Area of the Fetal Ascending and Descending Aorta by Spatiotemporal Image Correlation in the Rendering Mode: Reproducibility and Comparison with Pregestational Diabetic Mothers

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Abstract

Background: The objective of this study was to assess the ascending and descending aorta area measurements by three-dimensional (3D) ultrasound using spatiotemporal image correlation (STIC) in the rendering mode comparing these measurements with pregestational diabetic mothers and assessing the reproducibility of the method. **Methods:** We carried out a retrospective cross-sectional study with 58 normal and nine fetuses from pregestational diabetic mothers between 20 and 33 + 6 weeks of gestation. Fetal heart volumes were acquired at the level of four-chamber view to obtain the reconstructed planes for the ascending and descending aorta areas in the rendering mode. Linear regression was performed to assess the correlation between the fetal aorta areas and gestational age (GA). To assess the intra- and interobserver reproducibility, we used the concordance correlation coefficient (CCC). **Results:** The mean ascending and descending aorta areas were 0.12 (0.02–0.48) and 0.11 (0.04–0.39) cm^2 in normal fetuses, respectively. There was a moderate positive correlation between GA and ascending aorta area measurements (0.005676*GA – 0.01283; $r = 0.53$, $P < 0.0001$) and strong positive correlation between GA and descending aorta area (0.01095*GA – 0.1581; $r = 0.68$, $P < 0.0001$). We observed a weak intra- and interobserver reproducibility with CCC ranging from 0.05 to 0.91. The mean difference in the ascending and descending aorta area measurements of normal and fetuses of pregestational diabetic mothers was −0.03 cm^2 ($P = 0.276$) and −0.03 cm^2 ($P = 0.231$), respectively. **Conclusion:** The fetal ascending and descending aorta area measurements obtained by 3D ultrasound using STIC in the rendering mode increased with GA in normal fetuses. The method showed weak intra- and interobserver reproducibility.

Keywords: Aorta, area, fetal heart, pregestational diabetes, rendering mode, three-dimensional ultrasound

Introduction

The dorsal aortas are formed by the union of endothelial cells derived from the splanchnic lateral mesoderm, through the process of vasculogenesis. Each pharyngeal arch receives its own artery, called the aortic arch artery, which arises from the aortic sac and empties into the dorsal arteries. Neural crest cells participate in the emergence of the tunics of the vessels of the arches.[1] The ascending aorta, separated from the left ventricle by the aortic valve, is formed from the arterial trunk and the aortic sac. The aortic arch, in turn, is formed proximally from the aortic sac and distally from the left dorsal aorta. The descending aorta is formed only from the left dorsal aorta.[2] The ascending part of the aorta begins at the aortic ostium and is intrapericardial. The aortic arch, on the other hand,

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curves superiorly, posteriorly, and to the left, then descending posteriorly to the left root of the lung, forming the descending part of the aorta.[3]

In an animal model of rats exposed in utero to maternal hyperglycemia, the maternal diabetes-induced deep changes in the vascular structure. The early narrowing of the microvasculature and the structural modifications of conductance arteries could be a preemptive adaptation to fetal programming of hypertension.[4] In humans, both fetal abdominal aortic diameter compliance and cross-sectional compliance were greater in diabetic than in nondiabetic mothers.[5]

Two-dimensional (2D) echocardiography is the gold-standard test for the diagnosis of congenital heart disease (CHD). Some CHDs that involve alterations in the diameter of the aorta, such as hypoplastic left heart syndrome and aortic coarctation, require accurate prenatal diagnosis and referral to tertiary referral centers in cardiology and neonatal cardiac surgery.[6] *Z*-scores of 2D measurements of the aortic isthmus and ductus arteriosus have been proposed to assess the risk of aortic coarctation.[7] However, the delimitation of the borders of the fetal aorta by 2D ultrasonography may be impaired by the fetal dorsum position, due to transmission artifacts from the ribs.

