

Reliability of the first-trimester cardiac scan by ultrasound-trained obstetricians with high-frequency transabdominal probes in fetuses with increased nuchal translucency

M. BELLOTTI*, V. FESSLOVA†, C. DE GASPERI*, G. ROGNONI*, V. BEE*, I. ZUCCA*, A. CAPPELLINI‡#, G. BULFAMANTE§¶ and C. M. LOMBARDI**

Departments of *Obstetrics and Gynecology and §Human Pathology, University of Milan, DMCO S. Paolo, Milan, †Centre of Fetal Cardiology, Policlinico S. Donato IRCCS, Milan, **Studio Diagnostico Eco, Vimercate, Milan and ¶Fondazione Policlinico, Mangiagalli, Regina Elena, Milan and ‡Department of Human Pathology, University of Milan, Bicocca, Italy

KEYWORDS: congenital heart disease; fetal echocardiography; fetal heart; first trimester; nuchal translucency

ABSTRACT

Objective To examine prospectively the reliability of ultrasound-trained obstetricians performing a first-trimester fetal cardiac scan with high-frequency transabdominal probes, by confirming normal or abnormal heart anatomy, in pregnancies referred for increased nuchal translucency thickness (NT).

Methods Trained obstetric operators assessed the fetal heart in 133 fetuses with increased NT (>95th centile) at 11–14 weeks of gestation. A high-frequency transabdominal probe was used to confirm or refute normal cardiac anatomy rather than to establish a specific diagnosis. Following this preliminary screening by the ultrasound-trained obstetrician, specialized fetal echocardiographers rescanned the fetal heart in order to confirm the accuracy of the obstetric operators' findings and to establish a diagnosis in abnormal cases. Fetal cardiologists repeated the examinations at 20 and 32 weeks of pregnancy. Postnatal follow-up lasted 2 years. Twelve fetuses with normal karyotype and normal anatomy were lost to follow-up.

Results A total of 121 fetuses with increased NT between 11 and 14 weeks' gestation were studied. Congenital heart disease (CHD) was detected in 20/121 (16.5%) fetuses. In addition, there were three with mild ventricular disproportion, the right ventricle being larger than the left, considered as a minor non-specific cardiac abnormality.

CHD was associated with chromosomal anomalies in 12/20 (60%) cases. Among the 121 fetuses, there was agreement between ultrasound-trained obstetricians and fetal cardiologists in 116 (95.9%) of the cases, and the ultrasound-trained obstetricians correctly identified 18 cases with major cardiac defects. However, there was disagreement in five cases: two with small ventricular septal defects and three with ventricular disproportion.

Conclusions Our results provide evidence that obstetricians, trained to study the heart in the second trimester, can also differentiate reliably between normal and abnormal heart findings in the first trimester, when using a high-frequency transabdominal ultrasound probe. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Congenital heart disease (CHD) is among the most frequent of all congenital anomalies. Prenatal detection of CHD is limited mainly to the second trimester because screening programs among unselected populations are usually performed during the routine second-trimester scan. Fetal nuchal translucency thickness (NT) measurement screening programs create a new population of at-risk pregnancies and there has been a resultant increase in demand for early fetal echocardiography as extensive studies have reported an association between increased

Correspondence to: Dr M. Bellotti, Department of Obstetrics and Gynecology, University of Milan, DMCO S. Paolo, Via Rudini 8, Milan 20142, Italy (e-mail: bellotti.m@libero.it)

#Deceased.

Accepted: 16 February 2010

NT (>95th centile) measurement and increased risk for CHD¹⁻⁵. The majority of CHDs, however, occur in low-risk patients⁶⁻⁹. Currently, prenatal management of pregnancies with increased fetal NT includes invasive fetal karyotyping and a midgestation sonographic evaluation of fetal extracardiac and cardiac morphology. In a few specialized centers, fetal cardiologists carry out an early fetal cardiac investigation. Previously, transvaginal sonography was the preferred approach¹⁰ because it offered better image resolution. However, in the last 10 years, distinctly higher diagnostic accuracy has been reported with transabdominal ultrasound due to improvements in transducers and processors¹¹ and this is currently the ultrasound method of choice for fetal cardiologists. Unfortunately, for financial reasons it is not feasible, even in specialized centers, to perform expert cardiac study on all fetuses with increased NT and only cases with NT above the 99th centile are offered early fetal echocardiography.

