CLINICAL STUDY

# Detection of Congenital Heart Disease by Fetal Echocardiography and Its Correlation with Karyotype

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## ABSTRACT

**Background:** Congenital heart diseases (CHDs) account for a third of all major congenital abnormalities in children; nearly 1,80,000 children are born with heart defect each year in India. Approximately, 10% of present infant mortality in India may be attributed to CHD alone. Such high mortality is due to laying less emphasis on its prenatal diagnosis by fetal echocardiography. This study was done with objectives to find out the incidence of CHD in high risk cases and its correlation with karyotype and also evaluating the diagnostic accuracy of fetal echocardiography. **Methods:** Fetal echocardiography was performed in 142 high risk cases who attended antenatal clinic of Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi between July 2014 to June 2016 with maternal/fetal risk for CHD (maternal diabetes mellitus, collagen disorders, teratogen exposure, maternal TORCH infection, *in vitro* fertilization [IVF] conceived pregnancy, familial history of CHD, abnormal four-chamber view, monochorionic twins). **Results:** The incidence of major CHD was 28/1,000 live births and 56/1,000 live births for minor CHD in high risk group. Ventricular septal defect (16.6%) and hypoplastic left heart syndrome (16.6%) were the most common CHD detected. Family history of CHD increases the risk significantly. Fetal echocardiography was 75% (46.77-91.11, 95% confidence interval [CI]) sensitive and 94.5% (89.22-97.35, 95% CI) specific, with 92.91% (87.44-96.1, 95% CI) diagnostic accuracy. It was seen that 16.6% cases of CHD had aneuploidy detected on karyotyping (trisomy 21 and trisomy 18). **Conclusion:** Fetal echocardiography is highly sensitive and specific, when done by an experienced operator. Prenatal diagnosis of CHD and planned delivery in a cardiac facility had satisfactory immediate outcomes.

**Keywords:** Congenital heart disease, fetal echocardiography, karyotype, prenatal diagnosis

As a group, congenital heart disease (CHD) constitute a significant proportion (up to 25% in some studies) of congenital malformations that present in the neonatal period, and are a major cause of perinatal mortality and therefore significantly contribute to the economic burden on healthcare systems.

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They are frequently not detected by routine ultrasound screening examinations. Fetal echocardiography, being more sensitive and specific, is able to detect most of the CHD cases. The main focus of this study was to find out the incidence of CHDs in high risk cases, the degree of risk associated with various individual risk factors, and the role of fetal echocardiography as a prenatal diagnostic tool. Newborns with structural anomalies were also investigated for any aneuploidy, to study the correlation.

## METHODS

The present study was a prospective observational study performed in high risk group (of fetal CHD) at the Dept. of Obstetrics and Gynecology, the Dept. of Radiodiagnosis & Imaging and Dept. of Cardiology, in the Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi, Uttar Pradesh.

All antenatal women attending the antenatal clinic at Dept. of Obstetrics and Gynecology, in Sir Sunderlal

Hospital (SSH), BHU with any maternal indication (risk) of CHD (i.e., maternal metabolic disorder, collagen disorder, first trimester teratogen exposure, TORCH infection, *in vitro* fertilization [IVF] conceived pregnancy, bad obstetric history, maternal/fetal sibling with CHD) or fetal indication (i.e., abnormal level 2 scan, monochorionic twins) were recruited for the study from July 2014 to June 2016. Written and informed consent was obtained from all the participants prior to their enrollment in the Dept. of Obstetrics and Gynecology. Ultrasound fetal biometry, measurement of nuchal fold thickness, targeted imaging for fetal anomalies were performed on each antenatal women with the indication of CHD. Echocardiogram was performed by transabdominal route between 18-20 weeks of pregnancy.

## RESULTS

The data were collected from 142 high risk cases for fetal CHD. The analysis of the data collected have indicated that majority of high risk cases were between 25-29 years age group (45.1%) followed by 33.8% between 20-24 years age group. Maximum patients were multigravida (71.8%), among whom 31.3% had previous mid-trimester abortions and 11.7% had previous term intrauterine deaths (IUDs)/stillborns; 2.8% were monochorionic twin pregnancies. Indications of fetal echocardiography in study group are depicted in Table 1, which shows abnormal level 2 scan was the most common indication.

