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Reliability of Early Fetal Echocardiography for Congenital Heart Disease Detection: A Preliminary Experience and Outcome Analysis of 102 Fetuses to Demonstrate the Value of a Clinical Flow-Chart Designed for At-Risk Pregnancy Management

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Abstract

Early fetal echocardiography (EFEC) is a fetal cardiac ultrasound analysis performed between the 12th and 16th week of pregnancy (compared with the usual 18-22 weeks). In the last 10 years, the introduction of "aneuploidy sonographic markers" in screening for cardiac defects has led to a shift from late second to end of the first trimester or beginning of the second trimester of pregnancy for specialist fetal echocardiography. In this prospective study, early obstetric screening was performed between January 2014 and October 2015, using "aneuploidy sonographic markers" following SIEOG Guidelines 2014. These parameters were then collected and strategically combined in an evaluation score to select the group of pregnancies for performing EFEC, in accordance with the American Society of Echocardiography guidelines for fetal Echocardiography. All second-level examinations were performed transabdominally using a 3D convex volumetric probe with frequency range of 4-8 MHz (Accuvix – Samsung). The outcome data included transabdominal fetal echocardiography from 18 weeks to term and after birth. Overall, 99 pregnant women in the first trimester underwent EFEC (95 singleton and 4 twin pregnancies). Specifically, 30 fetuses were evaluated for extra-cardiac anomalies evidenced by obstetric screening (30%), 25 for family history of congenital heart diseases (25%), 8 for family history of genetic-linked diseases (8%), 4 for heart diseases suspected by obstetric screening (4%) and 19 by normal screening (19%). Was detected 11 (10.7%) CHD, when EFEC detected CHD, were compared to those performed later in pregnancy (18 weeks GA-term), a high degree of diagnosis correspondence was evidenced. The higher sensitivity value of EFEC vs late-FE, in comparison with the post-natal value, coupled with the high EFEC specificity shown vs both the end points, enabled us to consider it as a really reliable diagnostic technology, at least in perienced hands. The introduction of a key combination of the more sensitive obstetric and cardiologic variables should facilitate the formulation of a possible flow-chart as a guide for CHD at-risk pregnancies.

Keywords: Congenital heart disease; Early fetal echocardiography; Clinical score

Introduction

Congenital Heart Diseases (CHD) are the most common malformations, occurring in 0.8% of the general population. While it is possible to screen CHD during fetal life by a prenatal routine ultrasound examination, this can identify only 60 % of CHD [1]. Major cardiac defects need specialist fetal echocardiography for complete diagnosis and counseling. It is necessary to improve the methods used to screen high-risk groups of pregnancies by standardizing the clinical evaluation of the maternal-placental-fetal unit with the use of a diagnostic protocol that can be shared by obstetricians, genetistics and fetal echocardiographers. The data obtained may then be used as a basis for the identification of sensitive criteria for formulating a clinical-sonographic score and flow-chart as a guide for the diagnostic and therapeutic management of CHD pregnancies.

CHD at-risk groups identified for referral through routine screening include: family history of CHD, maternal pathologies such as diabetes mellitus and connective diseases, maternal exposure to teratogens, and, in the last 10 years, the introduction of "aneuploidy sonographic markers" in screening for cardiac defects (NT thickness, abnormal flow through the ductus venosus and across the tricuspid valve) [2-7].

This approach has led to a shift from late second to end of first or beginning of second trimester of pregnancy for specialist fetal echocardiography. Fetal cardiac ultrasound analysis performed between the 12th and 16th week of pregnancy (compared with the usual 18-22 weeks) is defined as Early Fetal Echocardiography (EFEC) [8-15].

An important preliminary consideration is that the most complex CHDs do not develop in hearts that appear to be normal at an early stage and present similar images in the 1st, 2nd and 3rd trimesters (d/l-Transposition of Great Arteries, Hypoplastic Left Ventricle Syndrome, Atrioventricular Septal Defect, Double Outlet Right Ventricle, Tricuspid Atresia, Mitral Atresia, Pulmonary Atresia, Total Total Anomalous Pulmonary Venous Return, large Ventricular Septal Defect).

