Obstetrica şi Ginecologia LXIV (2016) 165-176 **Original article**

FIRST TRIMESTER DIAGNOSTIC ACCURACY OF A TWO-DIMENSIONAL SIMPLIFIED ULTRASOUND TECHNIQUE IN CONGENITAL HEART DISEASES AND GREAT ARTERIES ANOMALIES

Ştefania Tudorache*, Anda Ungureanu, Roxana Cristina Drăguşin*, Florea Maria Şorop*, Monica Laura Cara*, D. G. Iliescu***

** Department of Obstetrics and Gynaecology, Prenatal Diagnostic Unit, University of Medicine and Pharmacy, University Emergency County Hospital, Craiova, Romania.*
*** Pediatric Cardiology Department, University Emergency County Hospital, Craiova, Romania*

Abstract

Objectives *To assess the accuracy of a simplified standard first-trimester (FT) conventional two-dimensional ultrasound (2DUS) examination protocol in detecting congenital heart diseases (CHDs) in an unselected population.*

Methods *This is a single center prospective study, performed in a FT screening for aneuploidies program. We stored the cardiac sweep digital video clips, in duplex two-dimensional/two dimensional color, from an oblique lateral insonation from the right shoulder. We used 2DUS re-examination by a team of specialists, pathological examination, and subsequent re-examination as the reference standard methods.*

Results *In 3240 fetuses, positive 2DUS diagnosed both major and minor CHDs with high accuracy (specificity 99.9%). Positive likelihood ratios were 775.92 for major and 321.78 for minor heart anomalies. Sensitivity was lower for minor defects than for major CHDs (33.3% vs 80.8%) with discrepancies between positive predictive values (57.14% vs 87.5%).*

Conclusions *2DUS is a highly accurate tool for CHDs and great arteries anomalies screening in late FT. Using a standardized and low time-consuming technique will probably raise detection rates, by lowering the operator-dependency and by eliminating the fetal position-dependency, two main reasons for delayed diagnosis of CHDs.*

Rezumat: Acurateţea examinării ecografice 2D în primul trimestru, folosind o tehnică simplificată, în detecţia anomaliilor congenitale cardiace şi a anomaliilor de vase mari

Obiective *Stabilirea acurateţei în detecţia anomaliilor cardiace congenitale, în populaţia neselectată, dacă se foloseşte o metodă simplificată, standard, de ecografie convenţională 2D.*

Material şi metodă *Acesta este un studiu prospectiv, desfăşurat într-un singur centru, în cadrul unui program de screening pentru aneuploidii. Au fost stocate videoclipuri digitale, în duplex (2D şi 2Dcolor), dintr-o incidenă oblic-laterală, dinspre umărul drept fetal. Am folosit ca metode standard de referinţă reexaminarea în echipe multidisciplinare, examenul anatomo-patologic şi reexaminarea ecografică ulterioară.*

Rezultate *Într-o serie de 3240 de feţi, ecografia 2D pozitivă a detectat anomaliile cardiace congenitale, atât majore, cât şi minore, cu o acurateţe ridicată (specificitate 99.9%). Positive likelihood ratios (PLs) au fost de 775.92 pentru anomaliile majore, şi de 321.78 pentru anomaliile cardiace minore. Sensibilitatea a fost mai mică pentru defectele minore (33.3%) faţă de cele majore (80.8%), iar valorile predictiv pozitive au fost diferite (57.14% faă de 87.5%).*

Concluzii *Ecografia 2D a devenit o metodă de acurateţe în screeningul anomaliilor cardiace şi a anomaliilor de vase mari la sfârşitul trimestrului I de sarcină. Metoda standard descrisă este rapidă, şi are potenţialul de a îmbunătăţi ratele de detecţie, prin scăderea dependenţei de operator şi prin eliminarea dependenţei de poziţia fetală, cele mai importante două explicaţii pentru diagnosticul tardiv.*

Cuvinte cheie: trimestrul I de sarcină, anomalie cardiacă congenitală, ecografie 2D, acurateţe, protocol standard, ecografie Doppler, screening.

CORESPONDENŢĂ: Monica Laura Cara, e-mail:daimoniquelle@yahoo.com
KEY WORDS: First trimester, Congenital heart disease, Two-dimensional ultrasound, Accuracy, Standard protocol, Doppler ultrasonography, Screening.

Introduction

The first trimester (FT) cardiac scan started as a rank outsider for the prenatal care in the early years of the century[1]. The current guidelines still do not establish morphological protocols for the FT screening for congenital heart diseases (CHDs)[2]. Yet, many recent reports provide proof that most of the major CHDs (MCHDs) may be identified in late FT[3-9]. Lower detection rates are achieved in isolated CHDs and in low-risk population, probably depending mainly on FT scan protocols.