It would be optimal to involve first-level operators in performing a preliminary selection of fetuses with NT between 95th and 99th centiles in order to reassure women in cases with normal findings and to offer an early study by fetal cardiologists in cases with suspected anomalies. We designed a prospective multidisciplinary study aiming to examine the reliability of obstetricians, who were trained in and had extensive experience of ultrasound techniques, when performing a first-trimester fetal cardiac scan using high-frequency transabdominal probes¹² (≥ 7.5 MHz) in pregnancies referred for increased NT.

PATIENTS AND METHODS

This was a prospective multidisciplinary study conducted between June 2003 and June 2005, during which we recruited 133 fetuses with increased NT measurements at 11–14 weeks' gestation referred to our tertiary center (Prenatal Diagnosis Unit, Department of Obstetrics and Gynecology, University of Milan, Italy) for a more detailed investigation. NT measurements were between the 95th and 99th centiles in 50 fetuses and above the 99th centile in 83 fetuses. We obtained approval from our institutional ethics committee for the study and written informed consent was obtained from each participant. All fetuses were examined initially by ultrasound-trained obstetricians (C.D., C.L., G.R.), who categorized the heart as normal or abnormal. These operators were experienced in routine cardiac anomaly screening in the second and third trimesters and also had specialist training, for the purposes of this study, in the first-trimester cardiac scan, using the same protocol as that used in the second and third trimesters and applying color Doppler flow mapping for morphological evaluation of the four chambers and the great vessels. The duration of the cardiac examination did not exceed 30 min. Their diagnostic interpretations were then verified during the same session by one of two fetal cardiologists (M.B., V.F.) who were blinded to the findings of the obstetrician; in abnormal cases,

diagnoses were established. All scans were carried out transabdominally using either a 15–8-MHz linear probe (Acuson Sequoia 512, Siemens, Erlangen, Germany) or a 7.5-MHz curvilinear probe (Aloka Prosound SSD 5500, Tokyo, Japan). The mechanical index (MI) in B-mode and the thermal index for soft tissue (TIS) in color-flow mode were set not to exceed a value of 1.

The heart scan was performed according to the standard criteria used in the second-trimester scan¹³. Cases with inconclusive scans were rescheduled within 2 weeks, according to protocol. Women were routinely offered chorionic villus sampling to determine fetal karyotype and were referred for multidisciplinary counseling to explain the findings and limitations of the examination. Termination of pregnancy (TOP) beyond 90 days of gestation was supported in the presence of abnormal karyotype or major malformations and parental consent for subsequent pathological examination was always requested. Pathological investigation was carried out through microscopy. When the pregnancy continued, the fetuses underwent a complete ultrasound scan and echocardiographic examination by a fetal cardiologist at 20 and 32 weeks' gestation. Postnatal echocardiography and complete neonatal evaluation was performed in liveborn cases.

RESULTS

All 133 fetuses with NT measurements above the 95th centile at 11–14 weeks of gestation had a complete morphological and cardiac ultrasound evaluation both by an ultrasound-trained obstetrician and by a fetal cardiologist. Twelve fetuses with normal karyotype and normal anatomy were lost to follow-up and were excluded from analysis. Of the remaining 121 fetuses comprising the study group, 42 had increased NT measurements between the 95th and 99th centiles and 79 had NT above the 99th centile. The median maternal age was 36 (range, 18–44) years. The median crown–rump length was 66 (range, 46–84) mm. Nine fetuses were between 11 + 0 and 11 + 6 weeks, 37 fetuses were between 12 + 0 and 12 + 6 weeks and 75 fetuses were between 13 + 0 and 13 + 6 weeks. We obtained adequate results at the first scan in 119/121 (98%) women; only two patients were re-examined within 2 weeks, before reaching 14 weeks' gestation.