Our general working hypothesis is that the strategic combination of already acquired or new diagnostic and biotechnological tools (such as "aneuploidy sonographic markers", EFEC, genetic analysis) could be analyzed on the basis of their specific statistic reliability and used as key criteria for a clinical score to be included in the management of CHD "at risk" pregnancies.

Within this working hypothesis, the specific objective of the present study is to test the effective reliability of EFEC in selected CHD at-risk pregnancies in order to figure out the key clinical diagnostic elements to be used as a guide for fetal-maternal unit management.

Score	**0**	**1**	**2**	**3**
Age	< 30	31-35	> 35	/
NT	< 1	1-2	2,1-2,9	> 3
Nasal Bone	Present	/	Hypoplastic	Absent
Tricuspidregurgitation	Absent	/	/	Present
Ductus venosus wave a	Positive	/	Absent	Negative
Heart rate	151-170 b/m	140-150 b/m	> 170 b/m	< 140 b/m
History	Negative	• Thyroid disease	• Drugs • Previous CHD	• Diabetes mellitus • Autoimmunity • Maternal heart disease • Metabolic disease • Twins

Table 1: Score to select pregnancies for EFEC.

Minor defects	**Major defects**
Cardiomegaly	Atrioventricular septal defect
Ventricular septal defects	Trasposition of the great vessels
Disproportion:	Tetralogy of fallot
LV<RV	Hypoplastic left heart ventricle
AO<PA	Pulmonary atresia
PA<AO	Complex cardiopathies
RV<LV	
RA > LA	
LV : Left Ventricle; RV: Right Ventricle; AP: Pulmonary Artery; AO: Aorta	

Table 2: CHD classification in EFEC.

Methods

In this prospective intervention study, early obstetric screening was performed between January 2014 and October 2015, using "aneuploidy sonographic markers" following SIEOG Guidelines 2010 [16], including the first trimester ultrasound markers of early fetal right heart dysfunction. These parameters were then collected and strategically combined in an evaluation score (Table 1), to select the group of pregnancies for performing EFEC. Briefly, this evaluation method was considered as more indicative for a possible CHD when a cut-off level of > 4 was obtained by assigning an indicative value from 0 to 3 to each task, on the basis of statistical data analysis performed by our Obstetric Unit.

The study was approved by the Ethics Committee of the Policlinico Umberto I, Sapienza University of Rome.

A total of 99 pregnant women (103 fetuses) underwent EFEC screening (the first antenatal EFE screenings took place at 11-12 weeks gestation, based on the early fetal echography (EFE). At the first visit, the women received prescreening genetic counseling and an information booklet. They were informed of the limitations of the screening method and info med consent was obtained. Maternal family and personal health details were inserted in an internally networked database in Access format.

In addition to the cited score, the first level of early fetal heart study was performed by obstetricians at the Prenatal Diagnosis Unit for the evaluation of abdominal situs and heart position within the chest, four-chamber view, atrioventricular valve offsetting, ventricle filling with Color Doppler (CD), pulmonary artery-aorta crossing (X sign) with CD, forward flow and equal size at the confluence of the aortic arch and arterial ductus (V sign) [10].

The second cardiac diagnostic level (EFEC) concerns the specific cardiologic analysis, which was performed in accordance with the American Society of Echocardiography guidelines for fetal Echocardiography (AHA 2014 Circulation) [17] (Figures 1-3).

GR.1 n. 25	GR.2 n. 4	GR. 3 n. 30	GR. 4 n. 13	GR. 5 n. 8	GR. 6 n. 19
(25%)	(4%)	(31%)	(13%)	(8%)	(19%)
Family history of CHD	Suspected CHD (First level cardiac obstetric evaluation)	Obstetric screening alterations (score)	Maternal disease	Family history of chromosomal/genetic disorders	Control

Table 3: Obstetric selection of groups of pregnancies considered for EFEC evaluation: total n. 99. (Fetuses n. 103) (100%).