In a systematic review, Rasiah[9] found that most published studies included in the research were "lacking in the quality of their verification method and blinding". This is likely due to technical limitation of the conventional autopsy in FT specimens[10], to the low popularity of medically induced abortion in early pregnancy[11] and to low availability of alternative techniques for confirmation[12-14]. This has led to statements like: "certainly, only good, reliable images of the beating fetal heart represent, up to now, the gold standard for an early diagnosis of cardiac malformations[4]".

Among factors that have consistently been incriminated on the low diagnostic performance of FT cardiac scan, beside the ones that we cannot alter (the risk profile of the study population, high body mass index, anterior placenta, retroversion, surgical scars), there are factors that may be worked on: the training of examiners, the number of cardiac planes that are incorporated into the assessment, the addition of color Doppler imaging and the insonation angle used for data acquisition.

An early accurate screening test would be of benefit for at least three categories: normal pregnancies for reassurance, CHD that is not satisfactorily reparable, for which termination of pregnancy (TOP) should be offered and CHD for which the intra-uterine treatment reduces morbidity[15]. We previously demonstrated that 2DUS is feasible and repeatable within and between observers in visualizing the normal heart structures, if performed on a standardized protocol[16]. The goals of this study are to assess the accuracy of a simplified protocol for both major and minor cardiac defects (mCHDs) and great arteries anomalies detection or earlier suspicion, and to assess the sensitivity and specificity of this method.

Methods

This is a single center prospective study, performed between January 2011 and January 2015, in cases attending our Prenatal Diagnostic Unit, County Emergency University Hospital Craiova, Romania, for FT screening for aneuploidies[17]. Inclusion criteria were: crown-rump length of 44-74 mm, available proof from at least a standard test, known pregnancy outcome. We recruited pregnancies consecutively and offered them a complete follow-up program.

We used a Voluson 730 Expert series and an E8 (GE Medical Systems, Zipf, Austria) machine, equipped with 4-8-MHz curvilinear transducer and with 5–9 MHz curvilinear transducer. Using color Doppler was restricted by ALARA principle[18,19]. The sonographers were informed about the patient's history and personal data.

We targeted the heart before other segments of the fetal anatomy and stored, for each case, video clips, duplex two-dimensional/two dimensional color (2D/2DC, with the color/high definition flow mapping) preferred.

Cases that had inconclusive files or screened positive were rescheduled within the next several days. These cases were reexamined by a multidisciplinary team: two senior obstetrician experts in prenatal diagnostic, a cardiologist and a neonatologist.

All cases were offered a second trimester (ST) fetal cardiac scans including extended basic cardiac scan[20,21]. Echocardiography[22] was performed if indicated. The neonatal clinic exams[23,24], the pulse oximetry and the neonatal echocardiography (if indicated[25,26]) were performed by the attending neonatologist. The cardiologist reassessment was performed postpartum if requested, when difficult to interpret data cases and for cases prenatally screened as abnormal. All cases entered the general practitioner follow-up program and the feedback was obtained at six months and at one year of age.

The study population was unselected, but with a medium risk, as being a tertiary center, we examine referrals from primary or secondary centers (approximate 20% of the study group).

We obtained approval from the Ethical Committee of the University of Medicine and Pharmacy of Craiova for this study. All women have been provided with informed consent for the use of US images for research purposes.

The previously used protocol[16] was simplified for this study: it implied obtaining, from an oblique lateral insonation from the right shoulder, a cardiac sweep containing three planes: the four chamber view (4CV) plane, the crossing plane and the three vessels and trachea view (3VTv) plane, and one additional plane – the transversal abdominal plane for confirming the situs (apex, thoracic aorta and stomach image in the left side of the fetus). The interventricular septum was oblique, more or less at 45^0 to the US beam, with the fetal spine positioned between the 3 and 6 o'clock positions (Figure 1).

Whenever normal features were obtained in these planes, the case was declared "screen-negative for CHDs". If the operator did not obtain them the case was considered screen-positive and classified as "suspicion of CHD". The time elapsed after starting the scan until storing the cardiac sweeps was noted.

All digital video clips of the cardiac sweeps were subsequently exported to a DVD for offline review and audit, and for obtaining teaching materials and proofs.