The population was subdivided for purposes of analysis into three groups according to karyotype and associated anomalies diagnosed by a fetal cardiologist at the 11 + 0 to 13 + 6-week scan. Group A included fetuses with normal karyotype and normal extracardiac and cardiac morphology ($n = 81/121$ (66.9%)); among this group, 39 fetuses had NT between the 95th and 99th centiles and 42 fetuses had NT above the 99th centile; the median NT was 3.2 (range, 2.5–6.1) mm. Group B included fetuses with chromosomal anomalies ($n = 28/121$ (23.14%)); three fetuses had NT measurements between the 95th and 99th centiles (with normal cardiac morphology) and 25 fetuses had NT above the 99th centile (14 of which

had cardiac anomalies) (Table 1); the median NT was 3.2 (range, 2.5–10.4 mm). Group C included fetuses with normal karyotype and cardiac and/or extracardiac anomalies ($n = 12/121$ (9.91%)); all fetuses had NT measurements above the 99th centile (nine of which had cardiac anomalies); the median NT was 3.75 (range, 2.8–5.1) mm. Their characteristics are summarized in Table 2.

There were 23 cases with cardiac anomalies. Twenty (16.5%) cases of CHD were diagnosed and this was associated with chromosomal anomalies in 12 (60%) cases (Table 3), and there were three cases with a minor cardiac abnormality: mild ventricular disproportion, the right ventricle being larger than the left, not associated with any specific cardiac diagnosis, in two cases of trisomy 21 (Group B) and in one with body stalk anomaly (Group C).

We observed a modification over time of cardiac features with respect to the initial findings in two cases in Group B. In one fetus with trisomy 21 and mild pyelectasis, two proportionate ventricles were observed at 11 weeks; however, a week later moderate ventricular disproportion developed, the right ventricle being larger than the left, with normal mitral and aortic valves, without tricuspid regurgitation and with no apparent aortic arch anomaly. Autopsy information, however, was not reliable after TOP because of inadequate fetal material. In the second fetus, with a 45,X0 karyotype,

the fetal cardiologist diagnosed coarctation of the aorta, ventricular septal defect and a small left ventricle with opening mitral valve at 14 weeks; a week later, at autopsy, the left ventricle was found to be hypoplastic.

Agreement between obstetricians and cardiologists

The overall agreement between ultrasound-trained obstetricians and fetal echocardiographers was 95.9% (116/121 cases): the obstetricians correctly classified as abnormal all 18 cases with major cardiac defects, but did not detect five cases with minor cardiac anomalies, comprising two cases of small ventricular septal defects, and three cases with ventricular disproportion, the right ventricle being larger than the left. All 42 fetuses with NT between 95th and 99th centiles were correctly identified as being normal by the ultrasound-trained obstetricians.

Outcome

TOP was performed in 41/121 (33.9%) cases: in 26/28 (92.8%) of Group B cases, in 11/13 (84.6%) of Group C cases and in 4/80 (5%) Group A cases. The Group A women opted for TOP before 90 days of gestation due to an isolated cystic hygroma. All women with fetuses affected by major CHD opted for TOP, all but one having associated anomalies (Table 3). The three

Table 1 Characteristics of 28 fetuses with increased nuchal translucency at 11–14 weeks and with chromosomal anomalies (Group B)

