Journal of Human Sciences
ISSN: 2458-9489
Volume: 14 Issue: 1 Year: 2017

The effectiveness of extended fetal heart screening in a Tertiary Center

Fatma Çakır[1]
Bulat Aytek Şık[2]
Serkan Kumbasar[3]
Murat Bozkurt[4]
Yılda Arzu Aba[5]

Abstract

Our study is to evaluate the effectiveness of extended fetal heart screening in a tertiary center and research the sensitivity, specifity and the positive and negative values of echocardiography.

316 patients who were diagnosed with congenital anomalies among those scanned with the extended fetal heart screening protocol in the perinatology department of our hospital were included in our study. Patients who were not diagnosed with congenital anomalies were excluded. Fetal echocardiographies were perfomed on patients who were admitted to our perinatology clinic, in accordance with the ISUOG extended fetal heart screening protocol.
In our study, 55.3% of all cases with cardiac anomalies are concomitant with extracardiac anomalies. An interventional procedure was performed on 52.5% of the patients for karyotyping purposes. 19.3% was terminated early in the pregnancy, 5% and 12.5% were lost during the intrauterine and neonatal periods, respectively. In our study, upon comparison of the fetal and neonatal results, we determined that the false positive and negative rates for fetal echocardiography were 3.5% and 9.4% respectively.

In our study, the sensitivity, specificity, positive predictive value and accuracy of echocardiography were determined as 91%, 99%, 98% and 99% respectively during the application of ISUOG recommendations in a tertiary center.

Keywords: Prenatal Diagnosis; Fetal Anomaly; fetal cardiac anomaly; Fetal Echocardiography; Chromosome anomaly.

Introduction

With a rate of every 8 newborns out of 1000, the structural anomalies of the heart and large vessels are the most common structural defects. The major structural anomalies detected in 2-3% of all newborns are the second most common reason of perinatal mortality and morbidity (Manning, 2009; Gadow, 2001). In the recent studies done in our country, the prevalence of major

[1] Dr., Deparment of Gynecology and Obstetrics, Suleymaniye Maternity Hospital for Research and Training, Istanbul, Turkey. fatmacakir80@yahoo.com
[2] Assistant Professor, Ph.D., Istanbul Aydin University, Medicine Faculty, Deparment of Gynecology and Obstetrics, Istanbul, Turkey, bulataytek@hotmail.com
[3] Op. Dr., Sakarya University, Medicine Faculty, Deparment of Gynecology and Obstetrics, doktor1977@hotmail.com
[4] Op. Dr., Sakarya University, Medicine Faculty, Deparment of Gynecology and Obstetrics, jindrmb@yahoo.com
[5] Assistant Professor, Ph.D., Bandirma Onyedi Eylul University, Health Science Faculty, Faculty of Health Science, Nursing Department, Balıkesir, Turkey, yaba@bandirma.edu.tr

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anomalies was determined to be 5.85% (Özler et al., 2014). Fetal structural anomalies may stem from blastogenesis defects which affect a large part of the body or present with organogenesis defects, which affected organs (Opitz, Wilson & Barness, 1997). Usually, no reason is detected in the etiology of congenital anomalies. However, beside genetic factors, which are the most commonly accused cause in the etiology of this disease, maternal systemic diseases, environmental agents, alcohol, smoking, addictive substances, toxic agents intaken during pregnancy, radiation, maternal infections, disruption of placental blood flow and perinatal infections are also among the acknowledged causal factors of congenital anomalies (Kalter, 2013).

The aim of this study is to evaluate the effectiveness of extended fetal heart screening in a tertiary center and research the sensitivity, specifity and the positive and negative values of echocardiography.

Materials and Methods

316 patients who were diagnosed with congenital anomalies among those scanned with the extended fetal heart screening protocol in the perinatology department of Suleymaniye Maternity Hospital for Research and Training were included in our study between October 2007 and September 2009.

Patients without fetal congenital anomalies were excluded from the study. Our research is a retrospective, cohort study.