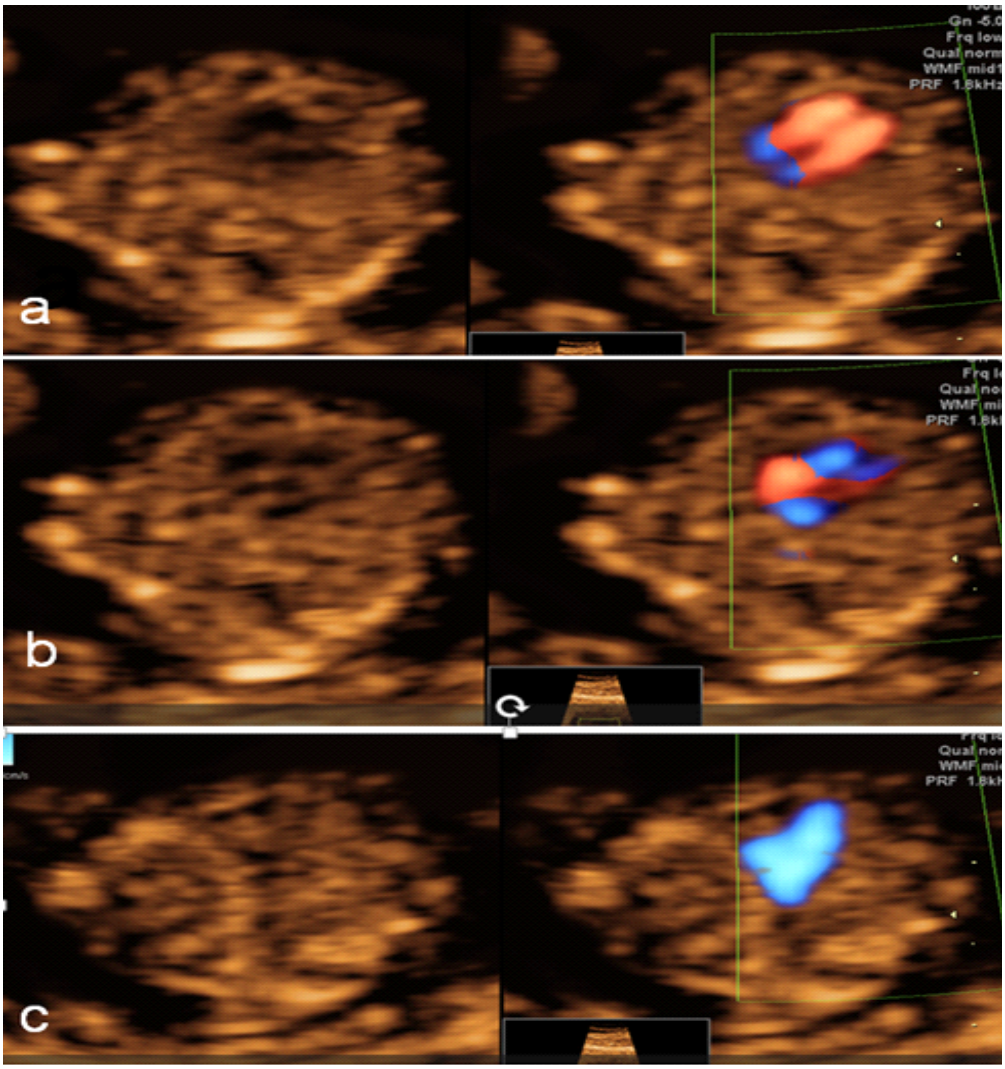

Figure 1. Simplified protocol used for the first trimester cardiac assessment: three planes, in the oblique view from the right shoulder, duplex gray-scale (used in sepia) and color Doppler:
a - Four-chamber view plane. The color Doppler imaging shows equal right and left atrioventricular flows.
b - Crossing plane. The color Doppler imaging shows the emergence of left ventricular outflow tract and the crossover of the great arteries.
c - Three vessels and trachea view plane. The color Doppler imaging shows the confluence of arterial arches, normal direction and equal flow in both arches.

The rationale of assessing the outflow tracts in late FT scan is based on the speculation that, similar to the ST scan, this approach could increase the detection rates for MCHDs above those achievable by the 4CV alone[20,21].

During the exam the operator completed the form: 2 cardiac features in grey scale (the abdominal transversal plane and the four chambered heart image) and 3 in color flow mapping (the equal atrioventricular flow, the crossing of the great arteries, and the equal flow in both arch - the V sign). He additionally answered the question "is this heart normal?" and the suspected anomaly was noted whenever possible, in case of a negative answer.

