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Fetal cardiac output and ejection fraction by spatio-temporal image correlation (STIC): comparison between male and female fetuses

Débito cardíaco e fração de ejeção fetal por meio do spatio-temporal image correlation (STIC): comparação entre fetos masculinos e femininos

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Abstract

Objective: **To compare the cardiac output (CO) and ejection fraction (EF) of the heart of male and female fetuses obtained by 3D-ultrasonography using spatio-temporal image correlation (STIC).**

Methods: **We conducted a cross-sectional study with 216 normal fetuses, between 20 and 34 weeks of gestation, 108 male and 108 female. Ventricular volumes at the end of systole and diastole were obtained by STIC, and the volumetric assessments performed by the virtual organ computer-aided analysis (VOCAL) rotated 30°. To calculate the DC used the formula: DC = stroke volume / fetal heart rate, while for the FE used the formula: EF = stroke volume / end-diastolic volume. The DC (combined male and female) and EF (male and female) were compared using the unpaired t test and ANCOVA. Scatter plots were created with the percentiles 5, 50 and 95.**

Results: **The average of DC combined, DC left, DC right, FE right and FE left, male and female were 240.07 mL/min, 122.67 mL/min, 123.40 mL/min, 72.84%, 67.22%, 270.56 mL/min, 139.22 mL/min, 131.34 mL/min, 70.73% and 64.76% respectively, without statistical difference (*P*> 0.05).**

Conclusions: **The fetal CO and EF obtained by 3D-ultrasonography (STIC) showed no significant difference in relation to gender.**

Descriptors: **Fetal heart. Cardiac output. Cardiac volume. Echocardiography, three-dimensional. Heart rate.**

Resumo

Objetivo: **Comparar do débito cardíaco (DC) e a fração de ejeção (FE) do coração de fetos masculinos e femininos obtidos por meio da ultrassonografia tridimensional, utilizando o *spatio-temporal image correlation* (STIC).**

Métodos: **Realizou-se um estudo de corte transversal com 216 fetos normais, entre 20 a 34 semanas de gestação, sendo 108 masculinos e 108 femininos. Os volumes ventriculares no final da sístole e diástole foram obtidos por meio do STIC, sendo as avaliações volumétricas realizadas pelo virtual *organ computer-aided analysis* (VOCAL) com rotação de 30º. Para o cálculo do DC utilizou-se a fórmula: DC= volume**

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Abbreviations, acronyms & symbols	
CRL	Crown-rump length
C O	Cardiac output
CHD	Congenital heart disease
SD	Standard deviation
EF	Ejection fraction
EFW	Estimation of fetal weight
FHR	Fetal heart rate
EF	Ejection fraction
GA	Gestational age in weeks
ROI	Region of Interest
STIC	Spatio-temporal image correlation
UNIFESP	Federal University of Sao Paulo
US 2D	Bi-dimensional ultrasonound
US 3D	Three-dimensional ultrasound
VOCAL	Virtual organ computer-aided analysis
SV	Systolic volume

sistólico/frequência cardíaca fetal, enquanto que para a FE utilizou-se a fórmula: FE= volume sistólico/volume diastólico final. O DC (combinado, feminino e masculino) e a FE (masculina e feminina) foram comparadas utilizando-se o teste t não pareado e ANCOVA. Foram criados gráficos de dispersão com os percentis 5, 50 e 95.

Resultados: **A média do DC combinado, DC direito, DC esquerdo, FE direita e FE esquerda, para feminino e masculino, foram 240,07 mL/min; 122,67 mL/min; 123,40 mL/min; 72,84%; 67,22%; 270,56 mL/min; 139,22 mL/min; 131,34 mL/min; 70,73% e 64,76%, respectivamente; sem diferença estatística (*P*> 0,05).**

Conclusões: **O DC e a FE fetal obtidos por meio da ultrassonografia tridimensional (STIC) não apresentaram diferença significativa em relação ao gênero.**

Descritores: **Coração fetal. Débito cardíaco. Ecocardiografia tridimensional. Frequência cardíaca.**

INTRODUCTION

Congenital heart disease (CHD) accounts for significant portion of the rate of perinatal morbidity and mortality by both anatomical and functional cardiac defects. The DCC is the most common major malformations at birth [1,2], with a prevalence of 0.6 to 5% of live births [3]. Despite great efforts and technological advancement of two-dimensional echocardiography in the past two decades, the accuracy in detecting congenital heart disease in pre-natal is between 31% to 96% [4,5].