Chromosomal anomaly	n	Isolated chromosomal anomaly	Associated anomaly		
			Cardiac anomaly only	Extracardiac anomaly with normal heart	Cardiac + extracardiac anomaly
Trisomy 21	17	$n = 9$	$n = 6$ (1 minor AVSD ($n = 4$) Small VSD ($n = 1$) Mild ventricular disproportion* ($n = 1$))	$n = 1$ Bilateral hydronephrosis	$n = 1$ (minor) Mild ventricular disproportion* at 12 weeks (normal proportions at 11 weeks) + mild bilateral pyelectasis
Trisomy 18	4				$n = 4$ AVSD + holoprosencephaly ($n = 1$) DORV + skeletal anomalies ($n = 1$) Malaligned VSD + renal hypoplasia ($n = 1$) DORV + holoprosencephaly + renal dysplasia ($n = 1$)
Trisomy 13	1				$n = 1$ AVSD + cystic hygroma
45,X0	3		$n = 1$ CoA + VSD§	$n = 2$ Cystic hygroma ($n = 2$)‡	$n = 0$
Other	3	$n = 2$ 46,XX/47,XX(+9q)† 46,XX-der8			$n = 1$ 45,XY(der15,18),(q10;q10) + AVSD + holoprosencephaly + exomphalos
Overall	$n = 28$	$n = 11$	$n = 7$	$n = 3$	$n = 7$

All cases except those indicated † and ‡ underwent termination of pregnancy. *Right ventricle larger than the left; minor cardiac anomaly. †Delivered at term and did not present any malformation after birth, or at 12-month follow-up. ‡Intrauterine death at 17 weeks. §Small left ventricle with opening mitral valve observed at 14 weeks; left ventricle found to be hypoplastic at autopsy 1 week later. AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; DORV, double outlet right ventricle; RV, right ventricle; VSD, ventricular septal defect.

Table 2 Characteristics of 12 fetuses with increased nuchal translucency at 11–14 weeks and with normal karyotype and cardiac and/or extracardiac anomalies (Group C)

Anomaly	n	Details	Outcome
Isolated ECA	3	Diaphragmatic hernia (<i>n</i> = 1) Bilateral hydronephrosis (<i>n</i> = 1) Hypoplasia cerebellum, pterygium colli, club foot, female genitalia in 46,XY karyotype (<i>n</i> = 1)	TOP 16 weeks, autopsy NR IUD 20 weeks, autopsy NP TOP 16 weeks, undefined specific syndrome, recurrent in the second pregnancy
Isolated CHD	4	AVSD (<i>n</i> = 1) DORV (<i>n</i> = 1) TGA (<i>n</i> = 1) Pulmonary atresia + intact ventricular septum (<i>n</i> = 1)	TOP 18 weeks, autopsy NP TOP 15 weeks, autopsy NR TOP 16 weeks TOP 15 weeks
CHD + ECA	5	HLH + hydrocephalus + renal dysplasia (<i>n</i> = 1) VSD (<i>n</i> = 1) Ectopia cordis + hydrothorax + body stalk anomaly (<i>n</i> = 1) AVSD + hypoplastic aorta + holoprosencephaly (<i>n</i> = 1) Mild ventricular disproportion* + body stalk anomaly (<i>n</i> = 1)	TOP 14 weeks TOP 22 weeks (at 20 weeks agenesis of corpus callosum + right hydronephrosis + left kidney double ureter) TOP 12 weeks TOP 14 weeks, autopsy NR TOP 12 weeks, autopsy NR
Overall	<i>n</i> = 12		TOP (<i>n</i> = 11) IUD (<i>n</i> = 1)

*Right ventricle larger than the left; minor cardiac anomaly. AVSD, atrioventricular septal defect; CHD, congenital heart disease; DORV, double outlet right ventricle; ECA, extracardiac anomaly; HLH, hypoplastic left heart; IUD, intrauterine death; NP, not performed; NR, not reliable; RV, right ventricle; TGA, transposition of the great arteries; TOP, termination of pregnancy; VSD, ventricular septal defect.

cases with ventricular disproportion also had extracardiac or chromosomal abnormalities and opted for TOP. Intrauterine death occurred in five (4.1%) cases, between 14 and 20 weeks' gestation. Four of these five cases, the fifth being a 45,X0 fetus, had normal karyotype and no other anomalies.