The following additional data were analyzed in the study: traditional maternal risk factors for CHD[20] (first-degree relative with CHD, prior child with CHD, type 1 diabetes, infections, autoimmune antibodies, teratogen exposure), fetal risk factors for CHD (associated extracardiac anomalies). We also noted additional genetic markers: nuchal translucency (NT) measurement, the nasal bone (NB), tricuspid valve and ductus venousus (DV) spectral Doppler interrogation. In continuing pregnancies, we noted the method used for confirmation the CHD, the features found at the ST scan and the birth outcome.

Couples that opted for FT TOP were referred to multidisciplinary counseling, to explain the findings and limitations of the FT US examination. If TOP remained the choice of the couple, the team advocated for medical TOP. In those cases where couples agreed, a pathologic specimen autopsy was offered.

We decided to use the team agreement on the existence of a CHD on the FT as a standard test, in addition to the wide-world accepted gold-standard tests (ST/third trimester cardiac scan, postpartum scan and pathology).

We elected this approach due to inherent limitation of FT cardiac pathological examination, and also due to limited access to modern non-conventional methods and to the circumstance that in our setting there is a general tendency for late FT surgical TOP.

By convention, when all specialists agreed on the fact that a CHD is present, the board examination was considered an appropriate standard test. If the patient declined the board reexamination or if at least one of the board members disagreed on this unspecific and general diagnostic of "CHD", we considered the standard test not obtained.

There are no universal guidelines on the workup of an asymptomatic neonate with a murmur[23], and the approach to these infants varies among practitioners and also between settings. The NICE guidelines were previously promoted in our hospital. The team already had a protocol for the timing and content of the postnatal examination and this study did not alter the clinical practice. The assessment is usually performed before discharge from hospital by a senior physician, but may also be performed by senior midwives or trainees (resident physician). Assessment of the cardiovascular system included in all cases checking the position of the heart, auscultation (heart rate, rhythm and sounds, murmurs) and palpation (femoral pulse volume)[24]. If any suspicious sign, pulse oximetry was performed[25, 26]. We frequently used the addition of a chest radiograph and an echocardiogram.

In our setting, the postnatal assessment by echocardiography is not a routine intervention. Although this tool was well established as the gold standard for diagnosing CHDs, it may also contribute to an apparent rising incidence of CHDs, mainly as a result of the detection of abnormalities which are of no functional or clinical significance. Echocardiography is likely to have significant limitations as a screening tool, mainly because of the high false positive (FP) rate, but also as a result of costs and lack of availability of trained personnel to perform the examinations[25].

The pathologist was not blinded to the scan results in medical TOP cases. We declared the standard pathology test obtained only if autopsy photographic files were available. The autopsy photographic files were obtained using a Sony DSLR A200 camera (10.2 megapixels), and a Leica IC80HD digital microscope camera (3 megapixels). In all autopsies, we identified the great arteries in situ, and the neck vessels arising from the aortic arch[27]. In the FT specimens intracardiac (interventricular and interatrial septum, atrio-ventricular valves) details could not be obtained.

In the ST specimens we used the six basic steps to opening the heart in situ, as described by the classical protocol[27]. Some malformed hearts required a customized approach to dissection, to correlate the defects with US data.

Statistical analysis

Descriptive statistics were used to report the relevant baseline characteristics of the patients.

Study design allowed us to construct a 2×2 table of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) values. We calculated estimates of sensitivity, specificity, with 95% confidence intervals, by confronting antenatal findings with subsequent verification of diagnosis. In order to assess the performance of the test we chose to report also the likelihood ratios (LRs) and the predictive values for both MCHDs and mCHDs.

We assumed that 2DUS has good repeatability, with very good intra- and inter-observer agreement[(16)] in assessing FT heart structures. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22. Armonk, NY: IBM Corp.

Results

The flow diagram is represented in figure 2. It provides information about the number of recruited participants, the dynamic of the case series and the reference standards, as recommended for accuracy studies[28].

3240 women were examined during the study period. Confirmation was obtained in 2908 cases (lost to follow up rate 10.24%). The median maternal age was 30 (range 16–43) years, the median gestational age at scanning was 12.2 (range 11.2 – 13.4) weeks, the median maternal body mass index was 20.09 (range 16.1 – 39) and the median crown-rump length was 64 mm (range 44.9-74 mm). The US method protocol was achieved in the vast majority of cases (97%) in less than 10 minutes (median 8 min, range 6-21).

