



Full length article

## Early fetal ultrasound screening for major congenital heart defects without Doppler



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### ABSTRACT

**Objective:** Congenital heart defects are the most common major structural fetal abnormalities. Color flow mapping has played a dominant role in the detection of abnormalities during the first trimester, regardless of the International Society of Ultrasound in Obstetrics and Gynecology warning on the use of Doppler during early pregnancy. The aim of our study was to investigate the use of transvaginal two-dimensional sonography without Doppler for assessing the four-chamber view and the outflow tract view of fetuses at 11–13 weeks of gestation for cardiac screening of major congenital heart defects.

**Study Design:** This was a prospective observational study conducted in the Fetal Medicine Unit of Cabueñes University Hospital, between May 2014 and August 2015. Only low risk-pregnancies were studied. All ultrasonographic examinations were performed by two experienced sonographers in maternal-fetal medicine. The combination of high-frequency transvaginal (nine MHz) and transabdominal (six MHz) ultrasonography transducers were used. An early cardiac screening was performed in 97% of cases. Statistical analysis was carried out using successive multivariate logistic regression models in order to investigate the effect of crown-rump length and body mass index on the probability of visualizing the four-chamber view and/or the outflow tract view.

**Results:** 663 low-risk pregnant women were included. Regarding the transvaginal approach, neither the crown-rump length nor the body mass index had a statistically significant relationship on the probability of visualization of the four-chamber view and outflow tract view. For the transabdominal approach, the crown-rump length and the body mass index presented a statistically significant effect on the visualization of the four-chamber view and the outflow tract view. Using the transvaginal approach: the success rate of performing a four-chamber view was 89.4% and 82.4% for the outflow tract view. Using the transabdominal approach: the success rate of performing a four-chamber view was 77.8% and 61.5% for the outflow tract view. Four major congenital heart defects were diagnosed, and the prenatal ultrasonographic diagnosis was confirmed for all cases.

**Conclusions:** Routine first-trimester ultrasonography without Doppler, when performed by experienced sonographers, can effectively identify major congenital heart defects. Additional multicenter well designed studies should clarify the feasibility of this approach.

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### Introduction

Congenital heart defects (CHDs) are the most common major structural fetal abnormalities, affecting approximately eight per 1000 live births in Europe. Half of the CHDs are major cardiac defects. An estimated 36,000 infants are born alive with a CHD,

and 3000 deaths due to CHD occur as terminations of pregnancy for fetal anomaly, late fetal deaths, or early neonatal deaths [1,2]. Although many risk factors for CHD have been identified, more than 90% of cases occur in low-risk patients [3,4]. Therefore, the guidelines of several ultrasound societies recommend second-trimester fetal screening for CHD for the entire population of pregnant women [5]. Careful prenatal evaluation for CHD, clearly allows optimal neonatal management and provides information on the appropriateness of aggressive neonatal resuscitation, palliative perinatal care, and pregnancy termination [6,7].

The study was conducted in Cabueñes Hospital, Gijón, Asturias, Spain.

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The performance of an adequate early examination of the fetal heart can be hampered by technical difficulties such as image resolution, limited clarity in relation to the size of the structures being examined, and fetal movements [8,9]. In addition, some cardiac abnormalities are not evident until later in pregnancy [8,9]. Advances in ultrasound technology and training over the last 10 years have resulted in increased rates of visualization of the four-chamber view (4CV) and outflow tract view (OTV) in the late first trimester (> 90% visualization at 13 weeks) [9]. Benefits of the early detection of major CHDs include the ability to perform additional assessments during the time allowed for legal pregnancy termination, the option for an early and safe pregnancy termination; and in cases with a normal scan, early reassurance that a major CHD is unlikely [10].

