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ARTICLE

Diagnostic Errors in Fetal Echocardiography and the Effect on Neonatal Management: Ten-Year Experience from a Middle-Income Country

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ABSTRACT

Introduction: Fetal echocardiogram allows early detection of critical congenital heart disease leading to a better outcome. However, data from lower- and middle-income countries is scarce. This study aims to evaluate the diagnostic error of fetal echocardiography and its impact on planned neonatal management. **Methods and material:** This retrospective observational cohort study includes all high-risk pregnant mothers who had fetal echocardiograms from 2008 to 2017. Fetal and postnatal echocardiograms were compared, while the diagnostic errors were categorized into false positive, false negative, and discrepant diagnoses. The impact of the diagnostic error on planned neonatal management and the long-term outcome was determined by comparing the outcome of expected and actual management. **Results:** A total of 2622 fetuses were included with the majority in the second half of the study. The mean gestational age of 2622 fetuses was 26.7 ± 3.42 weeks. Of 2622, 191 (7.3%) had congenital heart disease. Of 191, 130 (68%) were major lesions. Confirmatory postnatal echocardiogram was available in 153 fetuses with congenital heart disease and 905 fetuses with a normal heart. Of 1058, 123 were true positives, 30 were false positives, 26 were false negatives, and 879 were true negatives. Hence, the sensitivity, specificity, positive and negative likelihood ratio of fetal echocardiogram for detection of CHD in this study was 82.5% (95% confidence interval [CI]: 75.5% to 88.3%), 96.7% (95% CI: 95.3% to 97.8%), 25.0 (95% CI: 17.5 to 35.8) and 0.18 (95% CI: 0.13 to 0.26) respectively. Most of the false positives and negatives were mild lesions. There were 27% discrepant diagnosis between fetal and postnatal echocardiograms (8.1% partially different, and 18.7% no similarity), leading to 8.9% changes in planned neonatal management and 8.1% severity score. Most of the discrepant diagnoses were complex lesions. **Conclusions:** Despite relatively new services and limited resources, the diagnostic errors of fetal echocardiography in this study are comparable with centers in high-income countries. However, active participation of all stakeholders, changes in policy, and training are needed to improve fetal echocardiography services further. These are vital before the introduction of the national screening program.

KEYWORDS

Fetal echocardiogram; congenital heart disease; diagnostic error

1 Introduction

Congenital heart disease (CHD) is the most common malformation in infants with a worldwide prevalence of 7–10 per 1000 live births [1]. One in four has critical CHD and requires early intervention or surgery within the first year of life [2]. Delayed diagnosis of critical CHD, which occurs in 20–30% of cases [3], causes significant infant morbidity and mortality [4,5]. Hence, early detection is crucial to improve the survival of infants with critical CHD.

Several strategies were introduced to improve the detection of critical CHD. Among them is prenatal screening with a fetal echocardiogram, leading to an increase in the prevalence of prenatally detected critical CHD worldwide [6]. As a non-invasive test, fetal echocardiogram is safe, highly sensitive, and specific in screening CHD among high-risk pregnant mothers [7–9]. Fetal echocardiogram allows prenatal diagnosis of critical CHD, leading to reduced mortality and morbidity [10,11].

Although fetal echocardiogram is well established, the data on the accuracy and reliability of the test tend to be limited [12]. Furthermore, most studies differ in definition, methodology, and patient characteristics leading to different findings [13–16]. The definitive diagnosis is crucial to allow appropriate planning before and after the delivery of the fetus [17–20]. An accurate diagnosis is essential in both complex and critical CHD associated with poor prognoses. However, recent studies from well-established centers in high-income countries (HIC) showed a high rate of discrepant diagnoses between fetal and postnatal cardiac diagnoses leading to a significant change in neonatal management and long-term outcome [12,13].

Due to a lack of resources and expertise, fetal echocardiography services may not be readily available in lower-and middle-income countries (LMIC). As the service is relatively new in our center, we postulate that the discrepant diagnosis is high compared to the centers from HIC. Therefore, this study aims to investigate the diagnostic errors (false positive, false negative, and discrepant diagnosis) of fetal echocardiography and the impact on neonatal management and long-term outcome. This information is essential for future planning of fetal and neonatal services in limited resources countries.

2 Material and Methods

2.1 Study Design

This is a retrospective cohort study that included all consecutive fetuses who had a 2D-echocardiogram from January 2008 to December 2017 in the Pediatric Cardiology Unit, Hospital Sultanah Aminah Johor Bahru, Malaysia. This study was registered with the National Malaysian Research Registry (NMRR-18-1447-42225) and was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia. Medical Research and Ethics Committee waived consent from patients.