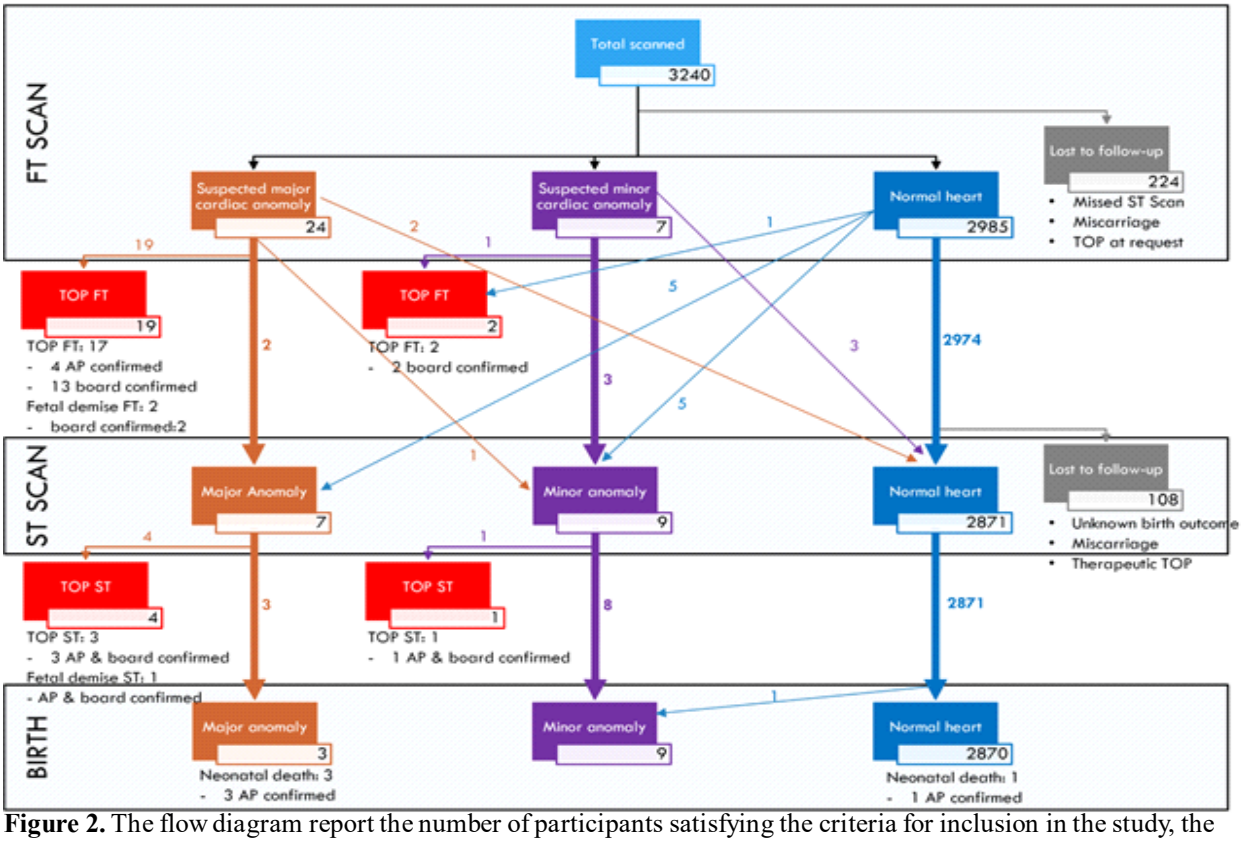

Figure 2. The flow diagram report the number of participants satisfying the criteria for inclusion in the study, the dynamic of the case series and the reference standards.

In our case series 38 heart defects were diagnosed. The correlations between FT US suspected diagnostic and the real diagnostic, the methods used for confirmation and the outcome are summarized in Table 1. MCHDs and major great arteries anomalies were identified in 26 pregnancies (8.94‰) and minor defects in 12 pregnancies (4.13‰). All MCHDs cases were antenatally diagnosed. FT US correctly identified 21/26 (80.77%) of MCHDs and 4/12(33.33%) of mCHDs (Table 2).

All but 3 MCHDs diagnosed cases (92.1%) belonged to the low risk patients group, considering the traditional maternal risk factor, as previously reported. In the normal case series, we had 43/2870 cases (1.5%) cases that belonged to the high risk group, having at least one risk factor.

Only 6/21 of the real positive cases of MCHDs and 3/4 real positive cases of mCHDs were confirmed by means of conventional standard tests.

Positive US diagnosed both major and minor CHDs with high specificity 99.9% (see Table 2). Sensitivity was lower for minor defects than for major CHDs (33.3% vs 80.8%) with discrepancies between PPV (57.14% vs 87.5%). Positive LRs for both were 775.92 for major and 321.78 for minor heart anomalies, providing strong evidence to rule in CHDs. Negative LRs were 0.19 for major, and respectively 0.67 for minor heart anomalies, showing moderate evidence for ruling out CHDs.