Spatiotemporal image correlation (STIC) is a software presents in some 3D ultrasound apparatus, which allows the evaluation of the heart and its vascular connections in multiplanar and rendering modes, as well as static or movement– cineloop (4D).[8,9] STIC in the rendering mode allows obtaining virtual planes, not accessible to 2D ultrasound, which improve the visualization of the interatrial and interventricular septa, in addition to the foramen ovale and atrioventricular valves.[10] Through adjustments in brightness and color, STIC in the rendering mode allows the area measurements of various structures of the fetal heart such as the interventricular septum,[11] atrioventricular valves,[12] and papillary muscles.[13]

The purpose of this study was to assess the area measurement of the fetal ascending and descending aorta by 3D ultrasound using STIC in the rendering mode comparing normal fetuses and fetuses from pregestational diabetic mothers. Furthermore, we assessed the intra- and interobserver reproducibility of the method.

Materials and Methods

A retrospective cross-sectional study was carried out at the fetal cardiology sector. STIC fetal cardiac volumes were selected in a database from 2012 to 2017. This study was approved by the Ethics Committee of Federal University of São Paulo (UNIFESP) (CAE: 87111116.4.0000.5505) and all participants signed the consent forms.

Inclusion criteria to normal pregnant women were the following: (1) singleton pregnancy, (2) gestational age (GA) between 20 and 33 + 6 weeks, (3) absence of fetal cardiac malformations, as well as other congenital anomalies, (4) absence of the electrical conduction beam of the fetal heart, and (5) absence of chronic maternal diseases, such as systemic arterial hypertension and collagenosis. Exclusion criteria were the following: (1) conditions that make it difficult and/or prevent adequate collection of STIC fetal cardiac volumes, such as abdominal scarring or maternal body mass index ≥35 kg/m^2 and (2) fetal back between 11 and 1 o'clock.

Regarding to diabetic mother, we did select only type 2 diabetes mellitus pregnant women. Pregestational diabetes mellitus was based at least one of the following parameters: glycated hemoglobin c ≥6.5% (≥48 mmol/mol), random plasma glucose ≥200 mg/dl (≥11.1 mmol/l), fasting plasma glucose ≥126 mg/dl (≥7.0 mmol/dl), and oral glucose tolerance test 2-h glucose in venous plasma ≥200 mg/dl (≥11.1 mmol/l). All pregestational diabetic mothers were selected from our high-risk pregnancy ambulatory, and all of them were well-controlled. The glycemic control was made by blood glucose report, being considered adequate if fasting <90 mg/dl and 1 h-postprandial <140 mg/dl. We did not select inpatients for glycemic control.

All fetal cardiac volumes were collected in a Voluson E8 apparatus (GE Healthcare, Milwaukee, WI, USA) equipped with a convex volumetric probe (RAB 4–8 L), according to a technique proposed by Gonçalves *et al*.[14] To acquire the volume of the region of interest (ROI), the entire fetal heart with its vascular connections should be encompassed in the smallest possible dimension. The fetal volume capture had the following standardization: opening angle between 20° and 40° and acquisition time between 10 and 15 s, fetal spine preferably between 5 and 6`clock, absence of fetal movements, and maternal apnea for a few seconds. A single STIC fetal cardiac volume was collected for each pregnant woman. To perform offline analysis of STIC fetal cardiac volumes, the main examiner (JPCS) used the 4Dviews version 10.0 program (General Electric Healthcare, Zipf, Austria). Before the beginning of the final analysis, the examiner was submitted to a specific training of 3 months to obtain the learning curve.[15]

Using the 4D views, the fetal heart image was displayed on the screen in the multiplanar mode: axial (a) – acquisition plane, sagittal (b), and coronal (c), being magnified until 1.23 times. Then, the axial plane (acquisition plane) was selected as reference, and the reference point was shifted to the crux cordis. The heart was rotated around the "z" axis, so that its apex is available at 10 o'clock, and then the reference point was shifted to the midpoint of the interventricular septum. After, making a slight movement on the "y" axis, we obtained the left ventricular outflow tract. Then, the reference point was moved above the aortic valve, and the A (reference) plane was rotated on the "z" axis to arrange the ascending aorta horizontally (3 o'clock). The ROI direction key was activated, and the green line (ROI) was positioned in the A plane in the left-right direction in a "think slice."[14] Then, the green line was shifted to the reference point above the aortic