Fetal echocardiographies were performed on patients who were admitted to our perinatology clinic, in accordance with the ISUOG extended fetal heart screening protocol. ISUOG extended fetal heart screening is based on viewing the four chambers of the heart as well as its outlet pathways. In basic heart examination, the localization, axis, position and size of the heart, its four-chamber image and presence of pericardial effusion were evaluated. Whether the atria were equal in size, foramen ovale flap was at the left, and atrium septum primum existed were investigated. It was checked whether the ventricles were equal in size, the moderator band was in the right ventricle and there was an intact ventricular septum. It was examined whether the apex than the mitral valve. In addition to these, it was seen that the diameters of the big vessels were equal in size and that they decussated each other at the right angle after exiting the ventricle. In our perinatology unit, the 3-7 mhz abdominal convex probe of the Voluson 730 Expert ultrasound device was used. Karyotype analysis was suggested to those diagnosed with anomalies. After detailed consents were taken, karyotyping was performed using the chorionic villus biopsy method between 11^{th}-14^{th} weeks, the amniocentesis method between 16^{th}-24^{th} weeks and the chordocentesis method after the 24^{th} week. All of the patients were called back to the hospital during the postpartum period and a gynecologist asked the patients about any existing chronic diseases, drug use, previous operations, smoking and alcohol use, familial diseases, consanguinity, whether any invasive procedures were performed during pregnancy, whether the pregnancy was terminated at an early stage, whether a neonatal echocardiogram was performed to the baby and its diagnosis, whether the baby underwent any cardiac operations and about intrauterine or neonatal mortality. The patients were informed and informed consents were obtained. Consent was received from the ethics committee. Fetal and neonatal results were compared.

SPSS for Windows 10.0 statistical package program was used for the evaluation of data. In determining the diagnostic value of extended fetal echocardiography, sensitivity, specificity, positive and negative predictive values were calculated. $p<0,05$ was considered significant.

Results

A total of 316 patients were called during the postpartum period for verification of diagnoses. 125 of these patients could not be reached and 191 patients were interviewed face to face (60.4%). All of the cardiac anomalies detected with fetal cardiography are listed in Table 1 along with the number of cases.

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Table 1. Listing of all Cardiac Anomalies

Major cardiac anomalies	n	Minor cardiac anomalies	n
Tetralogy of fallot	11	Hyperecogenous focus	36
Atrioventricular septal defect	45	Tricuspid regurgitation	56
Ventricular septal defect	73	Perdicardial effusion	16
Atrial septal defect	5	**Total**	**108**
Transposition of great arteries	8		
Trunkus arteriosus	5		
Double outletright ventricle	5		
Hypoplastic left heart	5		
Hypoplastic right heart	2		
Univentricular heart	4		
Hydrops fetalis (heart failure)	8		
Cardiomegaly	7		
Dysrythmia	16		
Ebstein anomaly	2		
Rhabdomyoma	3		
Aort coarctation	3		
Right aortic arc	1		
Pulmonary aneurysm	1		
Pulmonary stenosis	3		
Interrupted aortic arc	1		
Total	**208**		

Of 316 cases with congenital cardiac anomalies, 191 were reached (60.4%). 71 of the patients were nulliparous and 120 of them were multiparous. 69 patients were aged 35 and above. 35 patients reported smoking 5 cigarettes per day. Upon query of consanguinity, it was learnt that 37 patients were married to their 1st degree relatives and 11 patients were married to their 2nd degree relatives. 14 patients reported positive family history of 1st degree relatives for diabetes.

During query of chronic diseases, it was determined that 2 patients had asthma, 1 had epilepsy, 3 had goiter, 2 had Acute Rheumatoid Fever, 1 had Lupus, 1 had Coeliac Disease, 2 had diabetes and 1 had hypertension, adding up to 13 chronic diseases. It was learnt that 5 patients had appendectomies, 2 had ovary cystectomies, 3 had tonsillectomies and 1 had thyroidectomy, adding up to 11 patients with histories of previous operations (Table 2).

Table 2. The distribution of patients according to their demographic characteristics

Characteristic	n	%
Nulliparous	71	37.2
Multiparous	120	62.8
Below the age of 35	247	88.2
Above the age of 35	69	21.8
Chronic diseases	13	6.8
History of previous operations	11	5.7
DM in 1st degree relative	14	7.3
Consanguinity	48	25.1
Smoking	35	18.3

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Of the 315 patients diagnosed with cardiac anomalies after screening with extended fetal heart screening protocol, extracardiac anomalies were detected in 175 cases during ultrasound examinations and 141 cases did not show any extracardiac anomalies.