FT US missed 13 cases of cardiac anomalies: 5 cases of MCHDs (2 cases of tetralogy of Fallot and three evolving disease cases: cardiomegaly, critical aortic stenosis and major pericardial effusion) and 8 cases of mCHDs (3 cases of ventricular septal defects, one persistent patent ductus arteriosus (PDA), one case of cord triatriatum, one case of aortic coarctation, one minor pericardial effusion, and one isolated dextrocardia with normal heart, that was misinterpreted as a major defect, respectively as dextrocardia associated with great arteries transposition). All mCHDs cases were asymptomatic at birth and during the long-term follow-up, with the exception of the PDA, that required mini-invasive surgery, and the AoCo case, that was not a ductal-dependent lesion, and was correctly antepartum diagnosed and postnatally managed.

The FP rate (false alarm rate) was identical (0.1%) for both major and minor cardiac defects, but the FN rate was higher for mCHD (66.67% vs 19.23%).

The NT was higher than the 99th percentile for gestational age in 12 of the 26 major CHD (46.15%) suggesting that an elevated NT can be a moderate effective marker of major CHD. 166/2870 (5.78%) fetuses without cardiac defects had a NT>99th percentile (>3.5mm). Only in 2 cases out of the 12 minor CHDs the NT was abnormal (higher than the 99th percentile).

In the group of fetuses with MCHDs, reversed a-wave in the DV and TR regurgitation were present in 12 (50%) of cases and respectively 7 (26.92%); whereas in those without cardiac defects they were found in 1.7%, and respectively 5% (p“¨0.05). Fetuses with mCHDs, presented reversed a-wave in the DV in 1 case (8.33%) and TR regurgitation also in 1 case (8.33%).

Discussion

For CHDs - the leading cause of neonatal mortality due to birth defects - there is no primary preventive intervention available, the majority occurring in patients with low-risk for CHD. Although the fetal heart has a complex development in early gestation, being fully developed at the end of 8th week[29,] there are still low CHDs detection rates, regardless the GA[20,21,30-32.] We bind to these by proposing an early approach. The effectiveness of tests used for further follow-up is likely to be improved by increased detection rates in the FT.

It may be argued that a FT screening method is necessary. The WHO defines certain criteria for screening tests[33]. The prenatal diagnosis of MCHDs fulfills the criteria of a target lesion for a screening test. The strongest reason against elaborating a FT protocol is the circumstance that the fetal intervention, if needed, is technically feasible only in late pregnancy[34], and for the lifesaving effects of prenatal medicine, such as ductal-dependent lesion, an early

diagnosis would not be mandatory. Indeed, for continuing pregnancies, there is no disadvantage if a CHD would be diagnosed in the second half of the pregnancy.

Conversely, there are strong medical and ethical arguments against late TOPs. Moreover, the parents want to know about any fetal problems as early in pregnancy as possible and the parental psychological morbidity is high in these cases [35-39]. An important issue is that many positive cases are at risk for an early TOP. Generalizing testing may give selective abortion a growing trend. Thus, moral questions regarding the reproductive autonomy and informed consent for the prenatal screening may appear. In our view the moral benefits of FT fetal heart assessment are real, due to the high risk of neonatal cardiac surgery and long term central nervous system sequelae[40]. In a recent central paper on isolated MCHDs[30], J.S. Carvalho, a highly respected specialist in prenatal diagnosis, said: "I don't know a formal definition, but clinically tell parents that anything I can see prenatally is major". It is likely that this statement is even closer to the truth in the FT than in the ST. With regard to this controversial issue, it may make a morally relevant difference that if MCHDs detected, abortion can be done early. A lower moral status may be attributed to the fetus at that moment of its development.

The heterogeneity of CHDs and the progression of some cardiac lesions in utero represent particular problems for early screening. FT direct cardiac scan will probably have a different capacity to detect life-threatening CHDs and will fail to detect evolving diseases. Performing the screening should provide the early detection rate for MCHDs and offer the basis for organizing cost-effectiveness analysis. It will additionally better suit the ethical principles[41] and avoid in many cases the maternal anxiety state given by the referral for fetal echocardiography[38].

We proved that almost all MCHDs could be revealed at 11-14 weeks gestation, when using a standardized US protocol, even if searching for a small number of key parameters of fetal heart.

Sensitivity of FT US examination in detection of fetal MCHDs, calculated with respect to the findings at ST scan, has wide variations in low risk populations in the literature, between 36.8%[42], 57 %[43], and 84.2%[3]. We report a high sensitivity, but lower than a study on high risk with increased NT population[44].