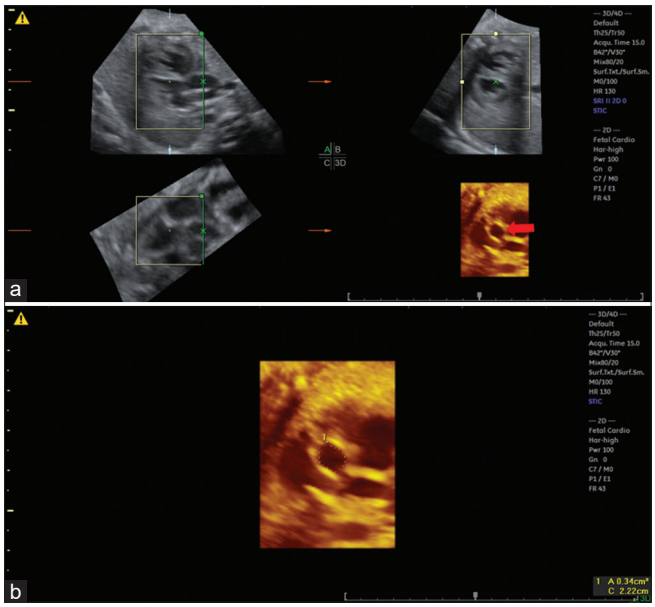

Figure 1: (a) Positioning of the green line (ROI) after the aortic valve, with automatic acquisition of the rendering image of the ascending aorta area (red arrow), (b) Rendering image of the fetal heart with delimitation of the internal area of the ascending aorta. ROI: Region of interest

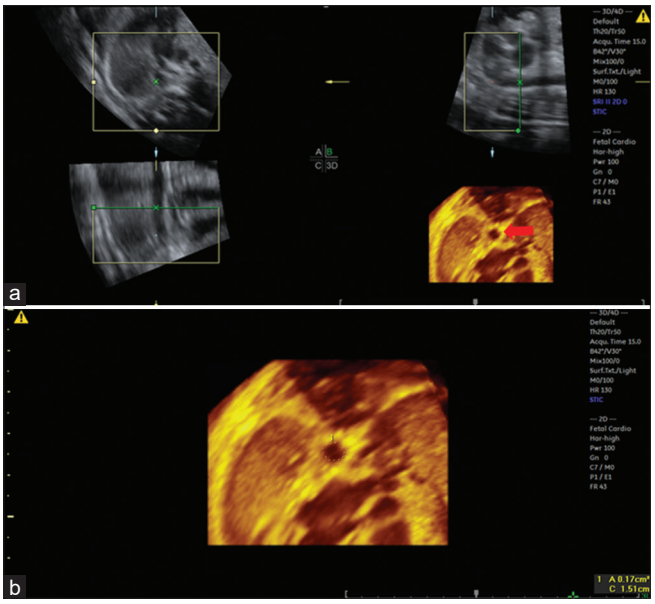

Figure 2: (a) Positioning of the green line (ROI) after emergence of the ductus arteriosus, with automatic acquisition of the rendering image of the descending aorta area (red arrow), (b) Rendering image of the fetal heart with delimitation of the internal area of the descending aorta. ROI: Region of interest

valve annulus, automatically obtaining the rendering image of the ascending aorta [Figure 1a]. In 1 × 1 (full screen) layout, in which only the rendering image of the fetal heart was displayed on the apparatus screen. The MEASURE key with area measurement was activated, which delimited the internal area of the ascending aorta [Figure 1b].