Despite the two-dimensional ultrasound (2D U.S.) is used for the study of cardiac anatomy with good accuracy for the analysis of fetal cardiac function by means of this diagnostic modality is still limited [6]. The analysis of the stroke volume (SV) and ejection fraction (EF) uses the formula Teichholz, which can be applied to wells of any size, assuming the ventricle has an elliptical shape, or using only a constant (X x Y x Z x 0.52) [7]. The Simpson's method is also employed for this purpose, but even more complex by dividing the ventricle in multi-cylinder, calculating the EP to each medium and maintaining the total of the fractions isolated [8].

The three-dimensional ultrasonography (3D U.S.) allows a more accurate volumetric evaluation that 2D ultrasound, especially for objects of irregular shapes, it allows the design of its outer surface [9], which may be of potential use for evaluation of fetal cardiac function. The Spatio-Temporal Image Correlation (STIC) is a software that allows a volumetric acquisition of the fetal heart with its vascular connections, and the images can be evaluated both on the multiplanar mode and surface (rendered). The images may be evaluated both a static and moving (4D) by means of a Cineloop sequence that simulates a complete cardiac cycle. The advantages of STIC to evaluate fetal heart are less dependent on operator's experience in obtaining diagnostic plans, shorter examination carried out with analysis of volumes in the absence of the patient, ability to assess structures by rendering mode to study their morphology and function [10-12]. With respect to cardiac evaluation at STIC, first study was performed by Messing et al. [13], who evaluated the volume of the ventricular chambers in both systole and diastole in 100 fetuses using methods Virtual Organ Computer-aided Analysis (VOCAL) associated with the inversion mode. Later, other authors also evaluated fetal cardiac function and Molina et al. [14] who used the STIC associated only with VOCAL, Uittenbogaard et al. [15] who used the STIC and 3D slice method and, more recently, Simioni et al. [16] and Hamill et al. [17], using only the VOCAL associated with STIC. However, no studies comparing cardiac function by means of 3D U.S. with STIC in relation to gender. It is known that in adults, by means of 3D echocardiography, women have a higher volume / ventricular mass than men of similar age [18].

The objective of this study was to compare cardiac output (CO) and EF heart male and female fetuses by 3D ultrasound using STIC and VOCAL software in order to try to determine if cardiac function is already dependent on gender antenatal period.

METHODS

We conducted a cross-sectional study, from May 2009 to July 2011, with healthy pregnant women between 20-34 weeks and 6 days. This study was approved by the Ethics Committee in Research of the Federal University of Sao Paulo (UNIFESP) No 0234/09, and the patients who consented to participate voluntarily signed a consent form.

Inclusion criteria were: 1) singleton pregnancy with live fetus, 2) gestational age determined by last menstrual period and confirmed by first trimester ultrasound, using as parameter the crown-rump length (CRL), with a difference less than 5 days.

Exclusion criteria were: 1) the fetal position with the dorsal anterior (between 11 and 1h), 2) excessive fetal movements, 3) severe attenuation of the sound beam (obesity, abdominal scars), 4) fetal malformation detected on ultrasound, 5) estimated fetal weight below the 10th percentile or above the 90th percentile, according to Hadlock et al. [19], 6) amniotic fluid index below the 5th percentile or above the 95th percentile, according to Moore & Cayle [20], 7) maternal chronic diseases that could interfere with fetal growth (chronic hypertension, diabetes mellitus and collagen) ; 8) cases in which it was not possible to identify the fetal external genitalia.

All patients were selected randomly, and these are coming from the Division of Prenatal Physiology, Department of Obstetrics, UNIFESP, or Basic Health Units of the metropolitan region of São Paulo (Brazil). Patients were evaluated only once, no data were obtained postnatally.

The following variables were evaluated pregnant women included: age, number of previous pregnancies and deliveries, gestational age, fetal weight, fetal heart rate (FHR), fetal gender, DC right ventricular and left ventricular EF and combined right and left. Age, number of previous pregnancies and deliveries of the pregnant women were obtained by questionnaires. The other variables were evaluated by ultrasonography.

