pregnancies with a suspicion of intrauterine growth restriction (IUGR)

| Variable | Normal cohort (n = 201) | Prolonged pregnancy (n = 107) | Suspected IUGR (n = 35) |
|----------|------------------------|-------------------------------|------------------------|
| Maternal data | Age (years) 30.1 ± 5.2 | 31.0 ± 5.2 | 30.8 ± 5.3 |
| | BMI (kg/m²) 23.7 ± 3.9 | 24.9 ± 5.2 | 25.1 ± 5.5 |
| | Spontaneous pregnancy 201 (100) | 100 (93.5) | 31 (88.6) |
| | Nulliparous 81 (40.3) | 45 (42.1) | 17 (48.6) |
| | Smoker 12 (6.0) | 2 (1.9) | 6 (17.1) |
| Ultrasound data | GA at scan/inclusion (weeks) 30.4 ± 7.2 | 41.1 ± 0.2 | 33.2 ± 3.4 |
| | UA-PI > 95th centile 0 (0) | 4 (3.7) | 14 (40.0) |
| | Apical position of fetal heart 107 (53.2) | 32 (29.9) | 14 (40.0) |
| | Frame rate 208.3 ± 6.8 | 206.3 ± 13.5 | 208.1 ± 10.4 |
| Pregnancy outcome* | Pre-eclampsia 4 (2.0) | 0 (0) | 11 (31.4) |
| | GA at delivery (weeks) 40.0 ± 1.4 | 41.7 ± 0.4 | 35.6 ± 3.8 |
| | Post-term delivery ≥ 42 + 0 weeks 19 (9.6) | 35 (32.7) | 0 (0) |
| | Preterm delivery < 37 weeks 4 (2.0) | 0 (0) | 19 (54.3) |
| Mode of delivery | Normal vaginal 147 (74.2) | 85 (79.4) | 18 (51.4) |
| | Vacuum extraction 22 (11.1) | 9 (8.4) | 0 (0) |
| | Cesarean section 29 (14.6) | 13 (12.1) | 17 (48.6) |
| | Elective NA | 3 (2.8) | 1 (2.9) |
| | Emergency NA | 10 (9.3) | 16 (45.7) |
| | Birth weight (g) 3576 ± 501 | 3840 ± 423 | 1973 ± 632 |
| | Female neonate 96 (48.5) | 55 (51.4) | 21 (60.0) |
| | Cord arterial pH† 7.25 ± 0.09 | 7.22 ± 0.09 | 7.29 ± 0.09 |
| | Cord venous pH‡ 7.32 ± 0.07 | 7.31 ± 0.07 | 7.38 ± 0.06 |
| | 5-min Apgar score < 7 0 (0) | 1 (0.9) | 2 (5.7) |

Data are given as mean ± SD or n (%). *Pregnancy outcome data were missing for three women in the control group who delivered in other hospitals. Data available for: †138, 83 and 21 cases in the normal, prolonged-pregnancy and IUGR cohorts, respectively; ‡49, 98 and six cases in the normal, prolonged-pregnancy and IUGR cohorts, respectively. BMI, body mass index; GA, gestational age; NA, not available; PI, pulsatility index; UA, umbilical artery.

© 2021 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.
Herling et al.

P = 0.006) and TAPSE (−0.60 ± 0.89; P = 0.002) were significantly lower in the IUGR group in comparison to the reference ranges of the normal population (mean Z-scores were zero for SAPSE, MAPSE and TAPSE) (Figure 2). The mean ± SD Z-score for MAPSE was −0.13 ± 0.67 (P = 0.160). When corrected for cardiac size, there were no significant differences in the mean Z-scores for SAPSE, TAPSE and MAPSE between the normal population and the IUGR group.