Hospital Sultanah Aminah is a tertiary government hospital for the State of Johor, which has a population of 3.5 million and an annual birth rate of 55,000 per year. It also serves as a fetomaternal and cardiac center for the state of Johor. Fetal echocardiography services by the Pediatric Cardiology unit were established in 2007, managed by a single pediatric cardiologist throughout the study period. Due to limited trained obstetricians in fetal echocardiography, a pediatric cardiologist was involved in both screenings and confirmatory CHD among high-risk pregnant mothers. There was no national CHD screening program at 20 weeks of gestation during the study period. The fetal cardiac diagnosis used in this study was based on the confirmatory echocardiography done by the pediatric cardiologist.

Data were retrieved from the Fetal Echocardiography Clinical Information System, a clinical database dedicated to fetal echocardiography. The data collected included gestational age, main indication, fetal cardiac diagnosis, associated non-cardiac anomaly, and fetal outcome. Poor fetal echocardiogram images were excluded from the study. Fetal echocardiography was performed by a pediatric cardiologist using iE33 (Philips Ultrasound, Bothell, WA, USA) in 2008 to 2013 and EPIQ 7 (Philips Ultrasound, Bothell,

WA, USA) from 2014 onward, with a 5-1 Mhz transducer. A combination of basic cardiac echocardiography examination, outflow tract view, three and two-vessel views, aortic arch, and ductal view with color and pulse doppler were used to detect CHD [21,22]. All images were digitally archived for review and for comparison with the postnatal echocardiogram.

The indications for fetal echocardiogram were divided into three main groups: family history, maternal and fetal factors [22]. Fetal echocardiogram findings were further divided into two groups: non-CHD and CHD. The non-CHD group includes fetuses with a normal heart or with no significant lesions such as an isolated right arch. A fetus with restricted foramen ovale or ductus arteriosus, causing significant fetal hemodynamic changes (dilated chambers and cardiomegaly), was also classified as a non-CHD. Abnormal findings such as pleural or pericardial effusion, cardiac arrhythmia, changes associated with twin to twin transfusion, or fetal cardiomegaly with normal intracardiac structure also put the fetuses into the non-CHD group.

In this study, both fetal and postnatal CHD were classified according to the Fetal Cardiovascular Severity Scale (FCSS) developed by Davey et al. [23]. Briefly, FCSS grades the severity of CHD into seven, with level one as no significant CHD and level seven as the most severe form of CHD. All lesions with a low risk for single ventricle repair were grouped into level 5, while those at high-risk were grouped into level 6. Additionally, all complex biventricular and univentricular hearts with poor prognosis were grouped into level 7. All lesions with level four and above were considered as major CHD. The presence of a non-cardiac anomaly and reduced cardiac function were also included in the FCSS. This inclusion is important since these factors have a significant impact on the long-term management of CHD in LMIC [24].

2.2 Diagnostic Error Categorization

A false positive, false negative, and discrepant diagnosis were used to categorize diagnostic errors [25]. The Pediatric Cardiology Clinical Information System (PCCIS) was reviewed to obtain the postnatal cardiac diagnosis. PCCIS is a clinical registry for congenital and acquired heart disease for the State of Johor and has been described in detail in our previous publication [26]. Briefly, PCCIS contains all personal, 2d-echocardiography, intervention, and outcome data of children with CHD in the State of Johor. Data was entered at the time of diagnosis, regularly updated, and maintained. The specificity, sensitivity, positive and negative likelihood ratios of fetal echocardiography for detecting CHD were subsequently calculated.

The discrepant diagnosis between fetal and postnatal echocardiograms was based on the differences in anatomical diagnosis, which can be either similar, partially different, or no similarity. A similar diagnosis was defined if the fetal and postnatal anatomical diagnoses were the same. Meanwhile, a partially different diagnosis was made if the fetal and postnatal diagnoses were in a similar group but different in the detailed anatomy. Examples of diagnoses in this category were cases of prenatally diagnosed double outlet right ventricle (DORV) without outflow tract obstruction with a postnatal diagnosis of DORV with outflow tract obstruction. “No similarity” was defined if the fetal and postnatal cardiac diagnosis was different. An example in this category was a case of prenatally diagnosed complete atrioventricular septal defect with a postnatal diagnosis of heterotaxia syndrome. In cases with partial and no similarity, all the images (fetal and postnatal echocardiogram) were reviewed by the same pediatric cardiologist to verify the findings.

2.3 Discrepant Diagnosis and Impact on the Early and Long-Term Neonatal Management

The change in initial neonatal management and the long-term outcome was used to investigate the effects of discrepant diagnosis between fetal and postnatal echocardiograms. A significant change in early neonatal management was defined if a discrepant diagnosis led to a change in planned neonatal medical care. An example includes a fetal diagnosis of Ebstein anomaly (no intravenous prostaglandin required) with a postnatal diagnosis of pulmonary atresia with an intact septum (prostaglandin required and percutaneous balloon valvuloplasty with or without PDA stenting to be done during the early neonatal period).