Groups: n. CHD suspected/ detected	GA (Weeks)	EFE Indications	Early (12-16 Weeks)	Late (18 weeks-end pregnancy)	Outcome	
					Top/Intra Uterine Death (IUD)	Postnatal
1: 2	14	Family history of long QT syndrome	Muscular VSD suspected long QT syndrome for relative bradycardia	Confirmed		Confirmed
	14	Family history of CHD	Normal	Small Muscular VSD		Confirmed
2: 4	15	Suspected AVSD	VSD and Suspected Aortic Coarctation+ Monosomy X	N.D.	Top	
	15	Suspected AVSD	AVSD-FALLOT + Trisomy 21 (Figure 1)	N.D.	Top	
	15	Suspected HLVS, Single Umbilical Artery	Suspected Shone Syndrome (Figure 2)	Confirmed	Top	
	14	Suspected CHD (Dilated ICV)	Agenesis Ductus Venosus: Umbilical Vein -> Iliac Veins-> ICV (Figure 3)	Confirmed		Right Lower Limb Venous Flow Insufficiency
3: 6	12	Cystic Hygroma, Increased NT and Tricuspid Regurgitation	VSD, Tricuspid Regurgitation Trisomy 21	N.D	Top	
	14	Cystic Hygroma, Hyperchoic Bowel Loops	Aortic Valve Stenosis	Confirmed		Confirmed Valvuloplasty in Second Day
	15	Increased NT, Hydrops	HLVS + Trisomy 18	Confirmed	IUD	
	16	Cystic Hygroma	DORV TGV AoCO	Confirmed		Confirmed, Switch Operation and Repaired AoCO
	16	Polymalformative Syndrome	LV < RV and AO < AP	N.D	Top	
	14	Cystic Hygroma, Hydrops, Nasal Bone Hypoplasia	Tricuspid Regurgitation Left Ventricle Prevalence	N.D.	Top	

TOP: Termination of Pregnancy; N.D: Not Detected; VSD: Ventricular Septal Defect; AVSD: Atrioventricular Septal Defect; HLVS: Hypoplastic Left Ventricle Syndrome; ICV: Inferior Vena Cava; CHD: Congenital Heart Disease; DORV: Double Outlet Right Ventricle; TGV: Transposition of the Great Vessels; AoCO: Coarctation of the Aorta; LV: Left Ventricle; RV: Right Ventricle; AP: Pulmonary Artery.

Table 4: EFEC and Late-FE detected-CHD within the groups.

All second-level examinations were performed transabdominally using a 3D convex volumetric probe with frequency range of 4-8 MHz (Accuvix A30-Samsung).

All the cardiac scan digital video-clips recorded were stored in the ultrasound equipment and subsequently collected and analyzed.

The outcome data included transabdominal fetal echocardiography from 18 weeks to term and after birth.

Applying the systemic sequential approach, 2D, CD and Power Doppler (PW) were used to visualize and analyze the images and the flow signals obtained by four- chamber view with atrioventricular valve setting, right and left ventricle outflow tracts and crossing, aortic and ductal arches, sweep from four- chamber to three-vessel view, and to evaluate ventricular function and heart rhythm with mechanical PR interval [11].