**DISCUSSION**

This study showed that automated measurement of AVPD in the LV, IVS and RV over several cardiac cycles from cTDI cineloops is feasible in the second half of pregnancy. The measurements at all three locations, i.e. MAPSE, SAPSE and TAPSE, increased with gestation; however, when corrected for cardiac size, all three variables showed a weak non-significant trend to decline from 18 weeks of gestation onwards. We observed a significant correlation between AVPD measurements obtained by M-mode and those obtained by cTDI. The AVPD measured by automated analysis of cTDI cineloops was similar to that measured by M-mode for SAPSE (had least bias), 20% lower for TAPSE and 38% lower for MAPSE with varied precision. In the group with a suspicion of IUGR, SAPSE and TAPSE Z-scores were significantly lower compared to the reference ranges, but these differences did not remain significant when data were normalized for cardiac size.

An increase in MAPSE, SAPSE and TAPSE throughout gestation has been shown previously using both anatomic and conventional M-mode. Previous studies using M-mode demonstrated the highest values in the RV wall and the lowest values in the IVS, which is in contrast to our finding of the lowest values being in the LV wall. The reason for this difference is unclear and might result from positioning of the ROI in the IVS to avoid disturbances from the valves or shadowing of the LV wall when a back-up apical four-chamber view is obtained.

![Figure 2](a) Scatterplots of mitral annular plane systolic excursion (MAPSE), septal annular plane systolic excursion (SAPSE) and tricuspid annular plane systolic excursion (TAPSE) obtained by color tissue Doppler imaging and analyzed automatically, in 201 low-risk pregnancies (○), 35 fetuses with a suspicion of intrauterine growth restriction (IUGR) (□) and 21 fetuses at ≥ 41 + 0 weeks of gestation that had an adverse outcome (○), plotted against gestational age. The fitted mean and 5th and 95th centiles, with corresponding 95% CIs (—–), of the low-risk cohort are shown. (b) Corresponding Z-scores for MAPSE, SAPSE and TAPSE. Mean in fetuses with suspicion of IUGR; mean in prolonged pregnancies with adverse outcome. ±1.645 SD.
Table 2  Measurements of fetal mitral annular plane systolic excursion (in mm), obtained by color tissue Doppler imaging and analyzed automatically, according to gestational age (GA)

| GA (weeks) | n  | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
|------------|----|-------|-----|------|------|------|------|--------|
| 18         | 15 | 1.11  | 1.19| 1.29 | 1.74 | 2.34 | 2.55 | 2.74   |
| 19         | 5  | 1.16  | 1.25| 1.37 | 1.86 | 2.53 | 2.76 | 2.98   |
| 20         | 4  | 1.22  | 1.31| 1.44 | 1.98 | 2.73 | 2.99 | 3.23   |
| 21         | 8  | 1.27  | 1.38| 1.51 | 2.11 | 2.93 | 3.22 | 3.50   |
| 22         | 4  | 1.32  | 1.43| 1.58 | 2.23 | 3.14 | 3.46 | 3.77   |
| 23         | 8  | 1.37  | 1.49| 1.65 | 2.35 | 3.35 | 3.71 | 4.05   |
| 24         | 6  | 1.41  | 1.54| 1.71 | 2.47 | 3.57 | 3.96 | 4.33   |
| 25         | 12 | 1.45  | 1.59| 1.77 | 2.59 | 3.78 | 4.21 | 4.62   |
| 26         | 6  | 1.49  | 1.64| 1.83 | 2.71 | 4.00 | 4.47 | 4.91   |
| 27         | 11 | 1.52  | 1.68| 1.88 | 2.82 | 4.21 | 4.72 | 5.21   |
| 28         | 6  | 1.55  | 1.72| 1.93 | 2.92 | 4.42 | 4.97 | 5.50   |
| 29         | 8  | 1.58  | 1.75| 1.97 | 3.02 | 4.63 | 5.22 | 5.79   |
| 30         | 10 | 1.60  | 1.78| 2.01 | 3.11 | 4.82 | 5.46 | 6.08   |
| 31         | 10 | 1.61  | 1.80| 2.04 | 3.20 | 5.01 | 5.69 | 6.36   |
| 32         | 9  | 1.62  | 1.81| 2.07 | 3.28 | 5.19 | 5.92 | 6.63   |
| 33         | 8  | 1.62  | 1.82| 2.08 | 3.34 | 5.36 | 6.13 | 6.88   |
| 34         | 13 | 1.62  | 1.83| 2.09 | 3.40 | 5.52 | 6.33 | 7.13   |
| 35         | 5  | 1.61  | 1.82| 2.10 | 3.45 | 5.66 | 6.51 | 7.36   |
| 36         | 5  | 1.60  | 1.81| 2.10 | 3.48 | 5.78 | 6.68 | 7.57   |
| 37         | 8  | 1.58  | 1.80| 2.09 | 3.51 | 5.89 | 6.83 | 7.76   |
| 38         | 8  | 1.56  | 1.78| 2.07 | 3.52 | 5.98 | 6.96 | 7.93   |
| 39         | 4  | 1.53  | 1.75| 2.05 | 3.52 | 6.06 | 7.06 | 8.07   |
| 40         | 4  | 1.50  | 1.72| 2.02 | 3.51 | 6.11 | 7.15 | 8.19   |
| 41         | 15 | 1.47  | 1.69| 1.98 | 3.49 | 6.14 | 7.21 | 8.29   |
| 42         | 9  | 1.43  | 1.64| 1.94 | 3.45 | 6.16 | 7.25 | 8.36   |