Two of the TOPs were performed in another institution and autopsy was not attempted. Of the 39 performed at our institution, following TOP we obtained fetal material for pathological examination and attempted autopsy in 23 (59%) cases; however, reliable pathological conclusions were possible in only 12 (31%) cases. Seventy-five of the 121 (62%) cases continued pregnancy and the infants were delivered at term. The postnatal follow-up (median, 21 (range, 12–29) months) confirmed absence of cardiac and extracardiac abnormalities in 73/75 cases (97.3%); two cases were found to have minor extracardiac defects.

DISCUSSION

In a previous study¹² we provided evidence that, using a high-frequency transabdominal probe, an ultrasound-trained obstetrician can distinguish normal from abnormal fetal hearts in a low-risk population at 11–14 weeks' gestation. These findings formed the basis of this multidisciplinary study aimed to demonstrate the reliability of early fetal heart assessment in cases with increased NT, performed by trained operators using such probes.

The motivation for our study was an increased demand for early fetal heart assessment in fetuses with an increased NT measurement above the 95th centile, several reports having indicated an increased association of cardiac

anomalies^{1–4}. In cases with NT measurements above the 99th centile, there is general agreement that specialized early fetal echocardiography is indicated^{7,12}. The problem arises in cases with NT measurements between the 95th and 99th centiles, in which the risk of cardiac anomalies is doubled with respect to the prevalence in the normal population^{8,14}, but in all of which it is not feasible to offer early fetal echocardiography due to limited resources. Yet these cases represent 4% of the population undergoing NT study. Pregnant women in this group are counseled that their risk for fetal cardiac anomalies is increased, but in most cases they will not undergo evaluation of the fetal heart until the cardiac scan at 20 weeks' gestation. It is our opinion, therefore, that in these cases ultrasound-trained obstetricians should carry out an early scan to identify normal versus abnormal cardiac morphology, allowing selection of a subset of women to undergo early fetal echocardiography.

The first reports of cardiac malformations detected prior to 14 weeks of gestation were by expert fetal echocardiographers using transvaginal probes in populations at risk mainly for increased NT measurement^{10,15,16}. The transvaginal approach was also used in an unselected population to perform early screening for cardiac anomalies¹⁷, although the rate of complete visualization of cardiac morphology was low. However, women's tolerance of transvaginal scanning is, in our opinion, questionable. Furthermore, there is a substantial learning curve to acquire the skills to carry out fetal heart assessment with the transvaginal approach. It is likely that these reasons contribute, along with improvements

Table 3 Characteristics of 20 fetuses with increased nuchal translucency at 11–14 weeks and with congenital heart disease (CHD)

CHD	n	GA (weeks, mean)	CHD isolated	CHD associated with other anomalies			Outcome	Postmortem
				Chromosomal anomalies	Extracardiac anomalies			
AVSD	8	12.6	n = 1	n = 6 Trisomy 21 (n = 4) Trisomy 18 + holoprosencephaly (n = 1) Trisomy 13 (n = 1)	Holoprosencephaly (n = 1)	TOP (n = 8)	Confirmed (n = 1) NR (n = 5) NP (n = 2)	
TGA	1	14	n = 1			TOP (n = 1)	NP (n = 1)	
DORV	4	13.2	DORV + HLIV (n = 1)	Trisomy 18 (n = 2) 45,XY (der 15,18)(q10;q10) (n = 1)		TOP (n = 4)	Confirmed (n = 1) NR (n = 2) NP (n = 1)	
HLH	1	13.5			Holoprosencephaly + kidney cystic dysplasia (n = 1)	TOP (n = 1)	Confirmed (n = 1)	
CoA + VSD	1	14		45,X0 hydrothorax (n = 1)		TOP (n = 1)	Confirmed HLH* (n = 1)	
PA + intact ventricular septum	1	12.6	n = 1			TOP (n = 1)	NP (n = 1)	
Ectopia cordis + VSD	1	12.5			Body stalk anomaly (n = 1)	TOP (n = 1)	Confirmed (n = 1)	
VSD	3	12.5		n = 2 Trisomy 18 + malaligned VSD (n = 1) Trisomy 21 (n = 1)	Agnesis of corpus callosum (n = 1)	TOP (n = 3)	Confirmed (n = 1) NP (n = 2)	
Overall	20	13.3	n = 4	n = 12	n = 4	TOP (n = 20)	Confirmed (n = 6) NR (n = 7) NP (n = 7)	