Of the 316 patients diagnosed with cardiac anomalies, amniocentesis was performed on 111 patients, chordocentesis was performed on 46 patients, chorion villus biopsy was performed on 9 patients, adding up to 166 invasive procedures.

A total of 33 karyotype anomalies were detected among these patients. The cardiac findings of these anomalies comprised Trisomy 21 and Trisomy 18. Ventricular septal defect + Tricuspid Regurgitation + Hyperecogenous Focus were detected in the fetus diagnosed with Trisomy 13 during prenatal echocardiogram. Hydrops Fetalis was seen in 2 cases with Turner Syndrome.

61 of the 316 patients diagnosed with cardiac anomalies were terminated early. During the calls made in the post-partum period, it was learnt that 16 fetuses were lost during the intrauterine period, 9 babies were lost after having operations and 15 were lost before they could be operated. (Table 3)

Table 3. List of the terminated cardiac anomalies

Terminated cardiac anomaly	n
Fallot Tetralogy	2
Atrioventricular Septal Defect	13
Ventricular Septal Defect	11
Trunkus Arteriosus	2
Double Outletright Ventricle	1
Hypoplastic Left Heart	4
Hypoplastic Right Heart	1
Univentricular Heart	2
Hydrops Fetalis(Heart Failure)	2
Ebstein Anomaly	1
Pulmonary Stenosis	1
Pericardial Effusion	1
Hyperecogenous Focus	7
Tricuspid Regurgitation	8
AVSD+DORV	2
AVSD+TGA	1
DORV+TGA	1
TOF+DORV	1
TOTAL	**61**

Of the 191 patients reached during the postpartum period, it was learnt that 44 had early terminations and 26 faced intrauterine or postpartum death before any diagnosis could be made. 77 patients did not have neonatal echocardiograms while 44 patients did. Of those who had neonatal echocardiograms, 9 cases' results were normal and pathological results in accordance with fetal echocardiographies were detected in 35 cases. According to this, the false positivity rate in our series was calculated as 20.4% (Table 4).

Table 4. Results of patients who had neonatal echocardiograms

Results of neonatal echocardiograms	n	%
Normal	9	20.4
Cardiac anomaly in fetal echo	35	79.6
Total	**44**	**100**

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Upon considering early terminations and stillbirths as patients with cardiac anomalies, the false positivity rate was calculated as 7.9%. Considering the fact that only ventricular septal defect could be expected from the fetal echocardiographic anomalies with normal neonatal echocardiograms, the corrected rate of false positivity was calculated as 3.5% (Table 5).

Table 5. The distribution of those with normal neonatal echocardiograms despite abnormal fetal echocardiogram findings

Normal neonatal echocardiograms despite abnormal fetal echocardiogram	n
Premature Atrial Beats	1
Ventricular Septal Defect	4
Tricuspid Regurgitation	4
TOTAL	**9**

The diagnostic value of fetal echocardiogram was determined after comparison of the fetal and neonatal diagnoses of all patients (Table 6).

Tablo 6. The comparison of Fetal Echocardiogram and postpartum diagnoses -1

Postpartum Diagnoses	Fetal Echo Normal	Anomaly In Fetal Echo	Total
Postpartum Normal	957	4	961
Postpartum Anomalies	13	68	81
Total	970	72	**1042**

As a result of our study comparing the fetal echocardiograms and postpartum diagnoses, relating to echocardiography, the sensitivity was 84%, the specificity was 99%, the positive predictive value was 94%, the negative predictive value was 98% and accuracy was 98%. 3 of the 4 cases who had fetal echocardiographic anomalies but were found out to be normal during the postpartum period were diagnosed with Premature Atrial Beats and 1 was diagnosed with Perimembranous VSD. Due to the fact that among these anomalies, only VSD was expected to be seen during the neonatal period and that it is acceptable to miss ASD and arrhythmia during the fetal echocardiogram, which may later cause Hydrops Fetalis, a new table was drawn up. The diagnostic value of fetal echocardiogram was recalculated in accordance with this table (Table 7).