The impact of a discrepant diagnosis on planned long-term outcome was determined by comparing the outcome of expected and actual management using the FCSS. A negative impact was defined if the severity scale in postnatal cardiac diagnosis was higher than the fetal score and positive impact if the postnatal score was lower than the fetal score.

2.4 Statistical Analysis

Statistical data were analyzed using Statistical Package for the Social Sciences version 23 (IBM Corp., Armonk, NY, USA). Group comparisons were made using Pearson chi-square or Fisher's exact test when any expected cell count was < 5 for categorical data. A p-value < 0.05 represented a statistically significant result.

3 Results

A total of 2628 pregnant mothers (10 triplets and 69 twin pregnancies) were referred for fetal echocardiogram during the study period. From the 2717 fetuses, 95 (3.5%) were excluded due to poor 2d-echocardiogram images. Of 2622, the majority (92.9%) had a fetal echocardiogram in the second half of the study (Fig. 1), and 191 (7.3%) had CHD.

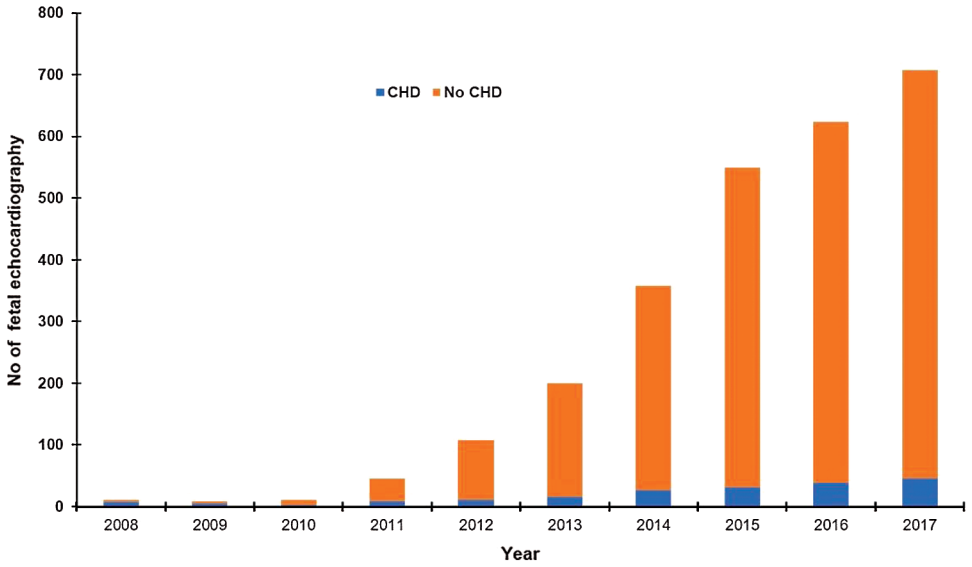

Figure 1: The trend of referral of fetal echocardiography and congenital heart disease (CHD) findings, 2008–2017

The mean gestational age of 2622 fetuses was 26.7 ± 3.42 weeks. The main indications for fetal echocardiogram were maternal factors followed by family history and fetal factors (Tab. 1).

The highest rate of CHD detection was in fetuses who were referred for suspected CHD by the obstetrician (62%), followed by fetuses with features of hydrops fetalis (24%), and fetuses with cardiomegaly (22%). The prevalence of CHD among mothers with pregestational diabetes mellitus was 5.3% and 4.8% for mothers with gestational diabetes mellitus. From the 191 fetal CHD, 55 (28.8%) had complex CHD associated with poor prognosis (Tab. 2). Forty-two percent of fetal CHD were ductal dependent lesions, and 19% were associated with an extracardiac malformation.

Table 1: The indications for fetal echocardiography and congenital heart disease detection rate

Indication	Total	CHD	
		N	†(%)
Maternal Factors	**1773**	**83**	**(4.7)**
Gestational diabetes	948	46	(4.8)
Pregestational diabetes	702	37	(5.3)
Teratogen (drugs) exposure	37	0	(0.0)
Others	29	0	(0.0)
Maternal lupus or Sjogren's	27	0	(0.0)
Assisted reproduction technology	22	0	(0.0)
Maternal infection	8	0	(0.0)
Fetal Factors	**413**	**120**	**(29.1)**
Suspected CHD by the obstetrician	144	89	(61.8)
Non-cardiac abnormality	83	12	(14.5)
Multiple pregnancy	70	1	(1.4)
Fetal cardiomegaly	41	9	(22.0)
Fetal dysrhythmias	42	2	(4.8)
Hydrops fetalis	17	4	(23.5)
Known or suspected chromosome abnormality	14	3	(21.4)
Thickened nuchal translucency	2	0	(0.0)
Family History	**595**	**15**	**(2.5)**
Sibling with CHD	348	8	(2.3)
Mother with CHD	215	7	(3.3)
First or 2nd degree associated with syndrome	32	0	(0.0)