* Evolution to HLH in 1 week as described in the text. AVSD, atrioventricular septal defect; CoA, coarctation of aorta; DORV, double outlet right ventricle; GA, gestational age; HLH, hypoplastic left heart; HLIV, hypoplastic left ventricle; NP, not performed; NR, not reliable; PA, pulmonary atresia; TGA, transposition of great arteries; TOP, termination of pregnancy; VSD, ventricular septal defect.

in the resolution of transducers, to the fact that transabdominal scanning is now the preferred approach by fetal cardiologists: in recent years, fetal cardiology studies at 11–14 weeks' gestation have been based mainly on this approach^{18,19}. However, a recent randomized controlled trial²⁰ of 36 299 fetuses highlighted the low prenatal detection rate of major CHD at both 12 and 18 weeks' gestation; at 12 weeks, the four-chamber view was obtained successfully in 10 274 of 18 148 (56.6%) fetuses. In contrast, in our study, fetal cardiologists confirmed the recognition of abnormal cardiac findings by ultrasound-trained obstetricians in all cases of major cardiac defects. Moreover, there were no false-positive results from the obstetricians' first scan and the five false-negative diagnoses were related to small ventricular septal defects and minor abnormalities (ventricular disproportion without other specific cardiac findings). Findings of ventricular disproportion are notable because they may indicate further evolution to a specific cardiac lesion, namely coarctation of the aorta. Our current study thus confirms the feasibility of ultrasound-trained obstetricians performing a cardiac scan before 14 weeks, specifically in the group of fetuses with NT measurements between the 95th and 99th centiles (with moderate risk for CHD), in which our operators correctly identified the heart anatomy in all 42 fetuses.

The reliability of examinations performed by our ultrasound-trained obstetricians can be attributed to several factors. With recent improvements in ultrasound technology, it is now possible during the first trimester to achieve, using high-frequency transabdominal transducers, increased spatial and axial resolution, thus giving a trained obstetrician the possibility to obtain all the standardized sections. Color flow mapping within a dedicated clinical setting could improve the sensitivity in the examination of cardiac structures in the first trimester. Moreover, with our study protocol, the learning curve of the obstetricians was optimized as they could compare their findings directly with those of an expert fetal cardiologist. Thus, despite the possibility of various factors, such as maternal body mass index and fetal position, impairing the visualization rate of the cardiac structures during the first trimester, inconclusive scan findings were obtained in only two patients (2% of the population). These cases were quickly rescheduled and successfully rescanned before reaching 14 weeks' gestation.

Gestational age plays a determinant role in the early heart scan: Smrcek *et al.*²¹ highlight that the rate of successful evaluation of the fetal heart in the first trimester increases with increasing gestational age. These results are consistent with the high success rate of our cardiac scans, performed in 86% of cases in fetuses between 12 and 13 + 6 weeks.

A potential limitation of our study was the relatively small number of cases and obstetricians involved. However the strength of the study is that the distribution of the detected cardiac anomalies corresponded to an

expected prevalence of congenital heart lesions and that the planned follow-up was adequate.