Transabdominal plus transvaginal sonography using high-frequency transducers are usually performed for a detailed assessment of the fetal heart in the first trimester. The basic principles for studying the heart in the first trimester are the same as those in the second or third trimester. The ultrasound screening markers that have been proposed for identifying patients during the first trimester who have low or increased risk of CHD include nuchal translucency and patterns of blood flow in the ductus venosus and through the tricuspid valve and assessing of the cardiac axis [3,8,11]. In addition to evaluating the presence of these markers, color flow mapping has played a dominant role in ultrasonography during the first trimester, regardless of the International Society of Ultrasound in Obstetrics and Gynecology warning on the safe use of Doppler in fetuses at 11–13<sup>+6</sup> weeks' gestation [12]. In this regard, the aim of our study was to investigate the use of transvaginal two-dimensional sonography without Doppler for assessing the 4CV and the OTV of fetuses at 11–13 weeks of gestation for cardiac screening of major CHDs [9].

## Materials and methods

### Study and patient population

This prospective observational study of low-risk pregnant women undergoing routine first-trimester screening ultrasound, was carried out at the Fetal Medicine Unit of Cabueñes University Hospital, Center of Reference in Prenatal Diagnosis in Asturias, Spain, between May 2014 and August 2015. The inclusion criteria were as follows: healthy Caucasian pregnant women with a gestational age between 11 + 0 and 13 + 6 weeks, fetal crown-rump length (CRL) between 45 and 84 mm, singleton pregnancy, and no previous history of chromosomal abnormalities or structural alterations. The exclusion criteria were as follows: high-risk diseases for cardiac malformations (such as diabetes mellitus or lupus erythematosus) or exposure to potential teratogenic agents.

### Clinical protocols

The clinical Protocol study included a combination of the following information: maternal age and maternal serum free  $\beta$ -human chorionic gonadotrophin ( $\beta$  HCG) and pregnancy-associated plasma protein "A" (PAPP-A) levels, and results of assessment of fetal nuchal translucency and nasal bone. The sonographers were blinded for  $\beta$ HCG and PAPP-A results. The maternal body mass index (BMI) was calculated in kilograms per square meter on the day of the ultrasonographic examination. All ultrasonography examinations were performed by two sonographers with extensive experience in maternal-fetal medicine, using a Voluson 730 Expert ultrasound machine equipped with a 5–7.5 MHz endovaginal probe and a 3–5 MHz convex transducer, and a Voluson E8 ultrasound machine (GE Medical Systems, Zipf, Austria) equipped with a 5–9 MHz endovaginal probe and a 3–6 MHz convex

transducer. Two-dimensional ultrasound was performed for transvaginal and transabdominal cardiac screening in each patient. The fetal crown-rump length and nuchal translucency were measured following recommendations of the Fetal Medicine Foundation [13] and a specific protocol that included a systematic evaluation of the situs (Fig. 1), the 4CV (Fig. 2) and the OTV (Fig. 3). The vena cava, ductus venosus, presence of tricuspid regurgitation, and cardiac axis were not assessed. Doppler was only employed for cases with abnormal findings.

According to our hospital clinical guidelines, all fetuses included in the study underwent a complete ultrasonographic follow-up during the second (18–21 weeks' gestation) and third trimester (32–34 weeks' gestation). Fetal karyotyping by chorionic villus sampling or amniocentesis was offered when the first-trimester assessment for aneuploidies or a CHD indicated high risk for a chromosomal abnormality [14]. All neonates underwent a physical examination performed by a pediatrician immediately after birth. Postnatal echocardiography was only performed for cases with cardiac murmur or with findings suggesting CHD. A prenatal diagnosis of CHD was verified by autopsy for all CHD cases except for one case managed with surgery.

### Statistical analysis

Data are reported as mean  $\pm$  SD or %. Statistical analysis was performed using The R Statistics Package 3.4.4 version for Windows. A prediction logistic regression model was used to assess the probability of visualization of the 4CV and/or the OTV (using transvaginal or transabdominal approach) by taking into account the CRL and BMI separately. Weight and height were also analyzed independently. It was evaluated if the TN value could be influenced by the maternal age. A global model was adjusted by logistic regression for the visualization of the 4CV and the OTV, either using the transvaginal or transabdominal approach. Odds ratios and 95% confidence intervals are expressed for each of the studied variables. The two sonographers involved in the study, were put in the model in order to evaluate if the probability of performing a cardiac screening was different between them.

