# Collaborative Study of 4-Dimensional Fetal Echocardiography in the First Trimester of Pregnancy

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***Objectives***—Accumulating evidence supports a role for 2-dimensional fetal echocardiography in the first trimester of pregnancy for the identification of congenital heart defects. Our objective was to investigate the role of 4-dimensional (4D) sonography in the identification of congenital heart defects between 11 and 15 weeks of pregnancy.

***Methods***—This study included 4 centers with expertise in first-trimester 4D fetal echocardiography. Fetuses with and without confirmed heart defects were evaluated between 11 and 15 weeks and their volume data sets were uploaded onto a centralized file transfer protocol server.

***Results***—Forty-eight volume data sets from fetuses with normal (n = 17) and abnormal (n = 16) hearts were evaluated. Overall, the median (range) accuracy, sensitivity, and specificity, as well as the positive and negative likelihood ratios, for the identification of fetuses with congenital heart defects were 79% (77%–83%), 90% (70%–96%), 59% (58%–93%), 2.35 (2.05–9.80), and 0.18 (0.08–0.32), respectively.

***Conclusions***—(1) Four-dimensional fetal echocardiography can be performed in the first and early second trimesters of pregnancy; and (2) 4D volume data sets obtained from fetuses between 11 and 15 weeks can be remotely acquired and accurately interpreted by different centers.

***Key Words***—congenital heart defects; echocardiography; fetal; first trimester; 4-dimensional sonography; obstetric ultrasound; prenatal diagnosis, spatiotemporal image correlation

Congenital malformations account for more than 20% of all infant deaths,[1] and congenital heart defects are the most common types of birth defects.[1] Our ability to identify heart defects in the prenatal period is limited by the following factors: (1) early or late gestational age (GA); (2) the structural complexity of the fetal heart, particularly in the abnormal heart; (3) the extensive training required to become proficient in, and maintain, expertise in fetal echocardiography; (4) frequent fetal and/or maternal motion; (5) maternal obesity; (6) a limited or excessive amniotic fluid volume; and (7) the fetal position.

Accumulating evidence supports the role of 2-dimensional fetal echocardiography in the first trimester of pregnancy.[2–18] Two-dimensional sonography in the first trimester relies on standardized anatomic planes for examination of the fetal heart, including the 4-chamber view, the left and right outflow tracts, as well as the 3-

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**Abbreviations**
*4D, 4-dimensional; GA, gestational age; STIC, spatiotemporal image correlation*

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vessel view, among others.[2–18] Visualization of these sonographic planes can be facilitated by color Doppler imaging.[2–18]

Prior studies demonstrated that among centers with technical expertise, 4D sonography with spatiotemporal image correlation (STIC) is an accurate and reliable method for fetal echocardiography in the second trimester of pregnancy,[19] as well as between 14 and 41 weeks' gestation.[20] The main objective of this study was to investigate the role of 4D sonography in the identification of congenital heart defects between 11 and 15 weeks of pregnancy.

## Materials and Methods

This study involved the participation of 4 international centers with expertise in 4D fetal echocardiography during the first trimester. Four-dimensional volume data sets were obtained by transvaginal sonography following the ALARA (as low as reasonably achievable) principles.[21] Each center uploaded volume data sets from fetuses with proven congenital heart defects (by neonatal echocardiography, surgery, or autopsy) and volume data sets from fetuses without congenital heart defects onto a centralized file transfer protocol server. The information technology department of the coordinating center created center-specific directories on its file transfer protocol server, designed to facilitate the uploading of volume data sets. A research coordinator not involved in the assessment of the volume data sets organized the reception and delivery of volume data sets and randomly assigned a number to each participating center and volume data set.

Participating centers were provided with those volume data sets submitted by each of the other sites. All centers evaluated each data set using 4D View software (GE Healthcare, Milwaukee, WI) and reported the diagnosis only during the analysis phase of the study.

