

Fetal Echocardiography Indications: A Single- Center Experience

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Abstract

Background

Congenital heart disease (CHD) is the most common lethal congenital anomaly. Early diagnosis of CHD by fetal echocardiography based on maternal and fetal indications is important and lifesaving. The aim of study was to assess the referral aspects of pregnant women to pediatric cardiologist.

Materials and Methods

This was a retrospective cross-sectional study on 250 documents of referred pregnant women, which was conducted in Imam Reza hospital (Mashhad city, Iran) from 2012 to 2017. Relevant factors of referral to pediatric cardiologist were assessed in an unselected population of pregnant women, mostly based on guideline indications. Data were analyzed using SPSS software version 16.0.

Results

From 250 fetuses 59.8% were male. The most common reasons of referral were abnormal ultrasonography and family history of CHD with 83% and 28.8 %, respectively, which were referred mostly by gynecologist (53.7%). Fetuses were mostly singleton (98.8%). Five and six percent had associated extra-cardiac anomalies, mostly central nervous system and renal disorders. The mean age of referred pregnant women was 31.5±5.14 years. The mean age of gestation was 24.5±6.09 weeks. Seventy-one cases (28.4 %) have similar history in prior children.

Conclusion

Timely referral to pediatric cardiologist as an extraordinary benefit for pregnant women and also ongoing follow-up for the baby requires an organized observation. Assessment and comparison with universal guidelines reveals our shortcomings. More than half of referred cases were identified too late in time and the whole indications were not done accurately.

Key Words: Congenital heart defects, Fetal echocardiography, Pediatric cardiologist.

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1- INTRODUCTION

Congenital heart disease (CHD) as the most common significant abnormality, accounts for approximately 0.8 percent of live births. The CHD diagnosis is of great importance during the fetal period of life, and its knowledge has been developed recently based on an interest in advancements in fetal cardiac studies (1-6). Nowadays, the role of fetal cardiology has evolved. It is not just limited to basic anatomic cardiac diagnosis, but as a way of counseling medical teams and also parents on their expectations, on the medical management, even fetal therapy, planning for labor, pregnancy termination if it is necessary, and more care on the post-delivery care of the arrival baby. The fetal CHD detection may increase survival rate, reduce complications, decline morbidity and mortality and decrease health-costs (7-13). Lots of factors are associated with an increased risk of diagnosing CHD. As different guidelines, the most renowned one, American Heart Association (AHA) stated fetal cardiac indications could be categorized into three groups as follows: Fetal, maternal and familial indications. With the indications, the pregnant women referral to the pediatric cardiologist is accomplished (14).

As AHA stated the most common reason of pregnant women's referral to a pediatric cardiologist for assessing fetal cardiac status is the suspicion of cardiac structural abnormality via obstetric ultrasonography, which is reported as forty percentage of referrals. Other fetal risk factors are arrhythmias, associated extra-cardiac abnormalities, suspicious or determined chromosomal abnormalities, increased nuchal translucency (NT), umbilical or placenta abnormalities, multiple births, fetal hydrops, intrauterine growth restriction (IUGR). Increased NT, based on its size, increases the CHD risk from three to sixty percentage. Any abnormality of the umbilical cord, placenta and fetal

venous system may intensify the risk up to 3.9 percent. CHD is more common in multiple pregnancies than singleton, and monozygotic twins intensify it more (14). CHD is more common in fetuses with extra-cardiac abnormalities, with the incidence of 20 to 45%, including omphaloceles, duodenal atresia, congenital diaphragmatic hernias, central nervous system malformations and genitourinary malformations. Suspected fetal arrhythmias have been reported to be linked with CHD, especially bradycardia up to 40%. Genetic basis for CHD is so evident; the risk is changeable up to 90 percent based on the type of chromosomal abnormality (10, 14). Diabetes mellitus as the most common leading maternal metabolic disease accounts for three to ten percent, in which the increase in serum hemoglobin A1C intensifies the risk of fetal CHD occurrence. Also, gestational diabetes is considered, but with less risk (<1%). Untreated phenylketonuria results in increasing the risk up to 12 %.

Connective tissue diseases as Sjögren's syndrome, Lupus increase the risk up to five percent, especially if they are associated with maternal hypothyroidism and vitamin D deficiency or a prior child has been affected with neonatal lupus or complete heart block (CHB). Using artificial assisted reproduction technology such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), intensifies the risk to 3 percent. As the age of the mother during pregnancy is so important, mothers older than 35 years are associated more with increasing risk of malformation. Therefore, maternal age is considered as a CHD risk factor and the indication for referral. Familial factors as a second main reason for referral included the history of cardiac structural disorders in parents, prior children or other family members, the consanguinity, etc. The risk of CHD incidence in association with maternal

cardiac disease is two times more prevalent than paternal diseases, and it reaches the highest possible age at the age of 14-18. But for most cardiac detections the risk is about three to seven percent. If only prior sibling is affected, the incidence becomes lower/the incidence lower (2 to 5 %). Survey on the CHD risk in other affected members of the family, which means second or third relatives, has not been determined properly. As the AHA mentioned, in just one study, less than 0.3 percent have been reported.