Tablo 7. The comparison of Fetal Echocardiogram and postpartum diagnoses -2

Postpartum Diagnoses	Fetal Echo Normal	Anomaly In Fetal Echo	Total
Postpartum Normal	963	1	964
Postpartum Anomalies	7	71	78
Total	**970**	**72**	**1042**

According to this, the sensitivity, specificity, positive predictive value and accuracy of echocardiography were determined as 91%, 99%, 98% and 99%

Discussion

Congenital anomalies comprise the fetal structural and functional anomalies that occur due to abnormal development during morphogenesis. The congenital anomaly prevalence throughout the population is 2-3%; and major anomalies comprise 1/3 of these (Simpson & Otano, 2007). In our study, the fetal cranium, neck, face, thorax, heart, abdomen, vertebrae and the lower and upper extremities were evaluated in accordance with the International society of ultrasound in obstetrics

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and gynecology (ISUOG) Guide (Salomon et al., 2011). One of the main aims of ultrasonographic evaluation during the second trimester is determining major structural anomalies during the prenatal period. In our study, the major anomaly rate among patients evaluated with routine detailed ultrasonographic imaging between the 18th and 23rd gestational weeks is higher than the results reported by different centers in our country (Tomatir et. al, 2009; Kurdoğlu et. al, 2009). This may be attributed to the fact that the study is based on the results of detailed ultrasonographic imaging performed in a perinatology clinic that is a tertiary reference center. However, in another recent study, the major anomaly prevalence was reported as 5.85% (Özler et. al, 2014).

Although fetal anatomical screening is recommended for evaluation along with nuchal translucency during the first trimester, the determination of CVS and face anomalies usually becomes possible during the second trimester (Chen et. al, 2008). Despite the fact that detection rate of major anomalies with detailed screening are reported to be around 47-76% during the first trimester, the combined detection rates during the first and second trimesters reach 89% (Chen et. al, 2008; Iliescu et. al, 2013).

The fetal echocardiographic imaging performed via the abdominal path show that the possibility of viewing all cardiac structures is 60% between the 12th week and 12th week + 6 days of pregnancy and that this rate increases up to 92% between the 13th week and 13th week + 6 days of pregnancy; thus, an effective fetal echocardiogram may be performed during the latter (Haak, Twisk & Van Vugy, 2002). While performing early fetal echocardiographies between the 12th-14th weeks has become possible thanks to improving technology, the evaluation week of routine practice is between the 18th-22nd gestational weeks (Güven, Günhan & Coskun, 2007).

A certain protocol must be followed during the evaluation of the fetal heart. Due to the Sequential segmental analysis (SSA) method and the usage of basic defining terms, many complex cardiac anomalies have become detectable during the prenatal period (Güven, Carvalho & Shinebourne, 2003). In the study done by Dashe et al. comprising one of the most extensive retrospective series, out of 672 pregnant women with polyhydroamniosis, 77 (11%) were diagnosed with fetal anomalies, of which 20 (25%) were cardiac anomalies. In this series, the general rate of anomaly was determined to be 10%. Therefore, serious polyhydroamniosis cases should be evaluated with respect to cardiac anomalies (Dashe et. al, 2002).

Bahado et al. detected cardiac anomalies in patients who were referred for detailed ultrasonographies or fetal echocardiograms despite normal karyotypes. In this study, 3003 fetuses were scanned mid-trimester and 95 patients (3.5%) were diagnosed with congenital heart diseases during the post-partum period. Using nuchal edema for detection of CHD in their own high-risk population, they calculated the sensitivity and specitifity rates as 47.4% and 70.5% respectively. This study showed that a history of anomalous children along with increased nuchal edema during the second trimester in the current pregnancy are the most important predictors of CHD. Used together, the deviation rate and specificity were 54% and 68% respectively. This study showed that nuchal edema measurement alone during the second trimester is an important predictor for left-based cardiac lesions.

In our study, the main gestational week is 18.1±1.4. Dağlar et al. found the mean gestational week to be 17.6±1.5 in their study (Timur et. al, 2013; Dağlar et. al, 2011). 88.2% (n=247) of the cases in our study are below the age of 35 and 21.8% (n=69) are above 35. The mean age of the cases in our study proved to be coherent with the other studies done in our country (Yıldırım et. al, 2006; Pala et. al, 2014).