Table 3  Measurements of fetal septal annular plane systolic excursion (in mm), obtained by color tissue Doppler imaging and analyzed automatically, according to gestational age (GA)

| GA (weeks) | n  | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
|------------|----|-------|-----|------|------|------|------|--------|
| 18         | 15 | 1.09  | 1.26| 1.44 | 2.10 | 2.77 | 2.95 | 3.12   |
| 19         | 5  | 1.24  | 1.41| 1.60 | 2.28 | 2.96 | 3.15 | 3.32   |
| 20         | 4  | 1.38  | 1.55| 1.75 | 2.45 | 3.14 | 3.34 | 3.51   |
| 21         | 8  | 1.51  | 1.68| 1.89 | 2.60 | 3.32 | 3.52 | 3.70   |
| 22         | 4  | 1.63  | 1.81| 2.02 | 2.75 | 3.49 | 3.69 | 3.88   |
| 23         | 8  | 1.75  | 1.93| 2.14 | 2.90 | 3.65 | 3.86 | 4.04   |
| 24         | 6  | 1.85  | 2.04| 2.26 | 3.03 | 3.80 | 4.02 | 4.21   |
| 25         | 12 | 1.95  | 2.14| 2.37 | 3.15 | 3.94 | 4.17 | 4.36   |
| 26         | 6  | 2.04  | 2.24| 2.47 | 3.27 | 4.08 | 4.31 | 4.50   |
| 27         | 11 | 2.12  | 2.32| 2.56 | 3.38 | 4.20 | 4.44 | 4.64   |
| 28         | 6  | 2.19  | 2.40| 2.64 | 3.48 | 4.32 | 4.56 | 4.77   |
| 29         | 8  | 2.26  | 2.47| 2.71 | 3.57 | 4.43 | 4.68 | 4.89   |
| 30         | 10 | 2.32  | 2.53| 2.78 | 3.66 | 4.54 | 4.79 | 5.00   |
| 31         | 9  | 2.36  | 2.58| 2.84 | 3.74 | 4.63 | 4.89 | 5.11   |
| 32         | 9  | 2.41  | 2.63| 2.89 | 3.80 | 4.72 | 4.98 | 5.20   |
| 33         | 8  | 2.44  | 2.67| 2.93 | 3.86 | 4.80 | 5.06 | 5.29   |
| 34         | 13 | 2.46  | 2.70| 2.96 | 3.92 | 4.87 | 5.14 | 5.37   |
| 35         | 5  | 2.48  | 2.72| 2.99 | 3.96 | 4.93 | 5.20 | 5.44   |
| 36         | 5  | 2.49  | 2.73| 3.01 | 3.99 | 4.98 | 5.26 | 5.50   |
| 37         | 5  | 2.49  | 2.73| 3.02 | 4.02 | 5.03 | 5.31 | 5.56   |
| 38         | 7  | 2.48  | 2.73| 3.02 | 4.04 | 5.06 | 5.35 | 5.61   |
| 39         | 4  | 2.46  | 2.72| 3.01 | 4.05 | 5.09 | 5.39 | 5.64   |
| 40         | 4  | 2.43  | 2.70| 3.00 | 4.05 | 5.11 | 5.41 | 5.67   |
| 41         | 15 | 2.40  | 2.67| 2.97 | 4.05 | 5.13 | 5.43 | 5.70   |
| 42         | 9  | 2.36  | 2.63| 2.94 | 4.04 | 5.13 | 5.44 | 5.71   |
MAPSE, SAPSE and TAPSE showed a weak non-significant trend to decline from 18 weeks of gestation when corrected for cardiac size. It is well-known that myocardial velocities and, consequently, displacement data depend on the size of the heart. Our results indicate that cardiac size largely explains the increase in AVPD measurement seen throughout gestation. Fetal size and different measurements of the heart such as the longitudinal diameter of the heart and heart area have been suggested to normalize AVPD. In this study, we chose to normalize the data using the longitudinal diameter of the heart, as this measurement was the most stable to perform in the four-chamber view acquired and has been used previously by other authors.