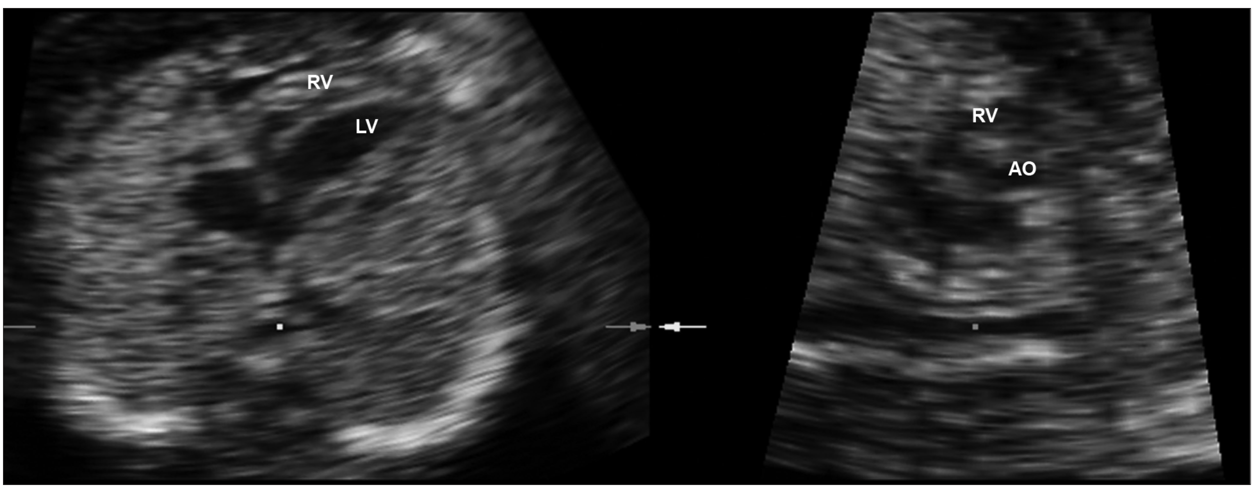
Inclusion criteria were as follows: (1) signed Institutional Review Board–approved informed consent forms; (2) GA between 11 and 15 weeks at the time of sonography; and (3) volume data sets obtained by the STIC technique using B-mode and/or color Doppler sonography.

Diagnostic indices, including accuracy, sensitivity, and specificity, as well as positive and negative likelihood ratios, of 4D fetal echocardiography in the first trimester of pregnancy were calculated. Intercenter agreement was determined by a generalized $\kappa$ statistic. The statistical packages used were SPSS version 12.0 (IBM Corporation, Armonk, NY) and MedCalc version 7.4.4.1 (MedCalc Software, Mariakerke, Belgium). $P < .05$ was considered significant.

## Results

Forty-eight volume data sets from fetuses with normal (n = 17) and abnormal (n = 16) hearts were included in the study. In some cases, more than 1 volume data set per case were included. The median GA was 13 weeks (range, 11–15 weeks). The GA distribution was as follows: 11 weeks (n = 2), 12 weeks (n = 12), 13 weeks (n = 15), 14 weeks (n = 2), and 15 weeks (n = 2). Heart abnormalities included atrioventricular canals, tricuspid atresia (Figure 1), aortic coarctation, a double-outlet right ventricle, tetralogy of Fallot (Figure 2), transposition of the great arteries,

**Figure 1**. Four-dimensional fetal echocardiography in a fetus with tricuspid atresia at 14 weeks 3 days. A hypoplastic right ventricle is seen in the 4-chamber view (left image). The corresponding ductal arch plane (right image) shows a small right ventricle and a tortuous ductus arteriosus. AO indicates transverse view of the aorta; LV, left ventricle; and RV, right ventricle.



Ebstein anomaly with pulmonary atresia, hypoplastic left heart syndrome, situs inversus with an atrioventricular canal, a persistent left superior vena cava (Figure 3), and a ventricular septal defect (Table 1).

Overall, the median (range) accuracy, sensitivity, and specificity as well as the positive and negative likelihood ratios, for the identification of fetuses with congenital heart defects were 79% (77%–83%), 90% (70%–96%), 59% (58%–93%), 2.35 (2.05–9.80), and 0.18 (0.08–0.32), respectively. Table 2 shows the corresponding diagnostic indices for each participating center.