### Abnormal Fetal Echocardiographic Findings and Postnatal Echocardiography

Table 2 shows that among 142 high risk cases studied, fetal echocardiogram was abnormal in 10.5% (15/142) with 7.04% (10/142) confirmed postnatally. Ventricular septal defect (VSD; 16.6%) and hypoplastic left heart syndrome (HLHS; 16.6%) were the most common CHD detected. One tricuspid atresia (TA) and 1 pulmonary stenosis (normal fetal echocardiography) were diagnosed in postnatal echocardiogram. The incidence of CHD was found to be 56/1,000 live birth for minor CHD and 28/1,000 for major cardiac defects.

### Correlation of Individual Risk Factor with Cardiac and Extracardiac Anomaly

Table 3 shows that among patients with metabolic disorder (i.e. diabetes mellitus) 6.7% neonates had cardiac anomaly and 20% had extracardiac structural anomaly. It was observed that in pregnancies conceived through IVF, extracardiac structural anomaly was detected in 37.5% neonates, which is statistically significant ($p > 0.05$). Cardiac anomaly was detected in none. The analysis indicates that 10.5% newborns with maternal TORCH infection had cardiac anomaly, while

**Table 1.** Indications of Fetal Echocardiography in Study Group (n = 142)

| | No. of patients | Percentage (%) |
|---|---|---|
| **Maternal risk factors** | | |
| Metabolic disorder (diabetes mellitus) | 15 | 10.6 |
| Collagen disorder | 1 | 0.7 |
| Teratogen exposure | 1 | 0.7 |
| IVF conceived | 8 | 5.6 |
| TORCH infection | 19 | 13.3 |
| Previous issue with extracardiac anomaly | 22 | 15.5 |
| Previous issue with cardiac anomaly | 18 | 12.7 |
| Maternal congenital cardiac disease | 20 | 14.1 |
| **Fetal risk factors** | | |
| Abnormal level 2 scan | 62 | 43.7 |
| Monochorionic twins | 4 | 2.8 |

**Table 2.** Abnormal Fetal Echocardiographic Findings and Postnatal Echocardiography (n = 142)

| Fetal echocardiography | No. of patients (%) | Postnatally confirmed (%) |
|---|---|---|
| Cardiomegaly | 5 (3.5) | 40 |
| Dextrocardia | 1 (0.7) | 100 |
| Left to right shunt | | |
| Prominent PDA | 1 (0.7) | 100 |
| VSD | 2 (1.4) | 100 |
| ASD | 1 (0.7) | 100 |
| Rhythm abnormality | | |
| Heart block/fetal arrhythmia | 1 (0.7) | 0 |
| Outflow tract abnormality | | |
| Coarctation of aorta | 1 (0.7) | 0 |
| Cyanotic heart disease | | |
| Tetralogy of Fallot | 1 (0.7) | 100 |
| Hypoplastic left heart syndrome | 2 (1.4) | 100 |

**Table 3.** Correlation of Individual Risk Factor with Cardiac and Extracardiac Anomaly (n = 142)

| Maternal risk factor | Cardiac anomaly | | P value | Extracardiac anomaly | | P value |
|---|---|---|---|---|---|---|
| | Not detected (%) | Detected (%) | | Not detected (%) | Detected (%) | |
| Metabolic disorder | 14 (93.3) | 1 (6.7) | 0.649 | 12 (80) | 3 (20) | 0.089 |
| Collagen disorder | 1 (100) | 0 (0.0) | 0.999 | 1 (100) | 0 (0.0) | 0.999 |
| Teratogen exposure | 1 (100) | 0 (0.0) | 0.999 | 1 (100) | 0 (0.0) | 0.999 |
| *In vitro* fertilization | 8 (100) | 0 (0.0) | 0.968 | 5 (62.5) | 3 (37.5) | 0.002 |
| TORCH infection | 17 (89.5) | 2 (10.5) | 0.726 | 15 (78.9) | 4 (21) | 0.033 |
| Previous issue with extracardiac congenital anomaly | 17 (89.5) | 2 (10.5) | 0.726 | 22 (100) | 0 (0.0) | 0.242 |
| Previous issue with congenital cardiac disorder | 10 (76.9) | 3 (23.1) | 0.046 | 17 (94.4) | 1 (5.6) | 0.636 |
| Maternal congenital cardiac disease | 15 (78.9) | 4 (21.1) | 0.033 | 20 (100) | 0 (0.0) | 0.298 |
| Monochorionic twin | 4 (100) | 0 (0.0) | 0.984 | 3 (75) | 1 (25) | 0.227 |

21% had other structural anomalies ($p < 0.05$). It was found that if the previous issue of a patient had cardiac anomaly, there was a possibility that this cardiac anomaly could resurface in her next pregnancy. The data indicated that 23.1% cases had cardiac anomaly in present issue also ($p < 0.05$), while among those with

previous issue with extracardiac anomaly, 10.5% had cardiac anomaly, in fetus ($p > 0.05$); 21.1% of newborns with maternal CHD had cardiac anomaly ($p < 0.05$). Among maternal risk factors studied, familial history of congenital heart defect (maternal CHD)/sibling CHD had maximum association with CHD in newborn.