In the group of fetuses with a suspicion of IUGR, mean TAPSE and SAPSE were significantly lower compared to the normal group. However, this difference did not remain significant when measurements were corrected for cardiac size, suggesting that the smaller AVPD measurements are related to the smaller heart of IUGR fetuses. This is in analogy with the fact that IUGR fetuses are suggested to maintain cardiac output in spite of alterations in hemodynamic afterload due to placental insufficiency and hypoxemia. Nevertheless, conclusions should be interpreted with caution, as the small number of patients with suspected IUGR and the broad inclusion criteria could have influenced the results. Furthermore, when correcting for cardiac size using the longitudinal diameter of the heart, this measurement was the most stable to perform in the four-chamber view acquired and has been used previously by other authors.

### Table 4

Measurements of fetal tricuspid annular plane systolic excursion (in mm), obtained by color tissue Doppler imaging and analyzed automatically, according to gestational age (GA)

| GA (weeks) | n  | 2.5th | 5th | 10th | 50th | 90th | 95th | 97.5th |
|------------|----|-------|-----|------|------|------|------|-------|
| 18         | 15 | 1.70  | 1.88| 2.09 | 2.84 | 3.59 | 3.80 | 3.98  |
| 19         | 5  | 1.88  | 2.08| 2.30 | 3.10 | 3.90 | 4.12 | 4.32  |
| 20         | 4  | 2.06  | 2.27| 2.51 | 3.35 | 4.19 | 4.45 | 4.64  |
| 21         | 8  | 2.23  | 2.45| 2.70 | 3.59 | 4.48 | 4.73 | 4.95  |
| 22         | 4  | 2.38  | 2.61| 2.88 | 3.81 | 4.75 | 5.02 | 5.25  |
| 23         | 8  | 2.53  | 2.77| 3.05 | 4.03 | 5.01 | 5.29 | 5.53  |
| 24         | 6  | 2.66  | 2.91| 3.21 | 4.24 | 5.27 | 5.56 | 5.81  |
| 25         | 12 | 2.78  | 3.05| 3.35 | 4.33 | 5.31 | 5.81 | 6.08  |
| 26         | 6  | 2.90  | 3.17| 3.49 | 4.61 | 5.74 | 6.06 | 6.33  |
| 27         | 11 | 3.00  | 3.28| 3.62 | 4.79 | 5.96 | 6.29 | 6.58  |
| 28         | 6  | 3.09  | 3.39| 3.73 | 4.95 | 6.17 | 6.51 | 6.81  |
| 29         | 8  | 3.17  | 3.48| 3.84 | 5.10 | 6.37 | 6.72 | 7.03  |
| 30         | 10 | 3.24  | 3.56| 3.93 | 5.24 | 6.55 | 6.92 | 7.25  |
| 31         | 10 | 3.29  | 3.63| 4.01 | 5.37 | 6.73 | 7.11 | 7.45  |
| 32         | 9  | 3.34  | 3.69| 4.08 | 5.49 | 6.90 | 7.29 | 7.64  |
| 33         | 8  | 3.38  | 3.73| 4.14 | 5.60 | 7.05 | 7.46 | 7.82  |
| 34         | 13 | 3.40  | 3.77| 4.20 | 5.69 | 7.19 | 7.62 | 7.99  |
| 35         | 4  | 3.42  | 3.80| 4.23 | 5.78 | 7.33 | 7.77 | 8.15  |
| 36         | 5  | 3.42  | 3.81| 4.26 | 5.86 | 7.45 | 7.90 | 8.29  |
| 37         | 8  | 3.41  | 3.82| 4.28 | 5.92 | 7.36 | 8.03 | 8.43  |
| 38         | 8  | 3.39  | 3.81| 4.29 | 5.98 | 7.66 | 8.14 | 8.56  |
| 39         | 4  | 3.37  | 3.79| 4.28 | 6.02 | 7.75 | 8.24 | 8.67  |
| 40         | 4  | 3.33  | 3.76| 4.27 | 6.05 | 7.83 | 8.34 | 8.77  |
| 41         | 15 | 3.28  | 3.73| 4.24 | 6.07 | 7.90 | 8.42 | 8.87  |
| 42         | 9  | 3.21  | 3.68| 4.21 | 6.08 | 7.96 | 8.49 | 8.95  |