The tests were conducted at Centro Paulista de Medicina Fetal (CPMF) and the Division of Three-Dimensional Ultrasound, Department of Obstetrics, UNIFESP, which were accomplished by only two investigators (CS and LLC), both with three years experience in 3D ultrasound in Obstetrics. All examinations were performed on branded handsets Voluson 730 Expert (General Electric Healthcare, Zipf, Austria) using a multifrequency convex volumetric transducer (RAB 4-8L). Initially, the observer, by means of 2D U.S., carried out the measurements of biparietal diameter, abdominal circumference and femur length to determine the estimated fetal weight [21]. The determination of the genus fetal was performed using the 2D U.S. [22]. The fetal heart rate (FHR) was determined by pulsed Doppler ultrasonography of the mitral valve. For the acquisition of the fetal heart volume, initially there was a two-dimensional evaluation in order to obtain an axial level of the four heart chambers. Then, with the fetus asking the home and pregnant breath for a few seconds, there was a 3D scan. Therefore, if the key-activated STIC, so that the region of interest (ROI) encompassing only the heart with their vascular connections. The sweep angle and speed of acquisition was determined by the examiner. The angle ranged from 20° to 25° in the first quarter, and 25° to 30° in the third quarter, while the acquisition time from 10 to 12.5 seconds. After the capture volume, it was found and the quality of that which is considered satisfactory, it was stored in the memory. After standardization of the position of the fetal heart Paladini proposed by [23], a single volume of each fetal heart was stored in the memory. Subsequently, volumes were recorded on compact discs (CDs) and transferred to a personal computer (PC).

The analyses were performed offline using the software 4D View version 9.1 (General Electric Healthcare). The axial plane of the multiplanar mode was selected as a reference. In order to evaluate the dynamics of the mitral and tricuspid valves, gradually reduce the speed of cinellop to obtain exact opening and closing of valves. The maximum diameter of the ventricle to the mitral and tricuspid valves determined the closed end of the ventricular diastole, whereas the smaller diameter end determined the ventricular systole. Then the key is activated VOCAL with a rotation angle of 30° (setting six consecutive planes). Thus, the reference point was moved to the center of the ventricle, and the axial plane rotated around the axis "y", so the cardiac apex is available within 12 hours. It was performed manually six planes defining the left ventricle after which the device provided the reconstructed image with the volume of the ventricular cavity. The same process was repeated for the right ventricle. Finally, there were obtained the volumes of the right and left ventricles, either at the end of systole and in the end of diastole. The stroke volume of each ventricle was determined by the formula: stroke volume = (ventricular volume at end diastole) - (ventricular volume at end systole). The DC each ventricle was determined by the equation: DC = (stroke volume) * (FCF). The combined DC was determined by adding the values obtained for the DC of the right ventricle and left. The EF of each ventricle was determined by the formula: EF = (stroke volume) / (ventricular volume at end diastole).

Statistical analysis was performed using the programs Excel 2007 (Microsoft Corp., Redmond, WA, USA), PASW (version 18.0, SPSS Inc., Chicago, IL, USA) and GraphPad (version 5.0, GraphPad Software, San Diego, CA, USA). The normal distribution was assessed using the Kolmogorov-Smirnov test. We compared maternal age, gestational age, fetal weight and FCF between the fetus pregnancies with female and male by means of the Student's t-test. Number of pregnancies and parity between groups was compared using the Mann-Whitney test. The DC (right, left and combined) and EF (right and left) were compared between groups by unpaired t-test and also by ANCOVA,

Table 1. Comparison of maternal age, number of pregnancies, parity, fetal weight and fetal heart rate between male and female fetuses.

	Female		Male		
	Mean	SD	Mean	SD	*P*
Age (years)	29.20	5.30	29.83	6.23	0.43
Number of pregnancies	1.55	0.83	1.64	0.96	0.49
Parity	0.43	0.70	0.51	0.75	0.29
Gestational age (weeks)	26.54	4.40	27.34	4.66	0.19
EFW (g)	1058.56	623.61	1195.21	685.46	0.13
Fetal heart rate (bpm)	141.19	9.69	140.08	9.37	0.39

EFW = estimated fetal weight, SD = standard deviation, P - value determined by unpaired t-test for age, gestational age, fetal heart rate and EFW, P-value determined by Mann-Whitney test for number of pregnancies and parity

Table 2. Comparison of fetal cardiac parameters evaluated between male and female fetuses.