†represent the percentage within the indication
CHD, congenital heart disease

Table 2: Fetal Cardiovascular Severity Scale and cardiac diagnosis in 191 fetuses with congenital heart disease detected by fetal echocardiogram

Fetal Cardiovascular Severity Scale (FCSS)† and cardiac diagnosis	N	(%)
Level 1 (no significant CHD)	**43**	**(22.5)**
VSD	43	(22.5)
Level 2 (mild CHD and may require intervention)	**12**	**(6.3)**
VSD	5	(2.6)
PS	2	(1.0)
ASD	2	(1.0)
AS	2	(1.0)
Mild hypoplastic left ventricle	1	(0.5)

(Continued)

Table 2 (continued).

Fetal Cardiovascular Severity Scale (FCSS)† and cardiac diagnosis	N	(%)
Level 3 (simple CHD and needs an intervention)	**6**	**(3.1)**
Hypoplastic arch/CoA	4	(2.1)
VSD	2	(1.0)
Level 4 (complex CHD and needs intervention)	**53**	**(27.7)**
DORV	9	(4.7)
TOF	8	(4.2)
Ebsteins anomaly	7	(3.7)
D-TGA	7	(3.7)
PAVSD	5	(2.6)
AVSD	5	(2.6)
PAIVS	3	(1.6)
Truncus arteriosus	2	(1.0)
PS with LVOT obstruction	2	(1.0)
ccTGA	2	(1.0)
VSD with LVOT obstruction	1	(0.5)
TAPVD	1	(0.5)
AS with hypoplastic arch/CoA	1	(0.5)
Level 5 (low-risk univentricular pathway)	**12**	**(6.3)**
Tricuspid atresia	10	(5.2)
Mitral atresia, no LVOTO/RVOTO	2	(1.0)
Level 6 (high-risk univentricular pathway)	**10**	**(5.2)**
Mitral atresia with LVOTO/RVOTO	8	(4.2)
Single ventricle, other, PA	2	(1.0)
Level 7 (complex CHD/univentricular pathway with poor prognosis)	**55**	**(28.8)**
Heterotaxia syndrome	19	(9.9)
HLHS	13	(6.8)
Single ventricle, other	7	(3.7)
Mitral atresia with Edward syndrome	3	(1.6)
Ebstein anomaly with hydrops fetalis	3	(1.6)
Severe Pulmonary stenosis with hydrops fetalis	2	(1.0)
Tricuspid atresia with congenital diaphragmatic hernia	1	(0.5)
TOF with Edward syndrome	1	(0.5)
PAVSD with hydranencephaly	2	(1.0)
PAIVS with poor cardiac function	1	(0.5)

Table 2 (continued).

Fetal Cardiovascular Severity Scale (FCSS)† and cardiac diagnosis	N	(%)
DORV with gross hydrocephalus	1	(0.5)
AVSD with hydrops fetalis	1	(0.5)
AS with gross hydrocephalus	1	(0.5)
All	**191**	**(100)**

VSD, ventricular septal defect; PS, pulmonary stenosis; PA, pulmonary atresia; ASD, atrial septal defect; TOF, Tetralogy of Fallot; AVSD, atrioventricular septal defect; D-TGA, D-transposition great arteries; PAVSD, pulmonary atresia with VSD; CoA, coarctation of aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; PAIVS, pulmonary atresia with intact septum; AS, aortic stenosis; DILV, double inlet left ventricle; ccTGA, congenitally corrected TGA; IAA, interrupted aortic arch; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction.
†Modified from Fetal Cardiovascular Severity Scale, Davey et al. (2014) [23].

3.1 False Positive and Negative

From the 2622 fetal echocardiograms, 1058 had postnatal echocardiograms available for comparison (Fig. 2). Of 191 fetal CHD, 38 had no confirmatory postnatal echocardiogram due to loss to follow-up and death, either in-utero or after delivery. Of the 153 fetuses with CHD, 30 did not have CHD on postnatal echocardiogram (false positive). Meanwhile, of 905 fetuses with a normal heart on fetal echocardiogram, 26 had CHD (false negative). Hence, the sensitivity, specificity, positive and negative likelihood ratio of fetal echocardiogram for detection of CHD in this study was 82.5% (95% confidence interval [CI]: 75.5% to 88.3%), 96.7% (95% CI: 95.3% to 97.8%), 25.0 (95% CI: 17.5 to 35.8) and 0.18 (95% CI: 0.13 to 0.26) respectively.