To obtain the descending aorta area, the process was restarted with alignment of the reference point at the fetal crux cordis with the aorta. Then, the reference point was shifted to the center of the aorta and the coronal plane (C) was rotated on the "z" axis so that the aorta was arranged at 12 o'clock, being automatically obtained in the sagittal plane (B) of the ductal arch. The ROI direction key was activated, and the ROI was selected in the left-right direction in B plane. Then, this line was positioned after the emergence of the ductus arteriosus, at the beginning of the descending aorta, automatically obtaining the rendering image of the descending aorta area [Figure 2a]. Then, in the 1 × 1 layout (full screen), only the rendering image of the fetal heart was displayed on the apparatus screen. The MEASURE key with area measurement was been activated, which delimited the internal area of the descending aorta [Figure 2b].

Data were collected in an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and Prism GraphPad version 7.0 (GraphPad Software; San Diego, CA, USA). The D'Agostino-Pearson's normality test was used to analyze whether the values present a Gaussian distribution. Nonparametric distribution variables were presented as medians and minimum and maximum values. Parametric distribution variables were presented as mean and standard deviation. To compare the variables between the groups, the *t*-Student and Mann–Whitney tests were used. The correlation between the areas of the ascending and descending aorta and GA was performed using the Spearman's test. Linear regression was performed to assess the ability of GA to predict the fetal area measurement of the ascending and descending aorta.[15]

For reliability and agreement calculations, the same examiner (JPCS) performed a second measurement of 19 randomly selected cases, trying to encompass the entire gestational period studied (intraobserver). For the interobserver assessment, a second examiner (NJBV) performed the same measurements of 19 cases blindly. For the reliability of intra- and interobserver measurements, the concordance correlation coefficient (CCC) was used through absolute and relative differences with their respective confidence intervals (CIs) of 95%.[16] The mean difference between intra- and interobserver measurements with its respective limits of agreement was assessed by the Bland–Altman plots.[17]

Results

We assessed 92 fetal heart volumes which were divided into two groups: 83 normal and nine from pregestational diabetes mellitus (all type 2 diabetes mellitus). To normal fetuses, both ascending and descending aorta area measurements were not possible in 25 fetal heart volumes, due to the low quality of the fetal heart volumes, preventing a proper visualization of fetal heart structures. To fetuses from pregestational diabetic mothers, the ascending and descending aorta area measurement were possible in all cases. Hence, for the final statistical analysis, we assessed 58 normal and nine pregestational diabetic mothers' fetal heart volumes. The clinical and

ultrasound characteristics of the population studied are shown in Table 1. The mean ascending and descending aorta area measurements were 0.12 (0.02–0.48) in 0.11 (0.04–0.39) cm^2 in normal fetuses, respectively. The mean ascending and descending aorta area measurements were 0.12 (0.08–0.14) and 0.11 (0.04–0.15) cm^2 in fetuses from pregestational diabetic mothers, respectively. There was no significant effect on maternal age (P = 0.110), GA at the time of ultrasound examination (P = 0.922), and area of the ascending (P = 0.266) and descending aorta (P = 0.305).

Considering all normal cases, there was a moderate positive correlation between GA and ascending aorta area (0.005676*GA– 0.01283; r = 0.53, P < 0.0001). Although significant, only 10.0% of ascending aorta area was linearly related to GA. The 1-week increase in GA accounts for the area of the ascending aorta at 0.005 cm^2 [Figure 3a]. There was a strong positive correlation between GA and descending aorta area (0.01095*GA– 0.1581; r = 0.68, P < 0.0001). Although significant, only 47.0% of the descending aorta area was linearly related to GA. The 1-week increase in GA accounts for the area of the descending aorta at 0.010 cm^2 [Figure 3b].