### Ethical approval

The research protocol of the study was reviewed and approved by the hospital ethical committee, Gijón, Asturias, Spain. All the women included were informed about the research (purposes and tools used), and written consent was obtained.

## Results

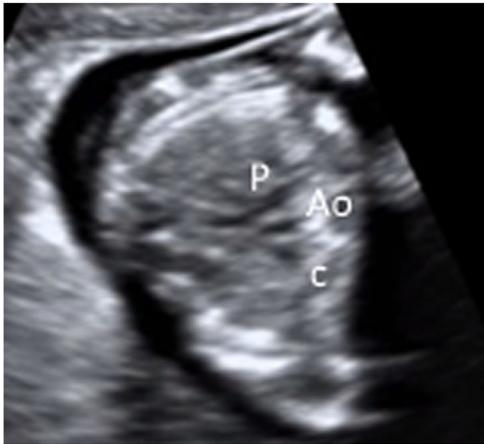
Of the 1630 women who underwent first trimester ultrasonography screening during the period of the study, 1219 met the



**Fig. 1.** Axial section of fetal thorax at the level of the stomach (st) which is located in the left side, Aorta (Ao) is just to the left side of the spine (sp).



**Fig. 2.** Axial section of fetal thorax at the level of the four-chamber view (4CV), cardiac apex is pointing to the left. Atria and ventricles are symmetrical on either side of the septum, Aorta is left to the spine. Lung fields with homogeneous and symmetrical echogenicity.



**Fig. 3.** Axial section of fetal thorax at the level of great vessels, showing Pulmonary artery (P), Aorta and vena cava (C).

inclusion criteria. Incorrect dating, multiple gestations, and nonviable pregnancy were the most common exclusion criteria. 45 women refused to participate in the study, being distrust the main reason. In addition, the two sonographers in charge of the study, were not always available as they also follow up other more complicated cases. Finally, a total of 663 women were included in the study. Characteristics of the participants are summarized in Table 1. Increased nuchal translucency (>99th centile) was seen in two fetuses; hypoplasia of the nasal bone was not detected in any case.

Regarding the transvaginal approach, neither the CRL nor the BMI have a statistically significant relationship on the probability of visualization of the 4CV and OTV. Nor weight and height, when

**Table 1**

Data is reported as mean  $\pm$  SD.

Parameter	Value
Mother Age (years)	34 $\pm$ 4.78
Body Mass Index (Kilogram per meter squared)	24.16 $\pm$ 4.22
Fetal Crown-Rump Length (millimeters)	66.82 $\pm$ 6.91
Nuchal Translucency (millimeters)	1.54 $\pm$ 0.41

considered independently. Regarding the transabdominal approach, the CRL (OR=1.078, 95% CI: 1.047–1.109) and BMI (OR=0.9, 95% CI: 0.863 to 0.939) present a statistically significant effect (they have an effect) on the probability of visualization of the 4CV. Weight (OR=0.959, 95% CI: 0.944 to 0.975) and height (OR=0.026, 95% CI: 0.001 to 0.758) each have a significant effect on the visualization of the 4CV. The CRL (OR=1.092, 95% CI: 1.064–1.12) and the BMI (OR=0.897, 95% CI: 0.861 to 0.935) have a statistically significant effect on the probability of visualization of the OTV. When we consider weight and height independently, we observe that weight has a statistically significant effect (OR=0.958, 95% CI: 0.943 to 0.973), but not height (OR=0.062, 95% CI: 0.003–1.228). TN results were not influenced by maternal age. The findings of the ultrasound are summarized in Table 2.

There were statistically significant differences between the two sonographers that performed the ultrasound examinations. Regarding sonographer “A” (reference category), sonographer “O” presented a lower probability of success (OR=0.294, 95% CI: 0.095 to 0.909).