	Female		Male					
	Mean	SD	Mean	SD	P^1	P^2	P^3	P^4
Cardiac output - right (mL/min)	123.40	96.39	131.34	104.36	0.56	0.46	0.27	0.30
Cardiac output - left (mL/min)	122.67	86.20	139.22	108.82	0.21	0.70	0.91	0.79
Cardiac output - combined (mL/min)	246.07	174.15	270.56	200.75	0.34	0.84	0.58	0.67
Ejection fraction - right (%)	67.22	11.34	64.76	11.55	0.11	0.20	0.22	0.20
Ejection fraction – left (%)	72.84	10.95	70.73	10.94	0.16	0.28	0.32	0.34

Cardiac output combined = (Cardiac Output - left) + (cardiac output - right), SD = standard deviation, P^1 = P-*value determined by paired t test,* P^2 = P-*value evaluated by ANCOVA using gestational age as a covariate;* P^3 = P *value assessed by ANCOVA using the estimated fetal weight as a covariate,* Pt = P-*value evaluated by ANCOVA using both gestational age and estimated fetal weight as covariates*

Table 3. Percentiles 5.50 and 95 for cardiac output - right, left and combined, considering both male and female fetuses.

	Right ventricle (mL/min) Percentile			Left ventricle (mL/min) Percentile			Combined (mL/min) Percentile		
GA	5	50	95	5	50	95	5	50	95
26	35.44	101.65	167.86	37.41	101.40	165.39	99.83	204.96	310.09
27	41.77	118.25	194.72	44.27	116.59	188.90	118.32	237.08	355.84
28	48.48	135.78	223.09	51.53	132.61	213.68	137.90	271.00	404.11
29	55.55	154.26	252.96	59.19	149.47	239.74	158.56	306.72	454.88
30	62.99	173.67	284.35	67.26	167.16	267.06	180.30	344.23	508.15
31	70.80	194.03	317.25	75.72	185.69	295.66	203.13	383.53	563.93
32	78.98	215.32	351.66	84.58	205.05	325.52	227.04	424.63	622.22
33	87.53	237.56	387.59	93.85	225.26	356.66	252.04	467.53	683.01
34	96.44	260.73	425.02	103.52	246.29	389.07	278.13	512.22	746.31
35	105.72	284.84	463.96	113.59	268.17	422.74	305.30	558.71	812.12

GA = gestational age in weeks; combined cardiac output = cardiac output of right ventricle + left ventricle cardiac output; percentiles estimated standard deviation, as suggested by Altman & Chitty [24] using gestational age and / or estimated fetal weight as covariates. Since we did not notice a difference in the evaluated parameters between fetuses were male and female, were determined curves of normal (5th percentile, 50 and 95) by the mean and standard deviation for the estimated gestational age [24], using data from all fetuses.

RESULTS

We initially evaluated 290 pregnant women; however, 34 were excluded due to unfavorable fetal position, 5 per estimated fetal weight below the 10th percentile for gestational age and 35 for failing to identify fetal sex. So for the final statistical