There was moderate intercenter agreement, as determined by a generalized κ statistic for multiple raters ($\kappa = 0.6$). Between 15% and 23% of the volume data sets were considered to have limited clinical value because the image quality was not adequate, the volume data set did not include sufficient anatomic information, or image artifacts limited visualization of the anatomic structures. Of note, participating centers with lower diagnostic indices reviewed a higher proportion of suboptimal volume data sets than those with higher diagnostic indices (Table 2).

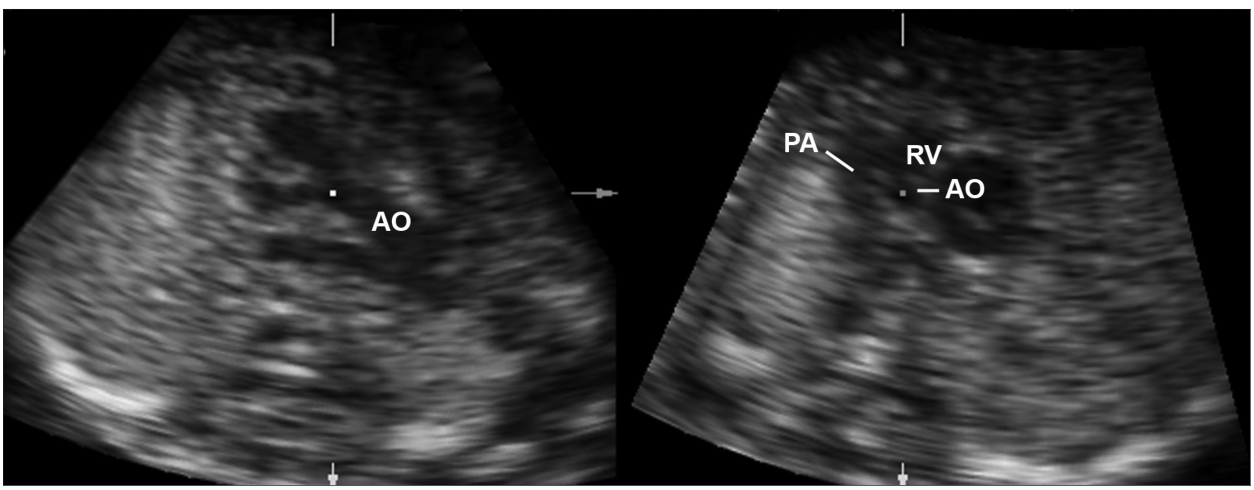
## Discussion

Our results indicate that volume data sets obtained with 4D sonography and STIC contain enough data to allow the clinician to distinguish normal and abnormal fetal hearts between 11 and 15 weeks of pregnancy. These results are in keeping with a prior report indicating that standardized planes for fetal echocardiography can be obtained from 4D volume data sets obtained in the first trimester of pregnancy in a reproducible manner[16] and with a more recent report indicating that 4D fetal echocardiography in the first trimester can identify congenital heart defects with 95.3% accuracy.[22]

Accumulating evidence indicates that first-trimester fetal echocardiography could play an important role in the prenatal diagnosis of congenital heart defects,[2,4,6,12–18] and that first-trimester fetal echocardiography is feasible in high-risk patients.[2,12] Of note, a study using transvaginal sonography reported that the success rate of visualization of the 4-chamber view, long axis of the aorta, pulmonary trunk with the 3-vessel view, and crossover of the great arteries increased with GA, from 20% in week 11 to 92% in week 13.[7] A more recent study, among women undergoing chorionic villous sampling between 11 and 13 weeks' gestation, reported 93.1% accuracy in the identification of congenital heart defects using a high-frequency linear transducer.[18] In another study in high-risk women, using a combination of transabdominal and transvaginal sonography, the authors reported sensitivity of 70% and specificity of 98% in the identification of congenital heart defects before 16 weeks.[13] In a large low-risk population, the authors reported that in 29 of 39 cases of congenital heart defects, the heart defect was suspected in the first trimester.[23] Of note, in the latter study, all examinations were performed with transabdominal sonography; however, in 7.3% of the cases, a transvaginal scan was also required.