Our study showed an effectiveness of 100% for detecting CHDs. Four CHDs were diagnosed (Case 1 ; Case 2 ; Case 3 ; Case 4 ).

## Discussion

A new approach for performing early cardiac screening is possible. The method directly assesses the cardiac anatomy

**Table 2**

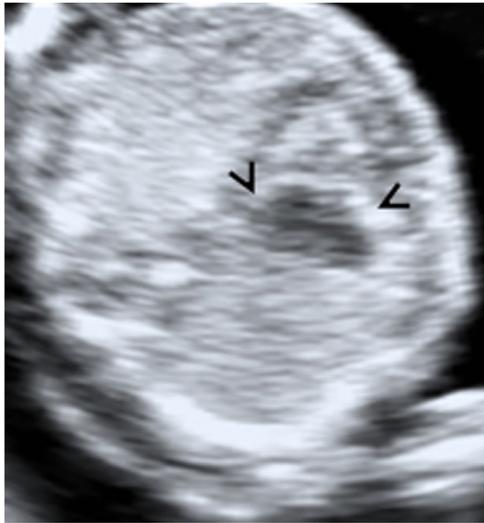
Findings of the ultrasound.

Parameter of Study	Results
Fetal Crown-Rump Length (millimeters)	66.81 $\pm$ 6.91
Nuchal Translucency (millimeters)	1.59 $\pm$ 0.41
Success Rate of Performance 4CV Using Transvaginal Approach	89.4%
Success Rate of Performance 4CV Using Transabdominal Approach	77.8%
Success Rate of Performance OTV Using Transvaginal Approach	82.4%
Success Rate of Performance OTV Using Transabdominal Approach	61.5%
Success Rate of Performance Early Cardiac Screening (4CV+OTV) Using Vaginal And Transabdominal Approach	97%

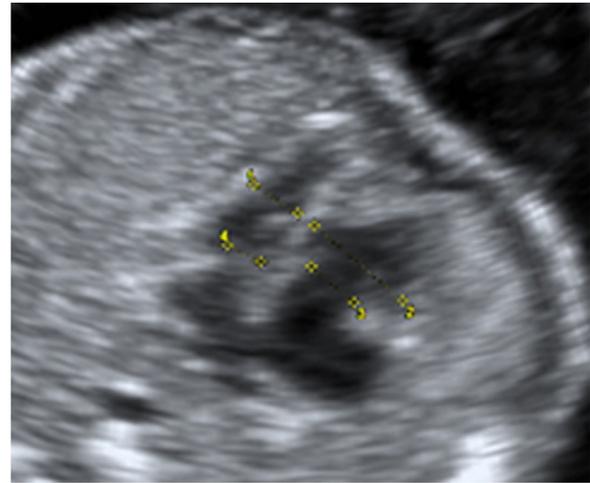
Data is reported as mean  $\pm$  SD or %.



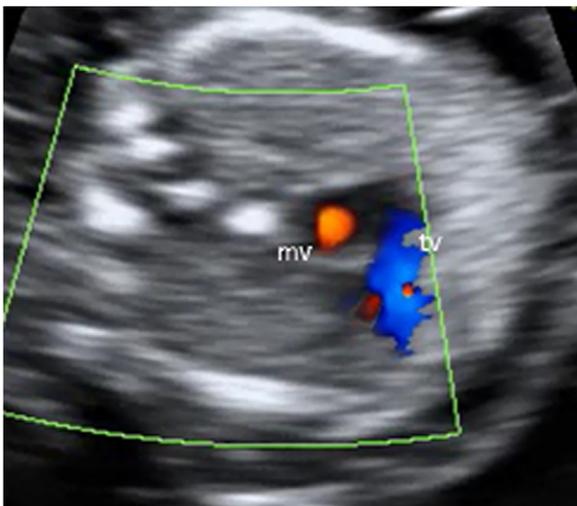
**Case 1.** Atrioventricular defect. Four-chamber view (4CV) showing a gap in the middle of the heart (Fig. 1). Congenital heart defect detected in a 45 years old patient, BMI 21.8, 12-week fetus with 4.6 mm NT and 55.47 mm CRL value. Amniocentesis result: 21 trisomy.