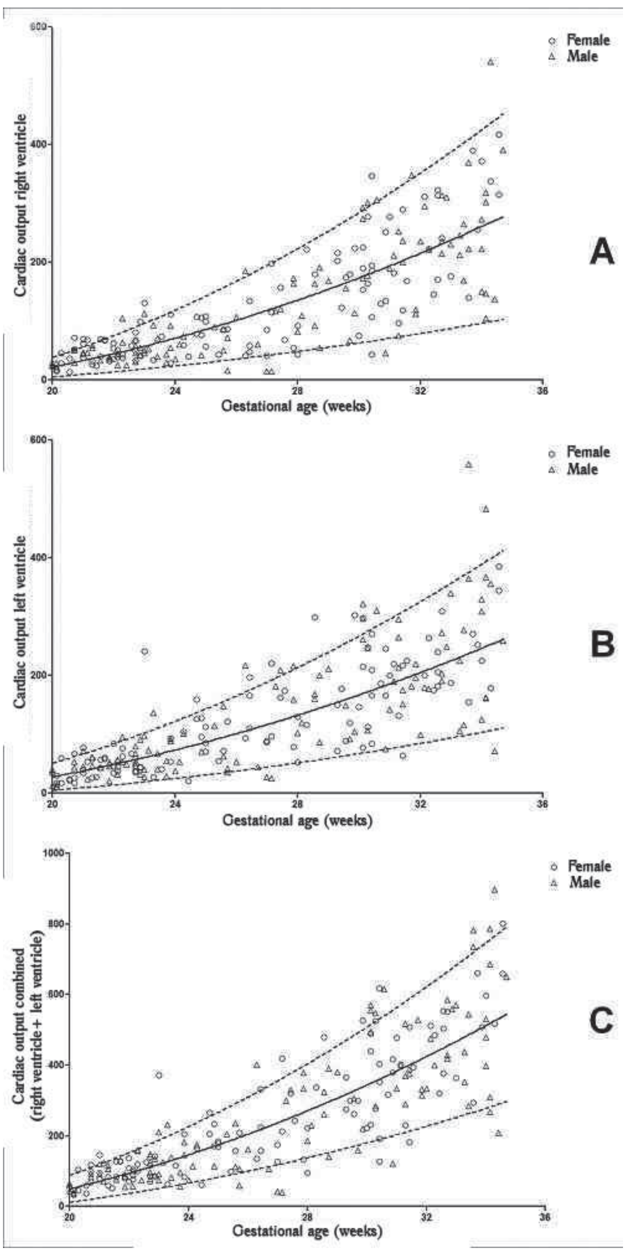

Fig. 1 - Curves of reference - 5, 50 and 95 percentile - for cardiac output: A) Right ventricle; B) Left ventricle, C) = cardiac output combined (right ventricle) + (left ventricle). The percentiles were evaluated as suggested by Altman & Chitty [24], using data from both fetuses, male and female

Table 4. Percentiles 5, 50 and 95 for the ejection fraction - right and left, considering both male and female fetuses.

	Right ventricle (%) Percentile			Left ventricle (%) Percentile		
GA	5	50	95	5	50	95
26	54.15	69.80	85.45	61.00	75.98	165.39
27	53.76	69.33	84.90	60.19	75.53	188.90
28	53.18	68.62	84.06	59.15	74.84	213.68
29	52.42	67.69	82.95	57.87	73.90	239.74
30	51.48	66.51	81.54	56.36	72.71	267.06
31	50.36	65.11	79.86	54.61	71.27	295.66
32	49.05	63.47	77.89	52.63	69.58	325.52
33	47.56	61.59	75.63	50.41	67.64	356.66
34	45.88	59.49	73.09	47.97	65.45	389.07
35	44.02	57.15	70.27	45.28	63.02	422.74

GA = gestational age in weeks; percentiles estimated standard deviation as suggested by Altman & Chitty [24]

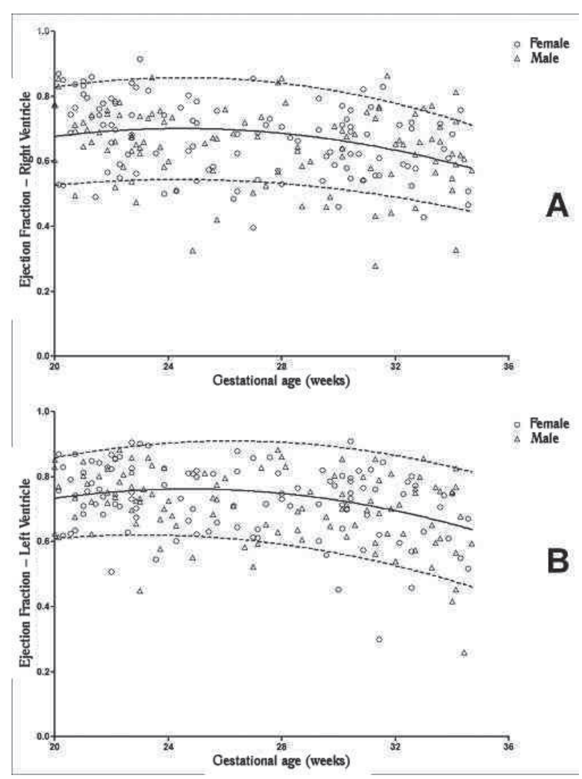

Fig. 2 - Curves of reference - 5, 50 and 95 percentile - for ejection fraction: A) Right ventricle; B) Left ventricle. The percentiles were evaluated as suggested by Altman & Chitty [24], using data from both fetuses, male and female.

analysis we included 216 fetuses, with 108 of each sex.

There was no significant difference between the fetuses of pregnant women with male and female regarding maternal age, number of previous pregnancies and deliveries, gestational age, fetal weight and fetal heart rate (Table 1).