With most CHDs being already present by 14 weeks, their detection rate in the first trimester is potentially high, approximately 87% according to another recent study by Smrcek *et al.*²². However, in agreement with other investigators^{22,23}, our study confirmed the limitations of first-trimester fetal heart assessment regarding the progressive and unpredictable development of certain cardiac anomalies (e.g. coarctation of the aorta, hypoplastic left heart, cardiomyopathies), which evolve with advancing gestational age and may not be diagnosed until the second- or third-trimester scans or even postnatally. In cases showing early potential signs of CHD, such as those with ventricular disproportion, counseling should emphasize the fact that it is not possible to predict the outcome in the first trimester. Two of our cases showed early evolution of cardiac defects within a short time interval: one towards hypoplastic left heart syndrome, as described in another case by Axt-Fliedner *et al.*²³, and in another, with trisomy 21, we observed progression from two proportionate ventricles at 11 weeks to moderate ventricular disproportion, the right ventricle being larger than the left, with normal atrioventricular valves and great vessels, without signs of tricuspid regurgitation; this has been reported in the literature as a negative prognostic sign in early pregnancy when associated with trisomy 21²⁴.

We encountered difficulties in obtaining clinically useful material for pathological examination of fetal hearts following TOP in first-trimester cases diagnosed with cardiac malformations. In fact, only a few 12/39 (30.7%) of our cases had suitable postmortem fetal material available to confirm first-trimester findings. This is in agreement with other reports^{10,25}: Smrcek *et al.*²², for example, obtained reliable confirmation of the prenatal heart diagnosis in only 8/25 (32%) fetal autopsy specimens. Certainly, only good, reliable images of the beating fetal heart represent, up to now, the gold standard for an early diagnosis of cardiac malformations.

In conclusion, there is an emerging trend for early assessment of the fetal heart due to significant interest in first-trimester NT measurement screening, which has been identified as a marker for chromosomal anomalies and CHD. However, due to constraints on time and resources, fetal cardiologists cannot carry out extensive cardiac studies on fetuses with only a moderately increased NT measurement (between the 95th and 99th centile) and thus a moderate risk for CHD. Our study provides evidence that obstetricians, who are trained to study the fetal heart at the second trimester, can also be trained successfully to distinguish reliably between normal and abnormal heart findings in the first trimester using high-frequency transabdominal probes, yielding a high negative predictive value.