Although AHA recommended fetal echocardiography in a persistence of positive family history of isolated CHD in second-degree relatives. Increasing risk for fetal cardiac disorders is also associated with heredity, Mendelian inheritance up to 50% (14). Anomalies which were associated with cardiac congenital malformations may be an intensifier of morbidity and mortality risks. AHA guidelines provided the lists of anomalies from the lowest to the highest risk (5 to 71 %), in which referral based on that will occur (10, 13, 14). Due to CHD's importance and its high prevalence and the need for timely and appropriate referrals, we carried out a survey to study the current practice on an unselected population of referred pregnant women. Epidemiologic, referral reasons, the timing of referral and various other variables have been studied.

2- MATERIALS AND METHODS

2-1. Study design and population:

The purpose of the study was to assess referral indications in our society (Imam Reza Hospital, Mashhad, Iran) and describe whether these referrals have been in line with the guidelines or not. This was a retrospective cross-sectional study on 250 documents of pregnant women, which were referred to the pediatric cardiologist for further diagnosis.

The variables to be assessed were as below:

- The referral reason,
- Maternal pregnancy history including gravidity, parity, number of live, aborted children and stillbirth,
- Screening and amniocentesis test results,
- Fetus karyotype,
- Consanguinity of parents and its degree,
- Consanguinity of maternal parents and its degree,
- The presence of Congenital heart disease in parents, in prior offspring and other family members,
- Baby gender,
- Gestational age at the time of referral,
- Multiple or singleton birth,
- The presence of an underlying disease in mother, such as diabetes, lupus, hypothyroidism, infections.

2-2. Methods

This was a retrospective cross-sectional study. The documents of all pregnant women which were referred to a pediatric cardiologist over a period of five years (2012-2017) in a tertiary healthcare center in Mashhad, Iran were studied.

2-3. Ethical consideration

The proposal of the study was also approved by the Institutional Ethics Committee of Mashhad University of Medical Sciences (MUMS).

2-4. Inclusion and exclusion criteria

All document data of mothers who referred to a pediatric cardiologist in the healthcare center in Mashhad have been reviewed.

2-5. Data Analyses

250 document data were collected; checklists were filled, and data were analyzed statistically by SPSS software version 16.0. Continuous data was expressed as mean \pm standard deviation (SD). Based on the current practice goal, comparison of variables was assessed by

using Chi-square or Fisher's exact tests. A value of $p < 0.05$ was considered statistically significant.

3- RESULTS

Out of 250 referred pregnant women for assessing fetal echocardiography indications, the mean age was (19-45) 31.5 ± 5.14 years and the mean gestational age was (12-38) 24.5 ± 6.09 weeks, respectively. The distribution of gravidity, parity, number of live children, abortion and stillbirth were 1.33 ± 2.55 , 1.18 ± 1.31 , 0.98 ± 0.98 , 0.61 ± 0.36 , and 0.52 ± 0.27 , respectively. The mothers were mostly referred during 16 to 19 weeks of gestational age (37.8 %), and the earliest was under 16 weeks (2.2 %) (**Figure.1**). The most common source of referral was obstetrician and gynecologist (**Table.1**). The most common causes of referral for fetal cardiac evaluation were the structural heart abnormality on ultrasound and positive family history of CHD and the least causes were drug consumption by mothers and the presence of fetal single artery cord (**Table.2**). One and two tenths percent of pregnancies were twins and

98.8 % were singleton. About 60% of fetuses were male and 40 % were female. Four mothers were using assisted reproductive technology to achieve pregnancy in which three fetuses were conceived via IVF and one by IUI. Out of 117 results of the first trimester screening tests, 18 cases were positive. Five cases of 11 have been reported abnormal, four cases were Turner syndrome and one was Down syndrome. Twelve mothers have diabetes as an underlying disease, 1.6% had DM and 3.2 % had GDM. Two and four tenths percent of mothers suffered systemic lupus erythematosus; 1.6% had Hypothyroidism and 0.8 had infections. Two cases had the similar disease history in parents (0.8%). Seventy-one cases had similar history in prior children (28.4 %) and 17 cases just had similar disease history in other family members (6.8%). Thirty-seven and one-tenth percent of parents had positive consanguinity, 64.5 % were in 3rd-degree cousins of consanguinity and 35.5 % were in more than 3rd degree. Extra-cardiac anomalies were detected in 5.6% of referred cases. Detailed research data is listed in **Table.3**.