No significant differences when comparing the CD and EF between the fetuses were male and female, both the analysis of initial data, even when adjusting for gestational age, estimated fetal weight, or both (Table 2). Thus, the percentiles for the CD and EF were calculated for gestational ages between 26 and 35 weeks, using data both from male fetuses as female (Tables 3 and 4, Figures 1 and 2).

DISCUSSION

In this study, we evaluated fetal cardiac function by means of 3D U.S., using the softwares STIC and VOCAL. We used the limit range of 20 to 34 weeks, because during this period the visualization of cardiac chambers is easier, providing better heart volume. In addition, below 20 weeks postnatal fetal viability is not possible, making it unnecessary to evaluation of their cardiac function. Used as standards for acquiring volumetric cutting four cardiac chambers, where possible position of the back in 6 hours, a sweep angle ranging from 20 ° to 30 ° according to the gestational age, as long as possible to acquire, in addition to exclusion of cases with back between 11 and 1am, as proposed by Gonçalves et al. [25].

This study aimed to evaluate possible differences in cardiac function according to fetal gender. However, we could not demonstrate significant differences for both the DC and for the FE, both adjusted for gestational age and the estimated fetal weight. In a study using 3D transthoracic echocardiography, the volume / left ventricular mass was significantly higher in women than in men of similar age. Another cause could be the largest pulmonary resistance of women relative to men, as a possible consequence of increased left ventricular EF. A previous study by 2D echocardiography has shown that heart failure with normal EF is often more common in women than in men of similar age [26]. Possibly, external factors acting in the postnatal period may justify the difference in cardiac function in relation to gender, in adults of the same age.

In this study, 290 pregnant women were initially evaluated, 34 were excluded due to poor quality of packages corresponding to a rate of 11.7% loss. In a recent study by Schoonderwaldt et al. [27], 84 women were initially evaluated between 20-34 weeks, however, excluded volume 54, corresponding to a rate of 64% loss. This high rate of loss due to low quality of cardiac volumes is due to inclusion of the previous position back as an exclusion criterion and the small number of cases evaluated in comparison to the study conducted by us.

In our study, as we have not identified differences in cardiac function in male and female fetuses, we determined reference values only for both the DC (right, left and combined) and for EF (right and left). We opted for the determination of reference values from 26 weeks, taking into account fetal viability. In relation to the previous study by Molina et al. [14], who evaluated 100 fetuses of both sexes, between 12 and 34 weeks, we observed that their values were overestimated compared to ours. We believe that one possible reason is the inclusion in the endocardium volume calculation, while in this study only the area delimited anechoic (blood) present in the cardiac chambers, the same as in previous studies by our group [16.28] . In comparison with longitudinal study carried out by Uittenbogaard et al. [15] who used the technique 3D slice, we observed that in the range 26 to 30 weeks, our values were also underestimated the likely cause is possibly also the inclusion of the endocardium in the volumetric calculations performed in that study. In a recent study by Hamill et al. [17], who evaluated 180 cardiac volumes by STIC and VOCAL, we found that DC increased with gestational age and did not differ between the right and left ventricles, whereas EF decreased with gestational age and was higher in the left ventricle . These results are in agreement with those obtained in our study, with 216 fetuses of both sexes.

This study did not evaluate the reproducibility of the method STIC and VOCAL, because it has been proven in a previous study conducted by our group [16], as well as other studies [14,27,29].

Limitations of this study relate primarily to the capture volume, which requires a fetal position right (back in 6 hours) or semi-ideal (back between 3 and 9), poor fetal movements and apnea in pregnant women, which sometimes makes testing extremely time consuming. Furthermore, the post-processing of images, with calculations of ventricular volumes at the end of systole and diastole, to obtain the CD and EF consumes a long time (10-12 minutes), making their use in clinical practice. Another limitation relates to biotype and the presence of maternal abdominal scars generating acoustic shadows difficult and sometimes impossible to capture a stroke volume to a satisfactory quality. The same limitations have already been described in a previous study carried out by Hamill et al. [29].

CONCLUSION

In summary, this is the first study that sought to assess differences in the intrauterine fetal cardiac function in relation to gender by US 3D. The lack of statistical difference observed in the CD and EF of male and female fetuses implies that external factors postnatal are responsible for these observed differences in adult life for people of different sex and same age. Further studies evaluating the cardiac function by means of 3D U.S. in childhood and adolescence are necessary to confirm our assumption.

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