The median sensitivity (90%) of 4D first-trimester fetal echocardiography for the identification of congenital heart defects reported in this multicenter study is comparable with the results of a study done at a single institution.[22]

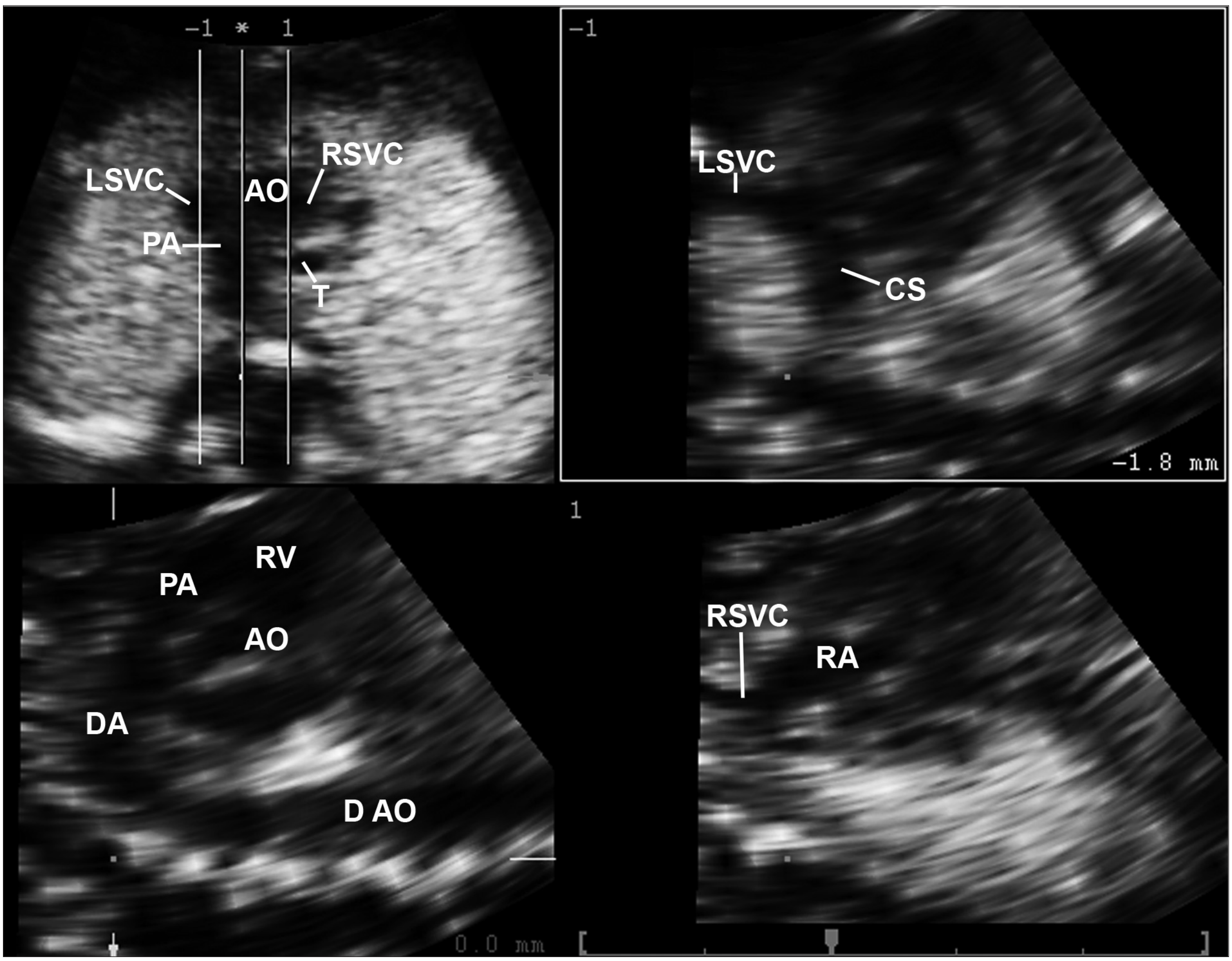
**Figure 2**. Four-dimensional fetal echocardiography in a fetus with tetralogy of Fallot at 15 weeks. A ventricular septal defect with an overriding aorta in seen in the left outflow tract view (left image). The pulmonary artery can be seen on the corresponding short-axis view (right image). AO indicates aorta; PA, pulmonary artery; and RV, right ventricle.