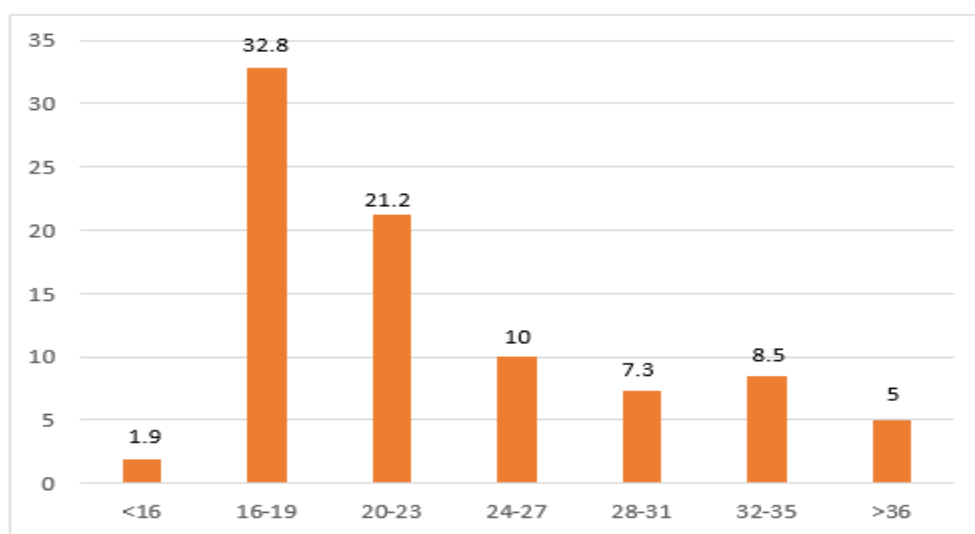


Fig.1: Percentage of referred mothers based on gestational age (week).

Table-1: Types of referral source for fetal echocardiography.

Referral type	Frequency (%)
Obstetrician and Gynecologist	83.7
Forensic Doctor	4.5
The patient's own family	10.4
Radiologist	0.9
Rheumatologists	0.5
Total	100

Table-2: Types of referral reasons for fetal echocardiography.

The reason of referral		Frequency	Percentage
Fetal factors	Abnormal fetal ultrasonography	60	33.9
	Rhythm abnormality	24	23.8
	Increased NT	7	4
	Single artery cord	1	0.6
	Abnormal amniocentesis or screening tests	3	1.7
Maternal factors	Maternal Lupus	5	2.8
	Maternal DM	3	1.7
	Maternal GDM	2	1.1
	Maternal infection	2	1.1
	Drugs	1	0.6
Family factor	Positive Family history	51	28.8
Total		177	100

NT: Nuchal translucency; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus.

Table-3: Associated extra-cardiac anomalies in referred population from 2012 to 2017 (n=250)

Associated Anomalies	Type	Frequency	Percentage
CNS	–	3	1.2
Renal	Renal disorders	3	1.2
GI	Diaphragmatic hernia	1	0.4
Musculoskeletal	Cleft lip + cleft palate	1	0.4
No anomalies	–	242	96.8
Total	–	250	100

CNS: central nervous system; GI: gastrointestinal.

4- DISCUSSION

The aim of the current survey was to study epidemiologic aspects and referral indications to the pediatric cardiologist on a non-selected population of pregnant women, comparing the results with existing studies. We collected 250 pregnant women's documents for five years, assessing their history, while most studies worked mostly on one year. In the present study, referred pregnant women were 31.5 ± 5.14 years-old, similar to Wiechec's study (32.3 years) (15). But in Sharma's study, the mean age of the population was 27.61 ± 4.68 , slightly

younger in age (16). In our study, 25.8 % of mothers were older than 35 years old, which might enhance the CHD incidence as well. Similar to our report in which the gestational age was 12-38 weeks, Stumpfelen mentioned 18-28 weeks (17), while Wiechec and Sharma stated 11-13 weeks and on average 20.37 in their surveys, respectively (15, 16). According to the studies, the most detected cardiac abnormalities were diagnosed at 16-19 weeks of gestation (17). Based on the AHA guidelines, the most suitable time for the referral is considered as the second trimester (14). Thus, the timing of referral in our study seems to be postponed.