REFERENCES

1. Ghi T, Huggon IC, Zosmer N, Nicolaides KH. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. *Ultrasound Obstet Gynecol* 2001; **18**: 610–614.
2. Atzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. *Ultrasound Obstet Gynecol* 2005; **26**: 154–157.
3. Makrydimas G, Sotiriadis A, Huggon IC, Simpson J, Sharland G, Carvalho JS, Daubeney PE, Ioannidis JP. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. *Am J Obstet Gynecol* 2005; **192**: 89–95.
4. McAuliffe FM, Hornberger LK, Winsor S, Chitayat D, Chong K, Johnson JA. Fetal cardiac defects and increased nuchal translucency thickness. *Am J Obstet Gynecol* 2004; **191**: 1486–1490.
5. Souka AP, Von Kaisenberg CS, Hyett JA, Nicolaidis KH. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol* 2005; **192**: 1005–1021.
6. Mavrides E, Cobian-Sanchez F, Tekay A, Moscoso G, Campbell S, Thilaganathan B, Carvalho JS. Limitations of using first-trimester nuchal translucency measurement in routine screening for major congenital heart defects. *Ultrasound Obstet Gynecol* 2001; **17**: 106–110.
7. Makrydimas G, Sotiriadis A, Ioannidis JP. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. *Am J Obstet Gynecol* 2003; **189**: 1330–1335.
8. Muller MA, Clur SA, Timmerman E, Bilardo CM. Nuchal translucency measurement and congenital heart defects: modest association in low risk pregnancies. *Prenat Diagn* 2007; **27**: 164–169.
9. Hafner E, Schuller T, Metzenbauer M, Schuchter K, Philipp K. Increased nuchal translucency and congenital heart defects in a low risk population. *Prenat Diagn* 2003; **23**: 985–989.
10. Huggon IC, Ghi T, Cook AC, Zosmer N, Allan LD, Nicolaides KH. Fetal cardiac abnormalities identified prior to 14 weeks' gestation. *Ultrasound Obstet Gynecol* 2002; **20**: 22–29.
11. Rasiah SV, Publicover M, Ewer AK, Khan KS, Kilby MD, Zamora J. A systematic review of the accuracy of first-trimester ultrasound examination for detecting major congenital heart disease. *Ultrasound Obstet Gynecol* 2006; **28**: 110–116.
12. Lombardi CM, Bellotti M, Fesslova V, Cappellini A. Fetal echocardiography at the time of the nuchal translucency scan. *Ultrasound Obstet Gynecol* 2007; **29**: 249–257.
13. Allan L, Dangel J, Fesslova V, Marek J, Mellander M, Oberhansli I, Oberhoffer R, Sharland G, Simpson J, Sonesson SE. Recommendations for the practice of fetal cardiology in Europe. *Cardiol Young* 2004; **14**: 109–114.
14. Bahado-Sing RO, Wapner R, Thom E, Zachary J, Platt L, Mahoney MJ, Johnson A, Silver RK, Pergament E, Filkins K, Hogge WA, Wilson RD, Jackson LG. First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening Study Group. Elevated first-trimester nuchal translucency increases the risk of congenital heart defects. *Am J Obstet Gynecol* 2005; **192**: 1357–1361.
15. Hyett JA, Perdu M, Sharland GK, Snijders RS, Nicolaides KH. Increased nuchal translucency at 10–14 weeks of gestation as a marker for major cardiac defects. *Ultrasound Obstet Gynecol* 1997; **10**: 242–246.
16. Gembruch U, Knöpfle G, Bald R, Hansmann M. Early diagnosis of fetal congenital heart disease by transvaginal echocardiography. *Ultrasound Obstet Gynecol* 1993; **3**: 310–317.
17. Rustico MA, Benettoni A, D'Ottavio G, Fischer-Tamaro L, Conoscenti GC, Meir Y, Natale R, Bussanni R, Mandruzato GP. Early screening for fetal cardiac anomalies by transvaginal echocardiography in an unselected population: the role of operator experience. *Ultrasound Obstet Gynecol* 2006; **16**: 614–619.
18. Carvalho JS, Moscoso G, Ville Y. First-trimester transabdominal fetal echocardiography. *Lancet* 1998; **351**: 1023–1027.
19. Becker R, Wegner RD. Detailed screening for fetal anomalies and cardiac defects at the 11–13 week scan. *Ultrasound Obstet Gynecol* 2006; **27**: 613–618.
20. Westin M, Saltvedt S, Bergman G, Kublickas M, Almstrom H, Grunewald C, Valentin L. Routine ultrasound examination at 12 or 18 gestational weeks for prenatal detection of major congenital heart malformations? A randomized controlled trial comprising 36,299 fetuses. *BJOG* 2006; **113**: 675–682.
21. Smrcek JM, Berg C, Geipel A, Fimmers R, Diedrich K, Gembruch U. Early fetal echocardiography: Heart biometry and visualization of cardiac structures between 10 and 15 weeks' gestation. *J Ultrasound Med* 2006; **25**: 173–182.
22. Smrcek JM, Berg C, Geipel A, Fimmers R, Axt-Flidner R, Diedrich K, Gembruch U. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. *J Ultrasound Med* 2006; **25**: 187–196.
23. Axt-Flidner R, Kreiselmaier P, Schwarze A, Krapp M, Gembruch U. Development of hypoplastic left heart syndrome after diagnosis of aortic stenosis in the first trimester by early echocardiography. *Ultrasound Obstet Gynecol* 2006; **28**: 106–109.
24. Falcon O, Faiola S, Huggon I, Allan L, Nicolaides KH. Fetal tricuspid regurgitation at the 11 + 0 to 13 + 6 week scan: association with chromosomal defects and reproducibility of the method. *Ultrasound Obstet Gynecol* 2006; **27**: 609–612.
25. Haak MC, Bartelings MM, Gittenberger-de Groot AC, van Vugt JMG. Cardiac malformations in first-trimester fetuses with increased nuchal translucency: ultrasound diagnosis and post-mortem morphology. *Ultrasound Obstet Gynecol* 2002; **20**: 14–21.