There were no critical lesions in the false negative group. Many of the false negatives were small ventricular septal defects, which closed spontaneously during early infancy (Tab. 3).

Table 3: The findings of the false positive (A) and false negative (B) of fetal echocardiogram

Fetal findings	Postnatal findings	Frequency	Percentage	Notes
A) False positive				
VSD	Normal heart	26	86.7	FE showed small VSD of less than 3 mm in all fetuses
ASD	Normal heart	1	3.3	FE noted large ASD secundum with pericardial effusion
Aortic stenosis	Normal heart	1	3.3	FE showed small LVOT for gestational age
PS	Normal heart	1	3.3	FE showed a small RVOT for gestational age
D-TGA, VSD	Large DA with PPHN features	1	3.3	
B) False negative				
Normal heart	VSD	25	96.0	Nineteen VSD closed spontaneously, four remains small, and two had surgery
Normal heart	CoA	1	4.0	Presented with a cardiac murmur at birth and surgical correction at three months of life

VSD, ventricular septal defect; ASD, atrial septal defect; FE, fetal echocardiogram; LVOT, left ventricular outflow tract; PS, pulmonary stenosis; RVOT, right ventricular outflow tract; PPHN, persistent pulmonary hypertension of newborn; D-TGA, transposition great arteries; DA, ductus arteriosus; CoA, coarctation of the aorta.