More than half (51.7 %) of mothers were referred too late. The moral aspects, religion and also Iranian legal system for pregnancy termination makes this issue even more crucial. In the Netherlands, the study had said that 73% of cases were referred after 24 weeks of gestation, which is the legal time for termination in that country. Their screening program led to the prenatal referrals occurring at 19 weeks of gestation, considerable decrease of 24/3% in late referrals. Basically, due to the more restrictions on legal therapeutic abortion in Iran, late referral leads to lack of time from diagnosis to treatment, which removes the opportunity for the abortion from us (18). Seventy-four percent of mothers were referred by a physician, obstetrician and gynecologist, and the main reason the referral was assessed as abnormality was prenatal ultrasonography with 33.9%. AHA mentioned that the leading cause of fetal cardiac referral was suspicion in fetal cardiac abnormality by using ultrasonography by an obstetrician and it comprised about 40 percent of referral reasons. Hsaio et al., reported that most referrals were noted by an obstetrician and it was because of abnormal ultrasonography appearance with 36.6 %. Manifestly, the results of global studies were extremely similar to our experience (14, 19).

Family history in this practice was estimated at 28.8 % as the second referral reason as AHA claimed. Hsaio also reported that positive family history as the second reason with 25.7 %. Inspired by AHA scientific statement, we assessed this variable into groups, a presence of similar disease in parents, in prior offspring and also other members of the family. The results showed that the frequency of positive history in prior children was more prominent and it seemed to have the most association with fetal cardiac abnormalities. Unlike the AHA statement, parental cardiac diseases were not so

significant, but the prior sibling diseases were (14, 19). Consanguinity, a kind of demonstrator for the autosomal recessive pattern in inheritance, was so marked in our practice. Since the 1st and 2nd degree relative marriages were prohibited in our country due to religion and governmental laws, like several other places, these two types of relatives which were mentioned with the most likelihood ratio by AHA, were ignored, and consanguinity through 3rd degree and higher were considered. Our results showed that 3rd degree as a referral indication was in the upper ranks in this field (64.5 %). But unfortunately, a similar practice working specifically on this variable was not found. Dissimilarity in the gender frequency of the fetuses was not so marked in this paper and in the same way, was not taken as a risk factor in recent studies, it was determined approximately fifty-fifty.

Layde et al. studied the whole survey about twins, compared to singletons, and highlighted the differences between the types of twins. Overall, it had been concluded that the increased risk of anomalies was more frequent in total categories twins compared to singletons, with 50% greater likelihood of congenital malformation, including cardiac abnormalities as well as with high amount (20). In various studies, twins were announced as an absolute referral reason, but because of the presence of only three sets of twins in the study, it could not be judged accurately. Recent studies obviously have shown that conception using reproductive technology as IVF has a strong association with CHD. This risk may be further increased, if the multiple pregnancies occurred. Several studies were done based on its effect as an only factor or in correlated with multiple pregnancies. Both these factors as referral reasons were much less in number, less than ten; but the amounts in our referrals were not significant and so they are not expressed as

percentages here. It was applied for amniocentesis and screening test results, too (14). Although we had four Turner and one Down's syndrome in our referral fetuses, there were no interesting statistics in amounts. Twelve mothers have diabetes as an underlying disease, 1.6 % had DM and 3.2 % had GDM. Two and four tenths percent of mothers suffered from systemic lupus erythematosus, 1.6% had Hypothyroidism and 0.8% had infections. Underlying maternal diseases, which, in diabetes, SLE, hypothyroidism, phenylketonuria, and infections are the most important and should be considered as the referral causes extensively.

While the prevalence of diabetes in Iran is about to 10.3 %, the presence of only twelve diabetes mothers in referred cases is questionable (13). This issue also points to other underlying maternal disorders, to some extent. In this survey, anomalies showed a significant association with frequency, partly CNS and Renal anomalies had the highest number. AHA claimed the genitourinary abnormalities, while HSAIO mentioned CNS disorders as being at the top of the list of anomalies.

4-1. Limitations of the study

The limitations of our study were the inaccessible information and reasons for referrals due to referral system defects or how the documents were designed. Poor family cooperation also restricted the assessment.

5- CONCLUSION

In this research, we have shown the importance of an organized and timely referral based on early prenatal diagnosis of CHD and its considerable benefit to the population of our country. Certainly the comprehensive awareness of determined referral indications is required. Comparing our results with recent literature demonstrates that in some indications, the referral was effective in

recognizing abnormal ultrasonography and positive family history of CHD. Also, several referral indications have been overlooked and more consideration is desired. More than half of the cases were referred after 19 weeks of gestational age which was too late for any therapeutic abortion, if needed, in Iran according to the moral aspects of religion and strict law limitations. The best time of the first referral is recommended to be considered according to the laws of each country. The several other indications were not performed well as in patients with systemic underlying diseases, using artificial reproduction technology and multiple gestations seem to have been forgotten. The outcome can be disseminated to the healthcare units which would lead to greater perception about how to refer more effectively.

6- CONFLICT OF INTEREST: None.

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