We observed very weak intraobserver (CCC = 0.09 [95% CI −0.20–0.38]] and interobserver (CCC = 0.05 [95%CI −0.18–0.28]) agreement for the measurement of area of the ascending aorta. The absolute mean difference between the second measurement and the first measurement from the same examiner was 0.15 cm^2 greater. The absolute mean difference between the second examiner's measurement and the first examiner's measurement was 0.12 cm^2 greater. We observed moderate intraobserver agreement (CCC = 0.91 [95% CI 0.83–0.99]) and weak interobserver (CCC = 0.87 [95% CI 0.76–0.97]) for the measurement of the area of the descending aorta. The absolute mean difference between the second and the first measurement from the same examiner was 0.04 cm^2. The absolute mean difference between the second examiner's measurement and the first examiner's measurement was 0.05 cm^2 greater [Table 2].

The mean relative difference in the area of the ascending aorta between intraobserver and interobserver measurements was 7.8 and 6.0 mm^2, respectively. The range of the ascending aorta area expected to meet 95% of the intra- and interobserver measurements was between −73.0 and 88.6 mm^2 and −72.2 and 84.2 mm^2, respectively [Figure 4].

The mean relative difference in the area of the descending aorta between intraobserver and interobserver measurements was 3.5 and −1.7 mm^2, respectively. The range of the descending aorta area expected to meet 95% of intra- and interobserver measurements was between −34.5 and 41.4 mm^2 and −34.1 and 30.7 mm^2, respectively [Figure 5].

The mean difference in the ascending and descending aorta area measurements of normal and fetuses of pregestational diabetic mothers was −0.03 cm^2 (P = 0.276) and −0.03 cm^2 (P = 0.231), respectively [Figure 6].

Table 1: Clinical and ultrasound characteristics of the studied population

Variable	Normal (n=58)	Pregestational DM (n=9)	P
Age (years)	32.3 (5.8)	28.8 (7.8)	0.110†
HbA1c (%)		8.0 (6.4–9.9)	
Gestational age (weeks)	26.0 (20.0–33.5)	25.9 (21.1–32.0)	0.922ƒ
Ascending aorta (cm^2)	0.12 (0.02–0.48)	0.12 (0.08–0.14)	0.266ƒ
Descending aorta (cm^2)	0.11 (0.04–0.39)	0.11 (0.04–0.15)	0.305ƒ

†Student's t-test: Mean (SD); ƒMann–Whitney test: Median (minimum–maximum). P<0.05. DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, SD: Standard deviation

Discussion

The development of fetal aorta shows some differences from adults. The bifurcation level of the abdominal aorta arose with GA, and at full term, reaches to the same level as adults. In the early fetal period, the bifurcation level of the common iliac artery is more inferior compared to the adults, and they reach the adult positions around full term.[18] The abdominal aorta grows linearly in both length and diameters and parabolically in volume with advance GA, without difference between male and female fetuses.[19]

The aim of this study was to establish a new technique that was more accurate than conventional 2D ultrasound to be applied

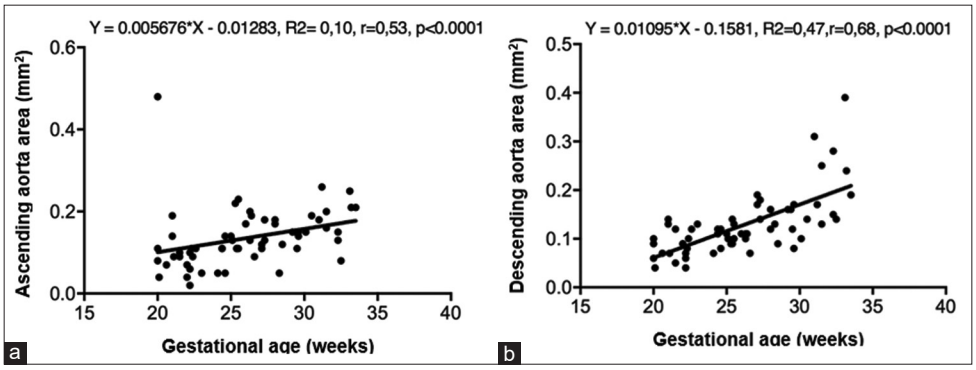

Figure 3: (a) Correlation between the fetal area measurement of the ascending aorta (cm^2) of normal pregnancies and GA (weeks), (b) Correlation between the fetal area measurement of the descending aorta (cm^2) of normal pregnancies and GA (weeks) Spearman's test P < 0.05. GA: Gestational age