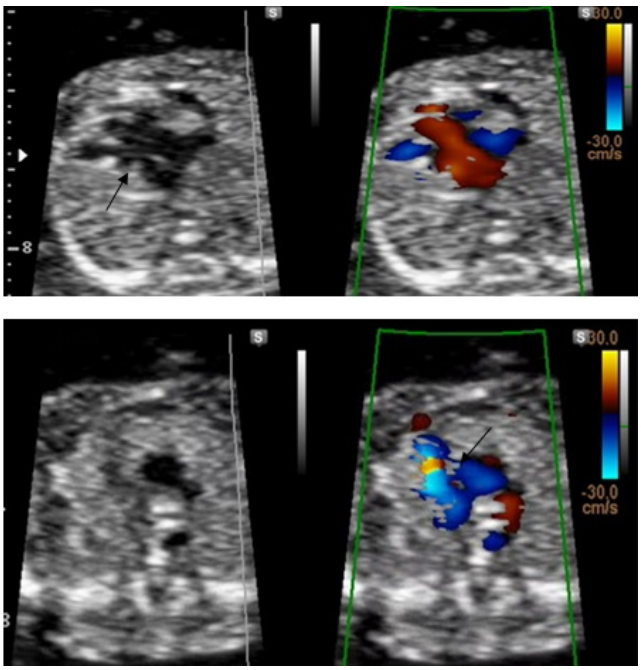

Figure 1: GA 15 Ws AVSD and tetralogy of fallot. AVSD: Atrioventricular Septal Defect (Arrow); IPS: Infundibular Pulmonary Stenosis (Arrow).

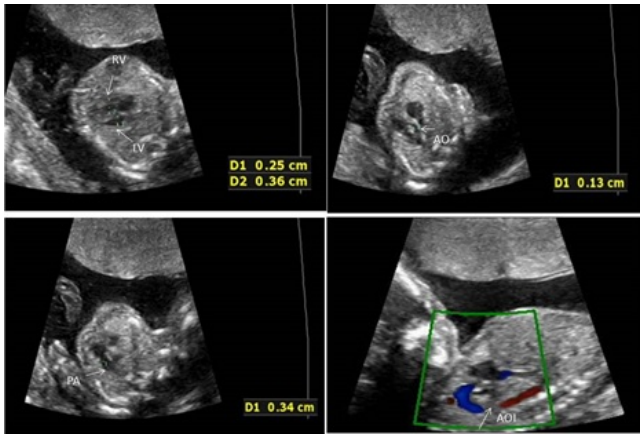

Figure 2: GA 15 Ws shone syndrome. LV: Left Ventricle; RV: Right Ventricle; AO: Aorta (arrow); PA: Pulmonary Artery.

First trimester classification of CHDs differs from the usual later and post-natal classification [10], when a complete diagnosis can be performed (Table 2).

Statistical Analysis

Late-FE and Post-natal Echocardiography were considered as diagnostic end-points for each EFEC-detected CHD. Sensitivity, specificity and predictive values of EFEC diagnosis, as well as receiver operating characteristic (ROC), were calculated following a binary classification test.

Results

EFEC indications and general clinical features of the pregnant women analyzed in our Unit are summarized in Table 3.

Overall, 99 pregnant women in the first trimester underwent EFEC (95 singleton and 4 twin pregnancies). Specifically, 30 fetuses were evaluated for extra-cardiac anomalies evidenced by obstetric screening (30%), 25 for family history of congenital heart diseases (25%), 8 for family history of genetic-linked diseases (8%), 4 for heart diseases suspected by obstetric screening (4%) and 19 by normal screening (19%).

As shown in Table 4, when EFEC-detected CHD were compared to those performed later in pregnancy (18 weeks GA-term), a high degree of diagnosis correspondence was evidenced.

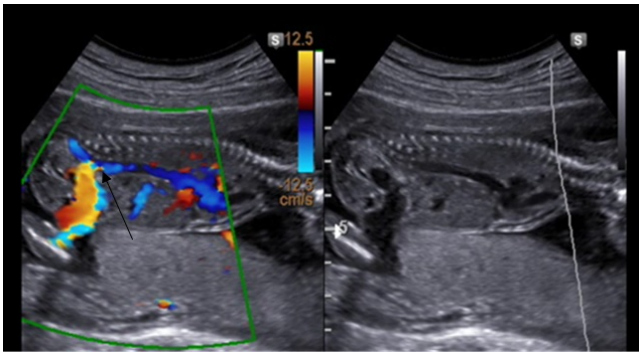

Figure 3: GA 15 Ws agenesis of ductus venosus. Umbilical vein drains in iliac veins and inferior vena cava (Arrow). UV: Umbilical Vein; IVC: Inferior Vena Cava.