### Table 5

Regression equations for MAPSE, SAPSE and TAPSE obtained by color tissue Doppler imaging and analyzed automatically

| Variable | n  | Fitted equation | a     | b     | c    | SE (of b) | SE (of c) | P (of b) | P (of c) | Adjusted R² |
|----------|----|----------------|-------|-------|------|-----------|-----------|----------|----------|-------------|
| Mean (mm)| 201| \(\text{log}(y) = a + bGA + cGA^2\) | -0.5281 | 0.0557 | -0.000727 | 0.012 | 0.0002 | <0.001 | <0.001 | 0.339 |
| MAPSE    | 199| \(y = a + bGA + cGA^2\) | -2.4385 | 0.3260 | -0.0041 | 0.060 | 0.0010 | <0.001 | <0.001 | 0.450 |
| SAPSE    | 200| \(y = a + bGA + cGA^2\) | -3.6869 | 0.4601 | -0.0054 | 0.082 | 0.0014 | <0.001 | <0.001 | 0.551 |
| TAPSE    | 201| \(a + bGA\) | 0.0290 | 0.0040 | — | 0.001 | — | <0.001 | — | 0.062 |
| SD       | 199| \(a + bGA\) | 0.2618 | 0.0141 | — | 0.005 | — | 0.0098 | — | 0.029 |
| MAPSE    | 200| \(a + bGA\) | -0.0753 | 0.0366 | — | 0.007 | — | <0.001 | — | 0.108 |

a, intercept; b, slope/coefficient; c, coefficient; GA, gestational age; MAPSE, mitral annular plane systolic excursion; SAPSE, septal annular plane systolic excursion; SD, standard error; TAPSE, tricuspid annular plane systolic excursion.

© 2021 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.
Automated analysis of AV plane displacement

Figure 3 (a) Scatterplots of mitral annular plane systolic excursion (MAPSE), septal annular plane systolic excursion (SAPSE) and tricuspid annular plane systolic excursion (TAPSE) obtained by color tissue Doppler imaging and analyzed automatically, with values corrected for measurement of cardiac size, in 201 low-risk pregnancies (○), 35 fetuses with a suspicion of intrauterine growth restriction (IUGR) (●) and 21 fetuses at ≥41+0 weeks of gestation that had an adverse outcome (▲), plotted against gestational age. The fitted mean and 5th and 95th centiles, with corresponding 95% CIs (---), of the low-risk cohort are shown. (b) Corresponding Z-scores for MAPSE, SAPSE and TAPSE. ---, mean in fetuses with suspicion of IUGR; -----, mean in prolonged pregnancies with adverse outcome. ±1.645 SD.