**Case 2.** Atrioventricular defect four-chamber view (4CV) showing a single atrioventricular valve (Fig. 1). Congenital heart defect detected in a 38 years old patient, BMI 24.9, 13-week fetus with 3.1 mm NT and 71.3 mm CRL value. Chorion biopsy result: 21 trisomy.



**Case 4.** Aortic coarctation. Four-chamber view (4CV) showing right cavities dominance (Fig. 1). A dominance of the Pulmonar artery (P) over the Aorta (Ao) was also appreciated in OTV. An interventricular communication (arrows head) and a left superior vena cava was also observed. Congenital heart defect detected in a 40 years old pregnant woman, BMI 20.7, and 13-week fetus with 3 mm NT and 66.82 mm CRL value. Amniocentesis result: 46 XX.



**Case 3.** Hypoplastic cleft heart syndrome. Four-chamber view (4CV) color Doppler image showing flow across the tricuspid valve (tv) but no flow over the mitral valve (mv) (Fig. 1). Congenital heart defect detected in a 27 years old patient, BMI 26.4, 12-week fetus with 1.29 mm NT, 59.59 mm CRL value. (Fig. 1). Chorion biopsy result: 18 trisomy. Omphalocele and hydrops fetalis were also observed.

without the use of Doppler, and our findings indicate that this approach could be a valuable diagnostic tool. Available evidence on screening a low-risk population for CHDs is very limited, and all the existing data are based on results obtained by Doppler examinations. To the best of our knowledge, no studies analyzing fetal cardiac anatomy without Doppler in the first trimester have been published [23–25].

The first trimester of pregnancy is a particularly vulnerable period for fetal development, such that acoustic exposure from ultrasound devices can disturb biological tissue that might be sensitive to certain types of ultrasonography examinations [15]. Because Doppler examinations expose tissue to much higher levels of energy than B-mode gray scale two-dimensional or three-dimensional ultrasonography, it has been hypothesized that Doppler ultrasound might produce adverse effects; especially

during the early gestation period, when the rate of cell division is highest and when fetal blood flow is less well developed and hence less likely to dissipate any heat created during the examination [16]. The documented harmful effects of ultrasonography on the fetus have been limited to animal studies [17–21], but the absence of evidence of harm in humans is not equal to the evidence of absence of harm. In this sense, maintaining the thermal index to lower than one and using the lowest possible output for the shortest possible time compatible with obtaining diagnostic information, is advisable. In addition, based on the International Society of Ultrasound in Obstetrics and Gynecology safety statement, a Doppler examination of fetal vessels should not be performed during early pregnancy without a clinical indication [22]. Operator experience and training are the most important factors associated with the successful identification of fetal cardiac defects. Well trained operators can achieve CHD detection rates of 40%–50% in low-risk populations, and in high-risk women, the detection rate can increase to >80% [26]. In this sense, chromosomal abnormalities are known to be associated with CHDs in 30% of fetuses with CHDs and ultrasound markers are known to only reveal 33.3% of CHDs [14,27,28].

Our study has several limitations; therefore further multicenter well designed studies of larger samples are needed to clarify the feasibility of this screening approach. First, since only two sonographers with extensive experience (more than ten years) in performing first trimester ultrasonography were involved with the study, we cannot assume that if all the ultrasonography staff members were involved in the study, that the results would be similar. Second, this was a single-center study; and because the prevalence of CHD in a low-risk population is low, the number of study participants was too small. Moreover, the unusually high prevalence of CHD in our study group could also have affected the results. And third, an evaluation of the cardiac axis was not performed. This assessment should be considered for future investigations because of recent data that support the conclusion that an abnormal cardiac axis found on ultrasonography should be considered to be a marker of CHD [29,30]. Despite the limitations of the study, our results suggest that the diagnosis of major CHDs on routine first trimester scan performed by experienced sonographers, is possible and effective without the use of Doppler.

## Mendeley datatest

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