Statistical Analysis for the evaluation of EFEC sensitivity and specificity in relation to the end-points considered (late FE and post-natal echocardiography) is shown in Table 4. The higher sensitivity value of EFEC vs late-EFEC, in comparison with the post-natal value, coupled with the high EFEC specificity shown vs both the end points, enabled us to consider it as a really reliable diagnostic technology, at least in experienced hands.

Discussion

There is a growing body of evidence that most of the major cardiac abnormalities can be diagnosed from 12-16 weeks of gestation. Furthermore, the reason for performing EFEC is that the combined EFEC-NT (nuchal translucency) approach (11th-13th week) gives a 60-70% increase in detection rate for CHD. Combined EFEC-NT analysis is also justified by the high CHD frequency in genetic syndromes and the similarity of anatomic relations between cardiac structures at 11-13 ws GA and those of the second trimester.

Thus, early evaluation could imply better decision making.

In this prospective study of first-trimester screening, the sequential combination of the obstetric "aneuploidy sonographic markers" with EFEC, performed on a selected group of 99 pregnant women, 11 CHD were detected, showing an excellent rate of reliability when compared with the regular late FE, with 91.7% sensitivity and 100% specificity (100% PPV and 98.8% PNV); only one case of small muscular VSD was diagnosed in late echo. These results were partly confirmed when EFEC was compared with the early post-natal control (neonatal period), with a 84.6 % sensitivity and 100% specificity (100% PPV, 97.7% PNV). The reduced sensitivity rate is due to postnatal diagnosis of a very slight pulmonary valve stenosis and an isolated uncomplicated aortic bicuspid valve: cardiac anomalies which are known to be rarely detectable before birth (Table 5).

Early VS Late	Early VS Postnatal	Late VS Postnatal
Sensitivity: 91.7%	Sensitivity: 84.6%	Sensitivity: 85.7%
Specificity: 100%	Specificity: 100%	Specificity: 100%
Positive Predictive Value (PPV): 100%	Positive Predictive Value (PPV): 100%	Positive Predictive Value (PPV): 100%
Negative Predictive Value (NPV): 98.8%	Negative Predictive Value (NPV): 97.7%	Negative Predictive Value (NPV): 97.7%

Table 5: EFEC-CHD detection sensitivity, specificity, PPV, NPV, evaluated in comparison with the diagnostic end-point (Post-Natal Echocardiography).

The technical limits of EFEC are CRL < 50 mm, an increase of maternal Body mass index (BMI), unfavorable fetal position and a possible progression of cardiac disease especially in outflow obstructions [12,13]. This means that the pregnant women should be informed about the limits of early screening and also recommended to have a further scan as from 18 weeks for a more complete diagnosis.

Nevertheless, taking into account the accuracy of this technology, EFEC gives the parents the opportunity to be more aware and to have more time to make an informed decision regarding continuation of the pregnancy with reduced long-term psychological sequelae. In this way, if the couple decides to continue the pregnancy, the timing, location, mode of delivery and direct postnatal care can be planned, with a consistent improvement of postnatal outcome. Where the EFEC shows no evidence for a major cardiac defect, it allows earlier reassurance of couples considered at high risk for CHD. Exclusion of a complex cardiopathy at an early stage of pregnancy is particularly reassuring for parents with a child affected by CHD in a previous pregnancy [14].

Conclusion

Overall, EFEC may be considered feasible, highly sensitive and specific when performed by experienced fetal cardiologists.

Moreover, the introduction of a key combination of the more sensitive obstetric and cardiologic variables, including the use of new technologies [18], should facilitate the formulation of a possible flow-chart as a guide for CHD at-risk pregnancies

Studies are currently under way in our Echo-Lab to develop a flow-chart by introducing a more complete clinical score which could also include new CHD-sensitive molecular markers (miRNAs) detectable in maternal peripheral blood [19].

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