Our research is the second study[45] reporting a simplified method in detecting MCHDs in the FT and the first addressing minor defects. It confirms that even a modest checklist has the ability to provide high detection rates in MCHDs and it underlines the differences between the two groups of diseases, with much higher FN in the latter. In our view, the FT rapid fetal movement pattern is involved in faster obtaining the optimal insonation angle.

The strength of our study is the use of a homogenous protocol for the FT heart assessment in all participants. We performed the study on unselected pregnancies, with a minimum context bias. If we use a standardized protocol we may reasonable hope to lower the operator dependency and eliminate the fetal position dependency, two important reasons for the delayed diagnosis of MCHDs.

A limitation is the fact that the operators are highly skilled and specialized in the FT assessment. Another source of bias in autopsy results is the fact that the pathologists were aware to the US data. In addition, the spectrum bias of the targeted anomalies, very characteristic for CHDs, is inevitable. Another possible limitation of our study was that not all children have been postnatally examined by cardiac US performed by a pediatric cardiologist. Therefore it is possible that we were not informed about minor heart defects that were neither prenatally, nor postnatally detected. However, these types of abnormalities could be considered not to have a significant clinical impact on child's growth and well-being, since their 6-12 months follow-up was negative.

We used gray-scale scanning and color Doppler duplex in almost all examinations. Therefore, we cannot reliably distinguish between heart defects detected in gray-scale or by using color Doppler, although we can speculate that the addition of color Doppler gate was important, due to subjectively low discrimination of signals in grey-scale in the FT.

In the early screening, the objective is not to give a precise complete diagnosis, but to spot an

Table 1 - Correlations between first trimester (FT) two-dimensional ultrasound (US) suspected diagnostic and real diagnostic, methods used for confirmation, outcome.

Case No	Real diagnosis classify	Real diagnosis	FT US suspicion classify	FT US suspicion	Board	Pathology	ST/TT scan	Birth	Outcome
1	major	Fallot RAA	major	Fallot RAA, GAT?, EIF	+	+	0	0	FT TOP
2	major	Isolated uncorrected GAT	major	GAT	+	+	+	+	Birth, nn death
3	major	Tr atr intact septum	major	HRHS	+	0*	0	0	FT TOP
4	major	Single ventricle heart	major	Single ventricle heart	+	0	0	0	FT TOP
5	major	Unkown, but major	major	CAT?, DORV?, large VSD, ventricular asymmetry, EIF LV, cardiomegaly	+	0	0	0	FT TOP
6	major	AVSD	major	AVSD	+	0	0	0	FT TOP
7	major	Fallot, cardiomyopathy	major	Fallot, cardiomyopathy	+	0*	0	0	FT TOP
8	major	HRHS	major	Tr A VSD, HRHS	+	0	0	0	FT TOP
9	major	AVSD	major	AVSD/large VSD	+	0	0	0	FT TOP
10	major	HLHS	major	HLHS, Ao stenosis	+	0	0	0	FT TOP
11	major	Ectopia cordis	major	Ectopia cordis, GAT	+	+	0	0	FT TOP
12	major	AVSD	major	AVSD	+	0	0	0	FT TOP
13	major	AVSD	major	AVSD	+	0*	0	0	FT TOP
14	major	AVSD	major	AVSD	+	0	0	0	FT TOP
15	major	HLHS	major	HLHS, Ao stenosis, Fallot, pericardial effusion	+	0	0	0	FT TOP
16	major	Cardiomyopathy	major	HRHS, pericardial effusion, large VSD, cardiomyopathy	+	+	0	0	FT TOP
17	major	AVSD, RAA	major	AVSD, RAA	0	+	+	0	ST TOP
18	major	Fallot + AVSD	major	Fallot + AVSD	+	0	0	0	FT TOP
19	major	Ectopia cordis	major	Ectopia cordis, GAT	0	+	0	0	FT TOP
20	major	AVSD?	major	AVSD, pericardial effusion	+	0	0	0	FT demise
21	major	HLHS	major	HLHS	+	0	0	0	FT demise
22	major	Fallot, pericardial effusion	normal heart	Normal heart	0	+	+	0	ST TOP

Legend

In bold letters – real major congenital heart diseases ; Highlighted in blue – false negative cases.; Highlighted in yellow – false positive cases.