Table 2: Values of the concordance correlation coefficient and their respective 95% confidence intervals with respect to intra- and interobserver reproducibility for the area of the ascending and descending aorta

	CCC	MD	95% CI	Relative difference			Absolut difference		
				Bias	LoA		Bias	LoA	
Intraobserver (cm^2)									
Ascending aorta	0.09	0.15	−0.20–0.38	7.8	−73.0	88.6	0.04	−0.28	0.35
Descending aorta	0.91	0.04	0.83–0.99	3.5	−34.5	41.4	0.00	−0.042	0.048
Interobserver (cm^2)									
Ascending aorta	0.05	0.12	−0.18–0.28	6.0	−72.2	84.2	0.04	−0.28	0.35
Descending aorta	0.87	0.05	0.76–0.97	−1.7	−34.1	30.7	0.00	−0.05	0.05

CCC: Concordance correlation coefficient, MD: Mean difference, CI: Confidence interval, LoA: Limit of agreement

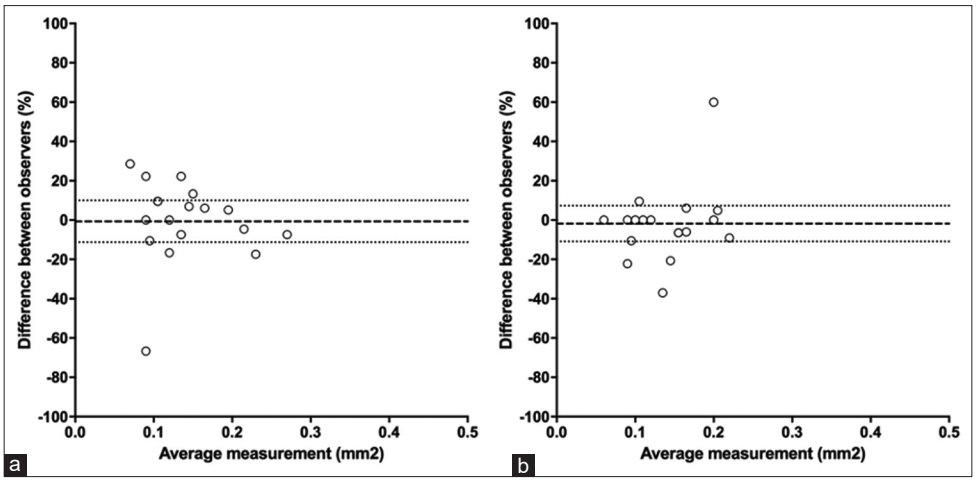

Figure 4: The Bland–Altman plots for the intra- (a) and interobserver (b) reproducibility of the fetal ascending aorta area measurement