Figure 4 Comparison of measurements of mitral annular plane systolic excursion (a), septal annular plane systolic excursion (b) and tricuspid annular plane systolic excursion (c) obtained by color tissue Doppler imaging (cTDI) and those obtained by anatomic M-mode, in 30 low-risk fetuses at 18+0 to 42+6 weeks’ gestation. The dashed line represents the line of equality. \( R^2 \text{adj}, \text{adjusted } R^2 \text{ value.} \)
weight < both IUGR fetuses at term and fetuses with an estimated.

This might also have influenced results, as

diameter of the heart, the width of the heart is not

M-mode overestimates AVPD in cases of angle
deviation, as opposed to cTDI which underestimates
the velocity and, thus, the AVPD, with increasing angle of
deviation. This is illustrated in this study by SAPSE
(which has the smallest angle of insonation being centrally
located), which showed similar values when evaluated by
cTDI and M-mode. MAPSE and TAPSE, which have
increasing angles of insonation, demonstrated higher
M-mode compared to cTDI measurements.

Inter- and intraobserver CVs ranged from 15.3% to
33.5%, with TAPSE and SAPSE showing lower and
MAPSE showing higher values. This is partly in line with
the findings reported by Peixoto et al.\textsuperscript{22}, who showed
poor-to-moderate intra- and interobserver agreement
when assessing AVPD using M-mode. The authors also
repeated the actual ultrasound examination in a similar
manner as we did in this study and, consequently, the
variability also reflected changes in fetal physiological
state and position as well as the resulting technical
challenges during the examination period, not only the
operator-related measurement variability. As expected,
repeat automated analysis of the same velocity recordings
always gave the same results with no measurement
variability.

A strength of this study is that the automated algorithm
simplifies the analysis of cTDI traces by evaluating
several cardiac cycles. As opposed to M-mode analysis,
this technique also provides an automated measurement
from a defined point in a well-defined curve, which is
likely to diminish the subjectivity of measurements. It
is also possible to assess what part of the movement
of the AV plane occurs during different cardiac phases.
Moreover, there is no variability from the point when the
traces have been obtained, as the automated algorithm
performs identically on every occasion. The variability
would come from factors such as the variability of the
examination itself, including intrinsic cardiac variability,
angle dependency when measuring velocities, the manual
positioning of ROIs and fetal movements.

Limitations of this study are the small number
of patients in the IUGR cohort and that only the
longitudinal diameter of the heart was used to normalize
measurements.

In conclusion, MAPSE, SAPSE and TAPSE, evaluating
longitudinal function in the fetal heart, could be measured
using an automated algorithm. All three variables showed
an increase with GA, but no significant change was
observed when corrected for cardiac size. A decrease was
seen in TAPSE and SAPSE in IUGR fetuses compared
with the normal population, but not after correction
for cardiac size. Comparison of AVPD measurements
obtained by the automated cTDI technique with those
measured by M-mode echocardiography showed similar
values for SAPSE, but relatively greater differences
for TAPSE and MAPSE due to the inherent technical
aspects related to both methods. Our results need to
be evaluated further in a larger cohort of patients in
which the automated method could potentially help in

Figure 5 Bland–Altman plots demonstrating agreement between
measurements of mitral annular plane systolic excursion (a), septal
annular plane systolic excursion (b) and tricuspid annular plane
systolic excursion (c) obtained by color tissue Doppler imaging
cTDI) and by anatomic M-mode in 30 low-risk fetuses at 18 \(+\) 0 to
42 \(+\) 6 weeks’ gestation. Solid line represents mean and dashed
upper and lower lines represent mean \(\pm\) 1.96 SD (95% limits of
agreement).
gathering larger amount of data to assist in the use of machine-learning/deep-learning models.

ACKNOWLEDGMENTS
The authors thank all women who participated in the study and all colleagues at Karolinska University Hospital, Stockholm, Sweden, involved in their care.

REFERENCES
1. Carlsson M, Ugander M, Mosen H, Buhre T, Arheden H. Atrioventricular plane displacement is the major contributor to left ventricular pumping in healthy adults, athletes, and patients with dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2007; 292: H1432–1439.