### Maternal-Newborn Correlation of Cardiac Anomalies

Recurrence of septal defect was seen in 14.2% (1/7 cases of atrioventricular septal defect in mother). One mother with ASD had tracheoesophageal fistula (TEF) in newborn, one mother with TEF had patent ductus arteriosus (PDA) in newborn, one mother with pulmonary stenosis had cardiomegaly in newborn.

### Risk Estimation for Cardiac Anomaly

The odds ratio (OR) and relative risk (RR) in a mother suffering with diabetes mellitus for having an issue with congenital cardiac malformation was 0.615 (0.075-5.068) and 1.560 (0.219-11.099), respectively, in maternal TORCH infection OR was 1.329 (0.268-6.594) and RR was 1.295 (0.307-5.46), in previous issue with extracardiac structural anomaly OR was 1.329 (0.268-6.594) and RR was 1.295 (0.307-5.46), in previous issue with cardiac anomaly OR was 4.0 (0.931-17.17) and RR was 3.308 (1.021-10.72), in cases with maternal congenital cardiac disease OR was 3.833 (1.029-14.28) and RR 3.237 (1.079-9.711).

### Risk Estimation for Extracardiac Structural Anomaly

The OR and RR in a mother with diabetes mellitus for having issue with any extracardiac structural anomaly was 3.278 (0.78-13.77) and 2.822 (0.856-9.295), respectively, in IVF conceived pregnancies OR was 8.33 (1.71-40.58) and RR was 5.58 (1.86-16.68), in maternal TORCH infection OR was 3.83 (1.029-14.28) and RR was 3.237 (1.079-9.711), in previous issue with cardiac anomaly OR was 0.604 (0.073-4.982) and RR was 0.62 (0.085-4.565), in monochorionic twins OR was 3.848 (0.368-40.17) and RR was 3.136 (0.523-18.77).

### Correlation of Cardiac Anomaly with Karyotyping Abnormality

Out of 142 high risk cases studied, aneuploidy was detected in 7 (trisomy 21 [5], trisomy 18 [1], monosomy X [1]). Table 4 shows that among newborns with aneuploidy 28.6% had associated cardiac abnormality, but the association was not statistically significant.

**Table 4.** Correlation of Cardiac Anomaly with Karyotyping Abnormality

| Cardiac anomaly | Karyotype | | | |
|---|---|---|---|---|
| | Normal | | Abnormal | |
| | No. | % | No. | % |
| Not detected | 125 | 92.6 | 5 | 71.4 |
| Present | 10 | 7.4 | 2 | 28.6 |

$\chi 2 = 3.8529$; $p = 0.0496$.

### Evaluation of Fetal Echocardiography in Study Group

Fetal echocardiography was found to be 75% sensitive (95% CI: 46.77, 91.11) and 94.5% specific (95% CI: 89.22, 97.35) with diagnostic accuracy of 92.9% (95% CI: 87.44, 96.1) in detecting CHDs prenatally with positive predictive value of 56.25% (95% CI: 33.18, 76.9) and negative predictive value of 97.6% (95% CI: 93.18, 99.18).

### Mode of Delivery and Pregnancy Outcome

Mean gestational age at diagnosis of fetal cardiac anomaly and at their delivery was 27.5 weeks and 37.3 weeks, respectively. While 22.1% pregnancies in overall study group were delivered by lower-segment cesarean section (LSCS), the cesarean section rate was slightly higher (27.6%) in pregnancies with anomalous babies.

Approximately 46.8% newborns with structural anomalies were treated successfully with proper NICU care and early surgical intervention, 21.1% newborns died in neonatal period, 4.2% pregnancies with major anomalies were aborted and 6.3% resulted in stillborn.