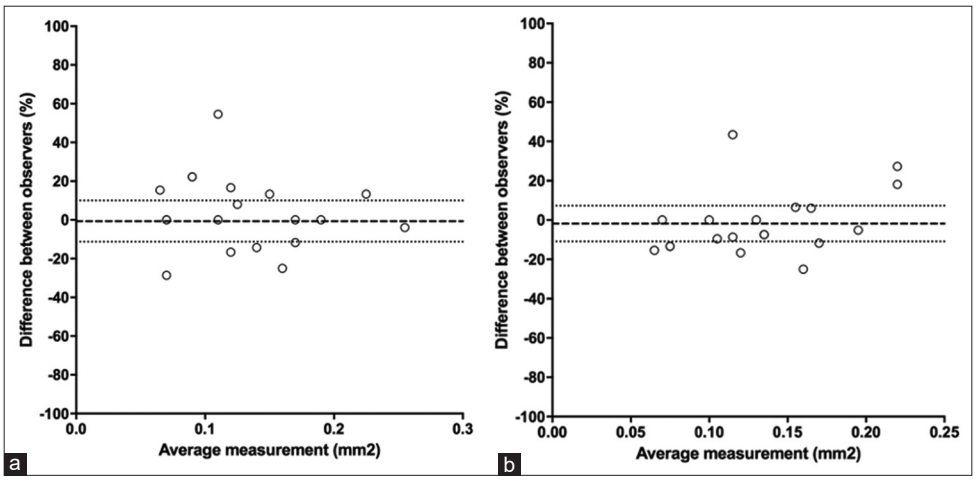

Figure 5: The Bland–Altman plots for the intra- (a) and interobserver (b) reproducibility of the fetal descending aorta area measurement

to the assessment of fetal aorta area measurement, since some of advantages of STIC in the rendering mode are the clearer identification of the edges of cardiac structures as chambers, valves, and vessels.

Maternal diabetes induces persistent alterations in fetal endothelial function and gene expression following glucose normalization.[20] High glucose inhibits the development of the blood vessel plexus, and the blood vessels formed show a narrower diameter than control vessels.[21] In an experimental animal model, pregnant rats with hypercaloric diet-induced gestational diabetes mellitus, the vasoconstriction was reduced in the thoracic aorta, but increased in the abdominal aorta.[22]

2D ultrasound has been traditionally used for the assessment of fetal vessels diameter during the pregnancy. Fetal left brachiocephalic vein diameter increased significantly throughout pregnancy, with a mean value of 0.7 mm at

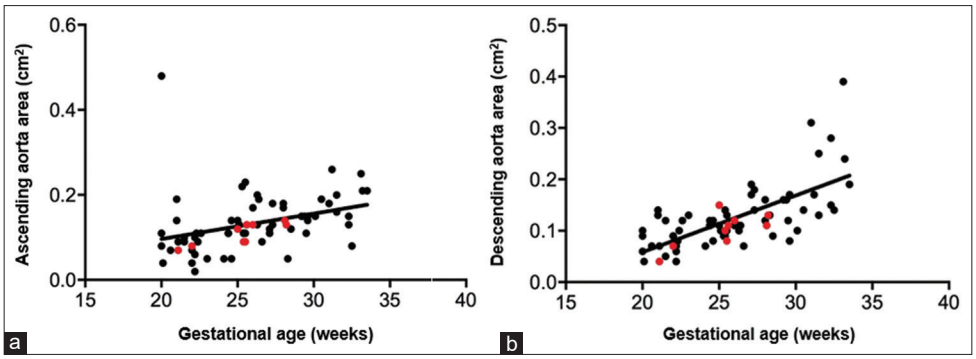

Figure 6: Scatter plot of the ascending (a) and descending (b) aorta area measurements of fetuses of normal (black circles) and pregestational diabetic mothers (red circles) according to GA. GA: Gestational age

11 weeks and 4.9 mm at term ([0.1442 × GA] − 0.8812; $r^2 = 0.87$), with good intra- and interobserver reproducibility.[23] However, in advanced GAs, the assessment of the inner edge of the fetal vessels may be hampered by transmission artifacts or fetal position, decreasing the accuracy of the 2D ultrasound. 3D ultrasound with STIC in the rendering mode improved visualization of the septa and the assessment of the defects, as well as the pattern of movement of the foramen ovale. Furthermore, STIC in the rendering mode improved evaluation of the alignment of the major vessels in relation to the atrioventricular annuli valves.[10]

In our study, we observed that both ascending and descending aorta areas increased with GA in normal fetuses. Cartier *et al*.,[24] in a prospective study including normal fetuses between 14 and 42 weeks of pregnancy, assessed the aorta diameter by 2D ultrasound and *M*-mode. They observed a high correlation between measurements made during systole and diastole ($r = 0.994$) and between 2D ultrasound and *M*-mode measurements ($r = 0.992$).