2. Lundback S. Cardiac pumping and function of the ventricular septum. *Acta Physiol Scand Suppl* 1986; 550: 1–101.

3. Acharya G. Measurement of atrioventricular annular plane displacement has been revived: will it prove to be useful in assessing fetal cardiac function? *Ultrasound Obstet Gynecol* 2013; 42: 125–129.

4. Carlsson M, Ugander M, Heiberg E, Arheden H. The quantitative relationship between longitudinal and radial function in left, right, and total heart pumping in humans. *Am J Physiol Heart Circ Physiol* 2007; 293: H636–644.

5. Asgeirsson D, Hedstrom E, Jogi J, Pahlm U, Steding-Ehrenborg K, Engblom H, Arheden H, Carlsson M. Longitudinal shortening remains the principal component of left ventricular pumping in patients with chronic myocardial infarction even when the absolute atrioventricular plane displacement is decreased. BMC Cardiovasc Disord 2017; 17: 208.

6. Pahlm U, Heiberg E, Engblom H, Gillenhammar T, Halvorsen S, Hansen HS, Erlinge D, Atar D, Heiberg E, Arheden H, Carlsson M. Longitudinal left ventricular function is globally depressed within a week of STEMI. *Clin Physiol Funct Imaging* 2018. DOI: 10.1111/cpf.12321.

7. Henein MV, Priestley K, Davaraneshi T, Buller N, Gibson DG. Early changes in left ventricular subendocardial function after successful coronary angioplasty. *Br Heart J* 1993; 69: 501–506.

8. Jones CJ, Raposo L, Gibson DG. Functional importance of the long axis dynamics of the human left ventricle. *Br Heart J* 1990; 63: 215–220.

9. Carvalho JS, O’Sullivan C, Shinebourne EA, Henein MY. Right and left ventricular long-axis function in the fetus using angular M-mode. *Ultrasound Obstet Gynecol* 2001; 18: 619–622.

10. Wandi B, Bojo L, Wranne B. Influence of body size and age on mitral ring motion. *Clin Physiol* 1997; 17: 633–646.

11. Cruz-Leal S, Carvajal K, Valenzuela-Aloaiza B, Figuera S, Sitges M, Gomez O, Rijnsburger AJ, Gratacos E. Value of annular M-mode displacement to assess fetal cardiac function in intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2013; 42: 175–181.

12. Gardiner HM, Pasquini L, Wolffenb, Barlow J, Arheden H, Halvorsen S, Hanss HS, Erlinge D, Atar D, Heiberg E, Arheden H, Carlsson M. Longitudinal left ventricular function is globally depressed within a week of STEMI. *Am J Physiol Heart Circ Physiol* 2007; 292: H1432–1439.

13. Herling L, Johnson J, Ferm-Widlund K, Lindgren P, Acharya G, Westgren M. Automated analysis of color tissue Doppler velocity recordings of the fetal myocardium using a new algorithm. *Cardiovasc Ultrasound* 2015; 13: 39.

14. Herling L, Johnson J, Ferm-Widlund K, Bergholm F, Elmstedt N, Lindgren P, Sonesson SE, Acharya G, Westgren M. Automated analysis of fetal cardiac function using color tissue Doppler imaging in second half of normal pregnancy. *Ultrasound Obstet Gynecol* 2019; 53: 348–357.

15. Saltvedt S, Almstrom H, Kubickics M, Reilly M, Valentin I, Grunewald C. Ultrasonic dating at 12–14 or 15–20 weeks of gestation? A prospective cross-validation of established dating formulae in a population of in-vitro-fertilized pregnancies randomized to early or late dating scan. *Ultrasound Obstet Gynecol* 2018; 52: 599–608.

16. Herling L, Johnson J, Ferm-Widlund K, Bergholm F, Lindgren P, Sonesson SE, Acharya G, Westgren M. Automated analysis of fetal cardiac function using color tissue Doppler imaging. *Ultrasound Obstet Gynecol* 2018; 52: 42–50.