Abbreviations: No = number, dg = diagnosis, ST = second trimester, TT = third trimester, RAA = right aortic arch, GAT = great arteries transposition, EIF = echogenic intracardiac foci, 0* = conventional autopsy attempted, results not reliable (photographic files not available), TOP = termination of pregnancy, nn = neonatal, Tr = tricuspid, atr = atresia, HRHS = hypoplastic right heart syndrome, CAT = common arterial trunk, DORV = double outlet right ventricle, VSD = ventricular septal defect, LV = left ventricle, AVSD = atrio-ventricular septal defect, HLHS = hypoplastic left heart syndrome, Ao = aortic, St = stenosis, CMV = cytomegalovirus infection, Rx = radiography, RAA-LD = right aortic arch with left ductus, PAC = persistent arterial canal, Co = coarctation, IUGR = intrauterine growth restriction, PTB = preterm birth, ARSA = aberrant right subclavian artery

23	**major**	**Fallot**	**normal heart**	**Normal heart**	**0**	**+**	**+**	**0**	**ST TOP**
24	**major**	**Cardiomegaly**	**normal heart**	**Normal heart**	**0**	**0**	**+**	**+**	**Birth, nn death**
25	**major**	**Critical AoSt**	**normal heart**	**Normal heart**	**0**	**+**	**+**	**0**	**ST demise**
26	**major**	**Major pericardial effusion**	**normal heart**	**Normal heart**	**0**	**0**	**0/+**	**+**	**Birth, early nn death CMV**
27	minor	Complete situs inversus, no heart anomaly	minor	Complete situs inversus, no heart anomaly	+	0	+	+	Birth, Rx confirmation
28	minor	Unknown, but minor	minor	Asymmetry	+	0*	0	0	FT TOP
29	minor	Double Ao arch	minor	RAA/double Ao arch	+	0	+	+	Birth
30	minor	RAA-LD	minor	RAA-LD	0	+	+	0	ST TOP
31	minor	Small VSD	normal heart	Normal heart	0	0	+	+	Birth
32	minor	PAC	normal heart	Normal heart	0	0	0	+	Birth
33	minor	VSD	normal heart	Normal heart	+	0	0	0	FT TOP
34	minor	Cord triatriatum	normal heart	Normal heart	0	0	+	+	Birth
35	minor	AoCo	normal heart	Normal heart	0	0	+	+	Birth
36	minor	Small VSD	normal heart	Normal heart	0	0	+	+	Birth
37	minor	Minor pericardial effusion	normal heart	Normal heart	0	0	+	+	Birth, IUGR
38	minor	Dextrocardia, no heart anomaly	major	Dextrocardia, GAT	+	0	+	+	Birth
39	normal heart	Normal heart	major	HRH, Tr dysplastic valve	0	0	+	+	Birth
40	normal heart	Normal heart	major	VSD, HLHS	+	0	+	+	Birth
41	normal heart	Normal heart	minor	VSD, ventricular asymmetry	+	0	+	+	Birth
42	normal heart	Normal heart	minor	Asymmetry of the arches, malposition, Ao stenosis	+	+	+	+	PTB, nn death, deletion 10p11.22 - p12.31
43	normal heart	Normal heart	minor	Isolated ARSA	0	0	+	+	Birth

anomaly and to assess its severity. Using a standardized approach we advocate for a policy that allows to all sonographers involved in routine prenatal screening to early and easily obtain key-features by almost no additional time, uniformly. We may hope that there will be lesser significant variation in FT detection rates of MCHDs between a specially trained observer and a less experienced one, less for a specific setting or country and between different countries.

In our view this study has a contribution to the FT fetal heart knowledge due to standardization and the simplicity and efficacy of the proposed protocol, a low cost and time consuming technique. We consider our results easily reproducible in other settings.

Table 2. Sensitivity, specificity, positive and negative likelihood ratio values with 95% CI for 2DUS method in MCHDs and mCHDs detection.

	MCHDs		mCHDs	
Se	80.77%	95% CI: 60.64 % - 93.97 %	33.33%	95% CI: 10.13 % - 65.05 %
Sp	99.90%	95% CI: 99.70 % - 99.98 %	99.90%	95% CI: 99.70 % - 99.98 %
PPV	87.50%	95% CI: 67.61 % - 97.20 %	57.14%	95% CI: 18.75 % - 89.58 %
NPV	99.83%	95% CI: 99.60 % - 99.94 %	99.72%	95% CI: 99.46 % - 99.88 %
LR+	775.92	95% CI: 246.56 – 2441.87	321.78	95% CI: 80.51 – 1286.03
LR-	0.19	95% CI: 0.09 – 0.42	0.67	95% CI: 0.45 – 1.00

CI = confidence interval, 2DUS = two-dimensional ultrasound, MCHDs = major congenital heart diseases, mCHDs = minor congenital heart diseases, Se=Sensitivity, Sp = Specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = Positive likelihood ratio, LR- = Negative likelihood ratio

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