## DISCUSSION

In this study, major indication of fetal echocardiography was fetal abnormal level 2 scan (43.7%) followed by familial/sibling CHD (in 28.2% cases patients had previous issue with congenital structural anomaly, in 14.1% cases mother had congenital cardiac disease). The incidences of CHD as seen in this study was 56/1,000 live births having minor CHD, 28/1,000 having major cardiac defects, which are higher if compared to the CHD prevalence in general population (6-8 per 1,000 pregnancies). The reason behind this difference could be due to undetected cases of CHDs in the general population, and present study being confined to high risk group at a tertiary center, with 43% already referred from periphery with abnormal anomaly scan. VSD (16.6%) and HLHS (16.6%) were the most common

CHD detected in our study. In this study, correlation of pregestational diabetes with structural anomalies was statistically insignificant ($p > 0.05$). Balsells et al[1] reported RR 2.66 (2.04-3.47) in cohort studies and OR 4.7 (3.01-6.95) in the single case-control study for major congenital heart defects in newborns of pregestational diabetic mothers. Present study indicates a lower risk as majority of cases had controlled diabetes (only 2/15 had glycosylated hemoglobin [HbA1c] >6) and due to presence of other confounding factors in nondiabetic mothers.

The correlation of IVF conceived pregnancy and maternal TORCH infection with cardiac anomaly was also found to be statistically insignificant. In IVF conceived pregnancy, cardiac anomaly was detected in none while RR/OR for extracardiac anomaly (1 Dandy-Walker syndrome, 1 renal dysplasia, 1 posterior urethral valve) were RR 5.58 (1.86-16.68)/OR 8.33 (1.71-40.58). However, Davies et al[2] conducted study on assisted conception in South Australia reported OR 1.26 (95% CI, 1.07-1.48) for any birth defect in IVF conceived pregnancies. Furthermore, in this study, 10.5% newborns with maternal TORCH infection had cardiac anomaly (2/19 cases - 1 dilated cardiomyopathy, 1 dextrocardia) and 21% had extracardiac anomaly (4/19 cases - meningomyelocele, cleft lip with cleft palate, hypoplastic kidney, club foot). The study also established that OR/RR for cardiac defect was OR 1.329 (0.268-6.594)/RR 1.295 (0.307-5.46), for extracardiac anomaly it was OR 3.83 (1.029-14.28)/RR 3.237 (1.079-9.711). Padmavathy et al[3] study done at Bangalore showed malformations in 25% newborns with TORCH IgM positive mother and in 3.5% newborns with TORCH IgG positivity.

Significant association could be noticed between CHD in newborn and maternal CHD (4/19 cases) with OR 3.833 (1.029-14.28) and RR 3.237 (1.079-9.711). Also recurrence of septal defect was observed in 14.2% cases (1/7 cases). Oyen et al[4] conducted study on 18,708 cases of CHD in Denmark reported overall RR 8.38 (6.82-10.3) for same CHD in baby and 2.68 (95% CI 2.43-2.97) for dissimilar CHD. Most importantly, it was observed in the study that the patients with the previous childbirth with congenital cardiac defects also had significant association with CHD in newborn; 23.1% newborns with CHD in sibling had cardiac defect, OR 4.0 (0.931-17.17), RR 3.308 (1.021-10.72). However, the recurrence risk of similar CHD in siblings could not be determined,

as data regarding the exact type of lesion in siblings were not available. Further, Gill et al[5] had observed that the incidences of CHD in pregnancies referred due to prevalence of sibling CHD to be 2.7%, and incidence of CHD for pregnancies referred due to maternal CHD was (2.9%). Such higher incidence in present study was due to presence of other confounding factors.

No cardiac defect was found in monochorionic twins and extracardiac congenital defects was identified in 25% cases (1/4 cases) with OR 3.848 (0.368-40.17) and RR 3.136 (0.523-18.77). Bahtiyar et al[6] concluded that monochorionic/diamniotic twin gestations are at a higher risk for CHDs with RR, 9.18 (95% CI, 5.51-15.29; $p < 0.001$) in presence of twin-twin transfusion syndrome (TTTS) and RR, 2.78 (95% CI, 1.03-7.52; $p = 0.04$) without TTTS.

Fetal echocardiography is an essential tool in the evaluation of CHD and has dramatically improved the accuracy of diagnosis of CHD. The reported sensitivity of fetal echocardiography has ranged from 4% to 96% in various series depending upon the equipment, level of training, study design and examination technique. It is highly sensitive and specific when done by an experienced operator. In present study, its sensitivity was found to be 75%, specificity 94.5% and diagnostic accuracy was 92.91% (87.44-96.1).