Visually, despite the absence of statistical difference, all measurements of the ascending aorta areas were at or below the 50th percentile for GA relative to normal fetuses. Likewise, in relation to the area of the descending aorta, only one measurement of the area was above the 50th percentile in relation to normal fetuses. Despite the small sample size and all pregestational diabetic mothers being well-controlled, it is already possible to observe the effect of diabetes mellitus on the measurement of the fetal aorta area measurement throughout pregnancy. The small sample size of pregestational diabetic mothers is because the comparison between normal and diabetic groups was a secondary objective of this study.

In an experimental study, Madri *et al*.[25] have demonstrated that yolk sac vasculopathy and failure of endocardial cushion epithelial-mesenchymal transformation occur in hyperglycemic conditions in murine whole conceptus culture and in embryos from streptozotocin-induced diabetic mice.

Our study demonstrated a low intra- and interobserver reproducibility for both measurements of the fetal ascending and descending aorta area measurements by 3D ultrasound using STIC in the rendering mode. The reproducibility difference was higher in the fetal ascending than descending aorta area measurement. We believe that this difference is consequence of different technique to obtain both measurements. In the ascending aorta area measurement, the examiner should perform several manipulations in the A plane. On the other hand, in the descending aorta area measurement, it is necessary only one manipulation in A plane and other one in C plane. Previous studies using this technology have demonstrated the CCC ranging from 0.83 to 0.86,[26] intraclass correlation coefficient (ICC) ranging from 0.97 to 0.98,[13] and from 0.85 to 0.95.[27] The main difference of this study from previous ones and that in these previous studies the measurements of fetal heart structure areas were performed in the acquisition plan, not being necessary reconstruction techniques to obtain the standardized plans, which decrease the reproducibility of the method. Moreover, although the examiner performed specific training for 3 months, the technique is complex and time-consuming and dependent on high-quality fetal heart volume. Although the technique was standardized, it was observed that, especially in advanced GA s, an adequate greater opening angle to scan all heart vascular connections was necessary to obtain the reconstructed planes, which may explain the inability to perform both measurements in 25 fetal heart volumes.

We observed one outliner in Figure 6a and two outliners in Figure 6b both in normal fetuses. Probably, it was consequence of the difficult identification of the inner edges of the aorta, making the measurement of the area less accurate. STIC is a new technology, time-consuming, and it is necessary a learning curve to obtain the adequate fetal heart structure views. According to Avnet *et al*.,[15] after an initial learning curve of 20 examinations, trainees succeeded in identifying 97%–98% of structures, with a highly significant degree of agreement with the expert's analysis ($P < 0.001$). They concluded that after an initial learning curve and under expert guidance, STIC is an excellent tool for trainees to master extended screening examinations of the fetal heart. Uittenbogaard *et al*.[28] assessed the feasibility of incorporating STIC into a tertiary fetal echocardiography program. Four sonographers participated in the study, one of whom had substantial previous experience of STIC volume acquisition and three of whom did not. More

experienced sonographer had a higher success rate in STIC volume acquisition (experienced vs. less experienced, 88.4% vs. 70.5%, $P = 0.02$). Of all analyzed STIC volumes, 64.8% were of high or sufficient quality. They conclude that STIC is as susceptible as conventional 2D ultrasound imaging to individual variations and limitations in scanning windows. Furthermore, due to the sample size of normal cases, these outliners did not interfere with the final statistical analysis.

New studies with higher case number, if possible multicenter, and with experienced examiners are necessary to prove the real applicability of the STIC in the rendering mode in the clinical practice to the assessment of the ascending and descending aorta areas.

Conclusion

In summary, we observed that the ascending and descending aorta area measurements obtained by 3D ultrasound using STIC in the rendering mode increased with GA in normal fetuses. The method to obtain the reconstructed views of the ascending and descending aorta showed weak intra- and interobserver reproducibility.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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