However, the median specificity (59%) is lower than previously reported.[22] This finding may be a reflection of moderate intercenter agreement. The observation that 4D volume data sets had limited clinical value in almost one-fifth of the cases appears to be a reflection of the challenges of 4D first-trimester fetal echocardiography due to frequent fetal motion, the size of the cardiac structures, and the frequent need to rely on color Doppler imaging to evaluate these structures. However, in many instances, the anatomic information contained in these volume data sets was sufficient to differentiate normal from abnormal cases and to diagnose the specific congenital heart defect.

Limitations of this study include the following: (1) Four-dimensional volume data sets cannot be obtained in all first-trimester fetuses due to the above-mentioned technical challenges. Thus, there is a potential for a selection bias. (2) There was no standardization of the sonographic settings or the frequency of transvaginal probes used before volume data set acquisition. The image quality contained in an STIC volume data set can be substantially improved by optimizing the 2-dimensional grayscale and color Doppler settings before volume acquisition. Thus, it is possible that optimization of the sonographic settings may have improved the diagnostic indices reported in this study. (3) By design, this study included only centers with expertise in first-trimester 4D fetal echocardiography.

**Figure 3**. Four-dimensional fetal echocardiography in a fetus with a persistent left superior vena cava (LSVC) at 13 weeks. Tomographic ultrasound imaging shows the 3-vessel and trachea view in the reference image (top left image). The top right image shows a persistent left superior vena cava draining into a dilated coronary sinus (CS). The bottom left image shows the ductal arch plane. The bottom right image shows the right superior vena cava (RSVC) draining into the right atrium (RA). AO indicates aorta; DA, ductus arteriosus; D AO, descending aorta; PA, main pulmonary artery; RV, right ventricle; and T, trachea.



Thus, the results of this study may not be reproducible in centers with less experience in 4D sonography.

Collectively, this study indicates that 4D fetal echocardiography can be performed between 11 and 15 weeks' gestation, and that 4D volume data sets obtained from fetuses in the first and early second trimesters can be remotely acquired and accurately interpreted by different centers.

**Table 1.** Four-Dimensional Volume Data Sets From Fetuses Between 11 and 15 Weeks' Gestation According to the Diagnosis

| Diagnosis | n |
|---|---|
| Normal | 17 |
| Atrioventricular canal | 4 |
| Transposition of the great arteries | 3 |
| Hypoplastic left heart syndrome | 2 |
| Tetralogy of Fallot | 1 |
| Double-outlet right ventricle | 1 |
| Aortic coarctation | 1 |
| Ebstein anomaly with pulmonary atresia | 1 |
| Tricuspid atresia | 1 |
| Isolated ventricular septal defect | 1 |
| Persistent left superior vena cava | 1 |

**Table 2.** Diagnostic Indices of First-Trimester 4D Fetal Echocardiography for Identification of Congenital Heart Defects at Each Participating Center

| Center | Accuracy, % | Sensitivity, % | Specificity, % | LR+ | LR– | Suboptimal Volumes, % |
|---|---|---|---|---|---|---|
| A | 79.0 | 95.2 | 58.8 | 2.31 | 0.08 | 18 |
| B | 83.0 | 70.0 | 93.0 | 10.00 | 0.32 | 15 |
| C | 77.3 | 95.5 | 59.0 | 2.33 | 0.08 | 21 |
| D | 78.3 | 84.2 | 58.8 | 2.05 | 0.27 | 23 |

LR+ indicates positive likelihood ratio; and LR–, negative likelihood ratio.

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