The cases in our study comprise different examples of fetal heart anomalies, which have a wide spectrum. These cases are made up of 316 patients with cardiac anomalies, most of which do not carry any risk factors. 55.3% of all cardiac anomalies are concomitant with extracardiac anomalies. An invasive procedure was performed on 52.5% for karyotyping purposes. Karyotype anomalies were detected in 19.8%. 19.3% were terminated early during the pregnancy and 5% and 12.5% of them faced intrauterine and neonatal deaths, respectively. In our study, upon comparison of fetal and neonatal results, the false positivity and false negativity of fetal echocardiography were

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determined as 3.5% and 9.4% respectively. In our study, as the results of normal and anomalous groups of patients who underwent the extended fetal heart screening protocol were compared with their postpartum results, relating to echocardiography, the sensitivity was 91%, the specificity was 99%, the positive predictive value was 98%, the negative predictive value was 99% and accuracy was 99%.

The clinical outcomes of prenatal diagnosis of congenital heart diseases are significantly related to extra-cardiac and chromosomal anomalies. In a series of 382 pregnant women diagnosed with CHD, Song et. al detected extra-cardiac anomalies in the postnatal and autopsy results of 141 fetuses (36.9%), of which 46 had chromosomal anomalies. In this series, the extracardiac anomalies were frequently seen in the urogenital (12.2%) and gastrointestinal (11.6%) systems. In our study, the extracardiac anomalies were most commonly seen in the urogenital (n= 19; 18.1%), central nervous (n=16; 15.2%) and skeletal systems (n=13; 12.3%).

In a study done by Özkutlu S. et al in 1999, the false negativity among fetuses who underwent fetal heart screening was 22.2%. False positive results were not obtained. In our series, the rates of false negativity and false positivity were 9.4% and 3.5% respectively. The reason for the low false negativity rate and high false positivity rate in our study is the inclusion of minor anomalies in the study group.

In their 5-year study published in 2001, Strauss et. al reported the accurate diagnostic rate of intrauterine cardiac anomalies as 38%. They determined the rates of chromosomal anomalies, neonatal operations and neonatal mortality to be 10%, 5% and 28% respectively. In our study, these rates were found to be 19.8%, 4.4% and 12.5%, respectively. The reason of the low mortality rate in our study was early termination of anomalies incompatible with life and the inclusion of minor anomalies in our research.

In a paper published in 2000, Sirinivasa S. et al write about the importance of fetal echocardiography in terms of early intervention during infancy in cardiac anomalies that are compatible with life and that fetal echocardiogram will have a huge role in the upcoming fetal heart surgeries.

Conclusion

Congenital heart disease has been approximately seen in 1% of all live births. Today, the examination of the normal anatomy of the foetal heart and its abnormalities can be possible by the development of high resolution ultrasonography devices. In this study, the rate of karyotype anomaly was found to be 19.8% in patients with cardiac anomaly. In addition, the early termination rate of pregnancy was 19.3% and the neonatal mortality rate was 12.5% in fetuses with foetal echocardiography anomaly.

Having a baby with an unexpected cardiac anomaly that has not been detected in the early stages of your pregnancy, the baby's treatment process, the loss of advanced gestational weeks or postpartum cause the serious mental problems in the parents.

The cardiac anomalies were detected by the fetal heart scan protocol have the legal right to terminate your pregnancy within the preference of the family. Thus, the difficulties caused by pregnancy are not unnecessarily moved forward week.

Fetal echocardiography and termination of pregnancy, if it is necessary, the cost is about 300 according to the length of stay in the hospital. The average operation cost of the cardiac anomaly is 30.000 in the new born. The early termination of pregnancy with fetal cardiac anomaly saves a serious financial burden on the patient and the country budget together with social benefits.

In our study, the sensitivity, specificity, positive predictive value and accuracy of echocardiography were determined as 91%, 99%, 98% and 99% respectively during the application of ISUOG recommendations in a tertiary center. ISUOG extended fetal Echocardiogprahy seems like an effective practice in developing countries. We recommend that all perinatology units of our country implement this procedure.

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