In this study, 16.6% cases of CHD had aneuploidy detected on karyotyping (2/12 cases). Trisomy 21 (in VSD) and trisomy 18 (in tricuspid atresia) were detected. Trevisan et al[7] reported the frequency of chromosomal abnormalities identified through karyotyping in cases of CHD to be 16.8%; Down syndrome being the most common (14.4%) followed by trisomy 18.

Intrapartum cesarean section was the mode of delivery in 22.1% patients while 77.9% patients delivered vaginally, in this study. Similarly, Walsh et al[8] reported LSCS is significantly higher in fetal CHD than nonanomalous controls (21% vs. 13.5%), predominantly related to cesarean section for nonreassuring fetal status. It was also identified that the rates of preterm delivery were higher in the cases of CHD.

In this study, 46.8% newborns with structural anomalies were treated successfully with proper NICU care and early surgical intervention on the other hand 21.1% newborns died during the neonatal period. The mortality rate was higher in neonates having cardiac defects with associated extracardiac or chromosomal anomalies (40% and 50%, respectively), and also in cases with severe cardiac defects (HLHS, TA). Brown et al[9] concluded that the setting in which neonatal CHD is first recognized (antenatal/postnatal) has an impact on preoperative condition, which in turn influences postoperative progress and survival after surgery.

Optimal screening procedures and access to specialist care will improve outcome for neonates undergoing cardiac surgery.

## CONCLUSIONS

It can be concluded that in the present study, the incidence of CHD was 56/1,000 live births for minor CHD, 28/1,000 for major cardiac defects. VSD (16.6%) and HLHS (16.6%) were the most common CHD detected. Major indication for fetal echocardiography was abnormal level 2 scan (43.7%). Majority of patients were multigravida (71.8%) among whom 31.3% had previous mid-trimester abortions and 11.7% had previous term IUDs/stillborns, emphasizing significance of previous obstetric history.

Among maternal risk factors studied, familial history of congenital heart defect (maternal CHD/sibling CHD) had maximum association with CHD in newborn; 16.6% cases of CHD had aneuploidy detected on karyotyping (trisomy 21 and trisomy 18). Any fetal karyotyping abnormality is an indication for fetal echocardiography. Fetal echocardiography was found to be 75% sensitive and 94.5% specific with diagnostic accuracy of 92.9% in detecting CHDs prenatally. Increased intrapartum cesarean section rate was seen in pregnancies with anomalous babies, fetal distress being a major indication. Prenatal diagnosis of CHD and planned delivery in a cardiac facility had satisfactory immediate outcomes.

## REFERENCES


1. Balsells M, García-Patterson A, Gich I, Corcoy R. Major congenital malformations in women with gestational diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2012;28(3):252-7.
2. Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, et al. Reproductive technologies and the risk of birth defects. N Engl J Med. 2012;366(19):1803-13.
3. Padmavathy M, Mangala G, Malini J, Umapathy BL, Navaneeth BV, Bhatia M, et al. Seroprevalence of TORCH infections and adverse reproductive outcome in current pregnancy with bad obstetric history. J Clin Biomed Sci. 2013;3(2):14-23.
4. Øyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PK, Melbye M. Recurrence of congenital heart defects in families. Circulation. 2009;120(4):295-301.
5. Gill HK, Splitt M, Sharland GK, Simpson JM. Patterns of recurrence of congenital heart disease: an analysis of 6,640 consecutive pregnancies evaluated by detailed fetal echocardiography. J Am Coll Cardiol. 2003;42(5):923-9.
6. Bahtiyar MO, Dulay AT, Weeks BP, Friedman AH, Copel JA. Prevalence of congenital heart defects in monochorionic/diamniotic twin gestations: a systematic literature review. J Ultrasound Med. 2007;26(11):1491-8.
7. Trevisan P, Zen TD, Rosa RF, Silva JN, Koshiyama DB, Paskulin GA, et al. Chromosomal abnormalities in patients with congenital heart disease. Arq Bras Cardiol. 2013;101(6):495-501.
8. Walsh CA, MacTiernan A, Farrell S, Mulcahy C, McMahon CJ, Franklin O, et al. Mode of delivery in pregnancies complicated by major fetal congenital heart disease: a retrospective cohort study. J Perinatol. 2014;34(12):901-5.
9. Brown KL, Ridout DA, Hoskote A, Verhulst L, Ricci M, Bull C. Delayed diagnosis of congenital heart disease worsens preoperative condition and outcome of surgery in neonates. Heart. 2006;92(9):1298-302.