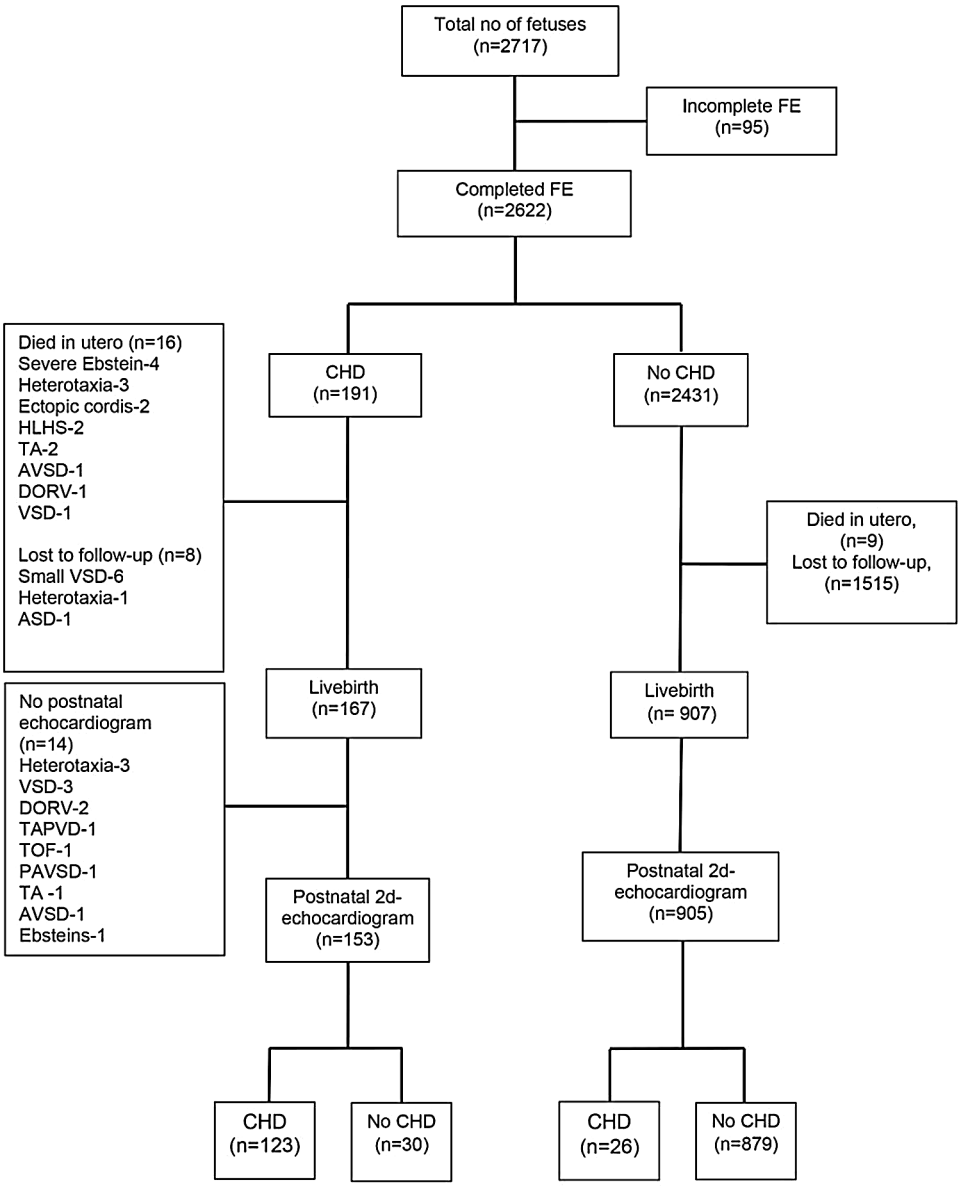

Figure 2: The immediate outcome of fetal echocardiography. FE, fetal echocardiogram; CHD, congenital heart disease; HLHS, hypoplastic left heart syndrome; TA, tricuspid atresia, AVSD, atrioventricular septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; TAPVD, total anomalous venous drainage; TOF, tetralogy of Fallot

3.2 Discrepant Diagnosis Between Fetal and Postnatal Echocardiograms and Their Impact on the Early Neonatal Management and Long-Term Outcome

There were 26.8% discrepant diagnoses (8.1% partially different, and 18.7% no similarity) between fetal and postnatal echocardiogram (Tab. 4).

Most of the discrepant diagnoses involved a fetal diagnosis of complex univentricular heart (n = 12, 36.4%). Meanwhile, fetal diagnosis of DORV was associated with the highest rate (71.4%) of discrepant diagnoses.

Table 4: Level of agreement between fetal and postnatal cardiac diagnosis

Fetal diagnosis	Total	Level of agreement with a postnatal diagnosis		
		Similar N (%)	Partially N (%)	No similarity N (%)
VSD	16	16 (100.0)	0 (0.0)	0 (0.0)
Heterotaxia syndrome	14	10 (71.4)	2 (14.3)	2 (14.3)
Mitral atresia	13	9 (69.2)	0 (0.0)	4 (30.8)
HLHS	11	11(100.0)	0 (0.0)	0 (0.0)
TOF	8	5 (62.5)	3 (37.5)	0 (0.0)
Tricuspid atresia	8	6 (75.0)	0 (0.0)	2 (25.0)
DORV	7	2 (28.6)	1 (14.3)	4 (57.1)
PAVSD	6	5 (83.3)	0 (0.0)	1 (16.7)
D-TGA	6	4 (66.7)	1 (16.7)	1 (16.7)
PS	5	5 (100.0)	0 (0.0)	0 (0.0)
AVSD	5	3 (60.0)	0 (0.0)	2 (40.0)
Ebstein anomaly	5	3 (60.0)	0 (0.0)	2 (40.0)
Hypoplastic arch/CoA	4	3 (75.0)	1 (25.0)	0 (0.0)
SV, other	4	2 (50.0)	0 (0.0)	2 (50.0)
PAIVS	4	2 (50.0)	0 (0.0)	2 (50.0)
Truncus arteriosus	2	2 (100.0)	0 (0.0)	0 (0.0)
ccTGA	2	1 (50.0)	1 (50.0)	0 (0.0)
AS	2	0 (0.0)	1 (50.0)	1 (50.0)
Hypoplastic LV	1	1 (100.0)	0 (0.0)	0 (0.0)
Total	123	90 (73.2)	10 (8.1)	23 (18.7)

(%) represent percentage within the fetal cardiac diagnosis.
VSD, ventricular septal defect; HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; PAVSD, pulmonary atresia with VSD; D-TGA, D-transposition great arteries; PS, pulmonary stenosis; AVSD, atrioventricular septal defect; CoA, coarctation of aorta; SV, single ventricle; PAIVS, pulmonary atresia with intact septum; ccTGA, congenitally corrected TGA; AS, aortic stenosis; LV, left ventricle.

The discrepant diagnosis between fetal and postnatal echocardiogram causes significant changes in neonatal management in 8.9% (Tab. 5). Of 23 cases with no similarity, only nine had significant changes in immediate postnatal management. Meanwhile, of the ten with a partially different diagnosis, only two cases had changes in neonatal management.

There were 18 (14.6%) significant changes in fetal severity score (Tab. 6). Of the 18, 10 had a discrepant diagnosis between fetal and postnatal echocardiograms, and eight had a similar diagnosis. Overall, discrepant diagnosis led to an 8.1% change in the fetal severity score.