17. Marsal K, Persson P, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr* 1996; 85: 843–848.

18. Avromsky K, Eliasson A, Hareide JH, Marsal K. Fetal blood velocity waveforms in normal pregnancies. A longitudinal study. *Acta Obstet Gynecol Scand* 1989; 68: 171–178.

19. Bergholm F. En algoritm för att finna maxima och minima i “periodisk” kolvsliknande rörelse. KTH Technology and Health: Stockholm, Sweden, 2016.

20. Garcia-Otero L, Gomez O, Rodriguez-Lopez M, Torres X, Soveral I, Sepulveda-Martinez A, Guirado L, Valenzuela-Alcaraz B, Lopez M, Martinez JM, Gratacos E, Cruiz F. Nomograms of Fetal Cardiac Dimensions at 18–41 Weeks of Gestation. *Fetal Diagnosis Ther* 2020; 47: 387–398.

21. Lee-Tannock A, Hay K, Goo A, Kumar S. Longitudinal Reference Ranges for Tricuspid Annular Plane Systolic Excursion and Mitral Annular Plane Systolic Excursion in Normally Grown Fetuses. *Ultrasound Med 2020*, 39: 929–937.

22. Peixoto AB, Bravo-Valenzuela NJ, Martinis WP, Tomis G, Mattar R, Moron AF, Pares DB, Araujo Junior E. Reference ranges for the fetal mitral, tricuspid, and interventricular septal annular plane systolic excursions (mitral annular plane systolic excursion, tricuspid annular plane systolic excursion, and septum annular plane systolic excursion) between 20 and 36+6 weeks of gestation. *J Perinat Med* 2020; 48: 601–608.

23. Rosyton P, Wright EM. How to construct ‘normal ranges’ for fetal variables. *Ultrasound Obstet Gynecol 1998*, 11: 30–38.

24. Bland JM, Altman DG. Measurement error in clinical research. *Lancet* 1986; I: 307–310.

25. Bland JM, Altman DG. Measurement error in method comparison studies. *Stat Methods Med Res* 1999; 8: 135–160.

26. Acharya G, Nitsas V, Erkkanen M, Makalkkilo K, Kavasuma T, Pakkala M, Huhta JC, Rasranen J. Experimental validation of uterine artery volume blood flow measurement by Doppler ultrasoundography in pregnant sheep. *Ultrasound Obstet Gynecol* 2007; 29: 401–406.

27. Hyslop NP, White WH. Estimating precision using duplicate measurements. *J Air Waste Manag Assoc* 2009; 59: 1032–1039.

28. Mao YK, Zhao BW, Wang B. Z-Score Reference Ranges for Angular M-Mode Displacement at 22–40 Weeks’ Gestation. *Fetal Diagnosis Ther* 2017; 41: 115–126.

29. Batterham A, Shave R, Oxborough D, Whyte G, George K. Longitudinal plane colour tissue-Doppler myocardial velocities and their association with left ventricular length, volume, and mass in humans. *Eur J Echocardiography* 2008; 9: 542–546.

30. Patoy O, Carvalho JS, Thilagathan B. Perinatal changes in cardiac geometry and function in growth-restricted fetuses at term. *Ultrasound Obstet Gynecol* 2019; 53: 655–662.

31. Kiserud T, Ebbing C, Kessler J, Rasmussen S. Fetal cardiac output, distribution to the placenta and impact of placental compromise. *Ultrasound Obstet Gynecol* 2006; 27: 126–136.

32. Hobbs JC, Gumina DL, Zaretsky MV, Driver C, Wilcox A, DeVore GR. Size and shape of the four-chamber view of the fetal heart in fetuses with an estimated fetal weight less than the tenth centile. *Am J Obstet Gynecol* 2019; 221: 495.e1–9.

SUPPORTING INFORMATION ON THE INTERNET
The following supporting information may be found in the online version of this article:

**Appendix S1** Z-score and centile calculator for mitral annular plane systolic excursion (MAPSE), septal annular plane systolic excursion (SAPSE) and tricuspid annular plane systolic excursion (TAPSE) obtained by color tissue Doppler imaging and analyzed automatically.