Table 5: The fetal and postnatal cardiac diagnosis in infants with significant changes in planned neonatal management

No	Fetal diagnosis	Postnatal diagnosis
Negative impact		
1	AVSD with no PA	Heterotaxia syndrome with PA
2	Ebsteins anomaly, severe TR	PAIVS, tripartite, severe TR
3	Ebsteins anomaly, severe TR	PAIVS, tripartite, severe TR
4	Single ventricle, other	Interrupted Arch
Positive impact		
1	Tricuspid atresia	Large VSD with small RV
2	Mitral atresia, with RVOTO	Heterotaxia syndrome, no RVOTO
3	PAIVS	Ebstein anomaly
4	PAIVS[†]	Ebstein anomaly
5	PAVSD	TOF, severe PS
6	Heterotaxia syndrome with PA	Heterotaxia syndrome, with PS
7	Hypoplastic arch, severe	Hypoplastic arch, mild

AVSD, atrioventricular septal defect; PA, pulmonary atresia; TR, tricuspid regurgitation; VSD, ventricular septal defect; RV, right ventricle; RVOTO, right ventricle outflow tract obstruction; PAIVS, pulmonary atresia with intact septum; PS, pulmonary stenosis; TOF, tetralogy of Fallot; PAVSD, pulmonary atresia with VSD.
[†], associated with poor cardiac function.

Table 6: The fetal and postnatal cardiac diagnosis with significant changes in Fetal Cardiovascular Severity Score

No	Fetal diagnosis	Postnatal diagnosis	Level of CHD severity[†]	
			Fetal	Postnatal
Increase in severity score				
1	*VSD, small	VSD, moderate	1	3
2	*VSD, moderate	VSD, moderate to large	2	3
3	*VSD, moderate	VSD, moderate to large	2	3
4	*DORV, no PS	Edward syndrome with DORV with mild PS	4	7
5	AVSD	Heterotaxia syndrome with PS	4	7
6	AVSD with no PA	Heterotaxia syndrome with PA	4	7
7	Tricuspid atresia	Tricuspid atresia with crisscross heart	5	6
8	Tricuspid atresia	Large VSD with small RV	5	6
9	Tricuspid atresia	Heterotaxia syndrome	5	7
10	*Mitral atresia	Edward syndrome with Mitral Atresia	5	7
11	Mitral atresia with LVOTO	HLHS	6	7
12	Mitral atresia, with RVOTO	Heterotaxia syndrome no RVOTO	6	7
13	*Mitral atresia	Edward syndrome with Mitral atresia	6	7

Table 6 (continued).

No	Fetal diagnosis	Postnatal diagnosis	Level of CHD severity†	
			Fetal	Postnatal
Decrease in severity score				
1	Mild AS	Small VSD	2	1
2	*Hypoplastic arch, severe	Hypoplastic arch, mild	3	1
3	Hypoplastic arch/CoA, severe	Hypoplastic arch/CoA, mild	3	1
4	*VSD, moderate	VSD, small	2	1
5	Heterotaxia syndrome	Mitral atresia with PS	7	6

VSD, ventricular septal defect; DORV, double outlet right ventricle; PS, pulmonary stenosis; AVSD, atrioventricular septal defect; PA, pulmonary atresia; RV, right ventricle; LVOTO, left ventricle outflow tract obstruction; HLHS, hypoplastic left heart syndrome; RVOTO, right ventricle outflow tract obstruction; AS, aortic stenosis.
† graded using Fetal Cardiovascular Severity Score Davey et al. (2010) [23].
* similar fetal and postnatal diagnosis with changes in the severity of illness or presence of lethal congenital malformation that was not recognized during antenatal ultrasound.

4 Discussion

4.1 Specificity and Sensitivity

In this study, a combination of basic cardiac echocardiography examination, outflow tract view, and three-vessel view were used to detect CHD in high-risk pregnant mothers. The sensitivity, specificity, positive, and negative likelihood ratios of fetal echocardiogram in this study were 82.5%, 96.7%, 25.0, and 0.18, respectively. The result is slightly low compared to that reported in a systematic review and meta-analysis by Zhang et al. [27] in 2015, which showed a pooled sensitivity with basic cardiac echocardiography examination, outflow tract view, and three-vessel view of 83.7%. However, it is encouraging that none of the false negatives and false positives were related to critical CHD. The sensitivity was slightly low due to the inclusion of small ventricular septal defects, which may spontaneously close either during pregnancy or in early infancy. If a small ventricular septal defect which closed spontaneously (26 from fetal and 19 from postnatal echocardiograms) was considered as a normal heart, the sensitivity, specificity, positive and negative likelihood ratio would increase to 94.6%, 99.6%, 220, and 0.05, respectively.

Although the outflow tract and three-vessel views were used in this study, we still missed one case of coarctation of the aorta and over-diagnosed two outflow tract lesions. Nevertheless, this finding is not surprising since most series faced a similar problem [12,16]. A high error of fetal echocardiogram related to outflow tract lesions is due to the dynamics of fetal heart development, which evolves during pregnancy rather than a missed diagnosis *per se*.

4.2 Discrepant Diagnosis Between Fetal and Postnatal Cardiac Diagnoses

Evaluation of the accuracy and reliability of fetal echocardiography is challenging due to the complexity of some lesions, change of lesion severity over time as well as various definitions applied in earlier studies. In this study, the actual anatomical diagnosis was used to compare fetal and postnatal cardiac diagnosis and to investigate the impact of the discrepant diagnosis on planned neonatal management and long-term outcome. This study showed a 73% similarity between fetal and postnatal cardiac diagnoses, which is almost similar compared to Bensemlali et al. at 71% [13]. However, using the Wald and Aristotle score, Clur et al. [16] noted a high similarity rate of 81% to 86%. Meanwhile, Velzen et al. [12] recorded that 82% of their fetal cardiac diagnoses were correct. Nonetheless, this suggests that approximately one in five fetuses may have partial- or completely different cardiac diagnoses following delivery.

Despite a comparable rate of similarity with previous studies, unfortunately, the rate of completely different diagnosis is high (20%) compared to Bensemlali et al. [13] (2.9% of liveborn) and Velzen et al. [12] (8.1%). The possible explanation could be due to error in the interpretation of complex single ventricle anatomy, or a part of the disease continuum. Furthermore, differentiation between DORV with pulmonary stenosis and tetralogy of Fallot with a small pulmonary artery *in utero* is challenging. Meanwhile, some lesions may have similar features, e.g., pulmonary atresia with an intact septum may have abnormal tricuspid valve mimicking Ebstein anomaly, and Ebstein anomaly may be associated with functional pulmonary atresia. Nevertheless, this illustrates the importance of follow-up echocardiogram during antenatal and postnatal periods as well as proper parental counseling.

4.3 Impact on the Planned Neonatal Management and Severity Score

In this study, fetal CHD was graded according to the level of severity using the modified FCSS. This CHD severity classification allowed planning of place of delivery, early neonatal, and long-term management. Fortunately, despite having a significant discrepant diagnosis, less than 10% of the cases caused a considerable impact on planned neonatal management, which is comparable to Bensemlali et al. [13]. However, there was a 10% negative impact on CHD severity following delivery. The percentage is rather high compared to that reported by Bensemlali et al. (4.9%) [13] and attributed to undiagnosed lethal congenital malformations. Hence, all fetuses with suspected CHD should have a detailed scan to exclude non-cardiac malformations or syndromes, which may significantly alter the overall outcome and vice-versa.

4.4 Indication for Fetal Echocardiogram

Most of the indications of fetal echocardiogram in our study were due to pre-existing or gestational diabetes mellitus, which is a well-known risk factor for developing a conotruncal defect in their offspring [28,29]. However, data for gestational diabetes mellitus tend to be limited. Our study shows that the risk of CHD in infants of mothers with gestational diabetes mellitus to be 4.8%, which is almost similar to infants of pre-existing diabetes mellitus mothers of 5.3%. This rate is also similar to a recent publication by Hunter et al. [30]. Hence, a mother with gestational diabetes mellitus is also at risk of having a baby with CHD and should be included in the current guidelines for fetal echocardiography.

4.5 Limitations of the Study

Although to our knowledge, this is the first large scale study over a ten-year duration in Malaysia, our study was limited by lack of post-mortem in fetuses who died *in utero* or immediately after delivery due to legislation and cultural issues. Secondly, a higher rate of lost to follow up was observed in cases with normal fetal heart findings which may be contributed by the change in our protocol from 2015 onward, i.e., a postnatal echocardiogram was no longer offered for all normal fetal echocardiogram findings which could have led to an underestimation of our findings.

Another limitation in this study is the risk of bias in the interpretation of the fetal and postnatal echocardiograms by the same pediatric cardiologist. Unfortunately, this is unavoidable as there is only a single pediatric cardiologist serving the entire state of Johor during the study period who can confirm the diagnosis. To make matters worse, there were limited obstetricians trained in fetal echocardiography. This highlights that fetal echocardiography services in LMIC are still at the infancy stage. Consequently, only 3% of CHD in Johor were detected antenatally [26]. Therefore, training of obstetricians and pediatric cardiologists in fetal echocardiography is vital before the introduction of the National CHD Screening program.

5 Conclusion

Despite insufficient resources and expertise, the sensitivity, specificity, positive and negative likelihood ratio of fetal echocardiogram in detecting CHD, and the discrepant diagnosis between fetal and postnatal

diagnosis in this study are comparable with centers in a high-income country. As fetal echocardiography is not perfect, counseling of parents with prenatally diagnosed CHD should be done carefully.

Active involvement of all stakeholders, significant changes in policy, and training are needed to improve fetal echocardiography services in LMIC.

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