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Prenatal detection of fetal heart disease at Jordan University Hospital: early experience in a developing country

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Abstract

Objective: To report on the first 5 years of establishment of fetal echocardiographic services at the Jordan University Hospital with emphasis on diagnosis and outcome. *Methods:* A retrospective chart review was conducted on all fetal echocardiographic studies performed between January 2011 and December 2015. Data collected included maternal demographics, referral indications, fetal cardiac diagnosis, correlation to post-natal diagnosis, outcome of pregnancy including pre-mature delivery and perinatal mortality. Basic statistical analysis was performed including demographic analysis, and calculation of fetal echocardiographic sensitivity and specificity. *Results:* A total of 208 fetuses underwent fetal echocardiographic evaluation at a mean gestational age of 26.5 (±5) weeks. The most common referral indication was a suspicion of CHD during the obstetric ultrasound (44.2%), followed by cardiac dysfunction (18.2%), and a family history of CHD (14.9%). Fetal echocardiography showed CHD in 71 fetuses (34%), heart failure in 26 (12.5%), arrhythmia in 9 (4.3%), and intracardiac masses in 2. In the remaining 100 fetuses (48%), fetal echocardiography showed normal evaluation. For detecting CHD, fetal echocardiography had a sensitivity and specificity of 91.7% and 95.4%, respectively. Perinatal mortality including termination of pregnancy, intrauterine fetal death, and neonatal mortality was highest in heart failure (77%), and was 41% for CHD. *Conclusion:* The fetal cardiac diagnostic services at the Jordan University Hospital have encouraging initial results with a relatively high sensitivity and specificity. The services further positively impacted the quality of counselling offered and facilitated pre- and post-natal management.

CHD is the most common congenital anomaly with a global incidence of 4–10 per 1000 live births and a leading cause of mortality and morbidity in children with congenital anomalies.[1,2] The reported incidence of CHD seems to be higher in the Middle Eastern countries with a range of 9–12 per 1000 live births, and may be attributed to genetic background, environmental factors, and consanguinity.[3–6] Incidence in our institution was 12.3 per 1000 live births.[7]

Over the past 20 years, antenatal diagnosis has gradually become one of the most important tools in the early detection and diagnosis of CHD. This resulted in the improvement, refinement, and standardisation of fetal echocardiography techniques.[8]

Fetal echocardiography in experienced hands was found to be the most reliable diagnostic method for detecting CHD antenatally.[9] The rate of prenatal CHD identification has gradually improved to reach up to 75% of pregnancies with severe forms of CHD by 2005–2008.[10]

Improved early detection resulted in improved outcome and a decrease in the mortality and morbidity of neonates born with CHD.[11] Moreover, it helped in optimising support to families by offering appropraite counselling regarding the affected pregnancy and future pregnancies.[12]

In addition to detection of CHD, fetal echocardiography proved to be an important tool in the functional evaluation of fetal heart, fetal arrhythmias, and intracardiac masses.[8–10]

The Jordan University Hospital is a leading academic tertiary centre in Jordan. Fetal echocardiography was initiated in our institution in 2007 and became a well-established service with a dedicated fetal cardiac clinic in 2011.

The purpose of this study is to report on the early experience of prenatal evaluation of fetal heart disease at the Jordan University Hospital, with correlation to post-natal diagnosis and outcome.

Materials and methods

This is a retrospective chart review conducted on all fetal echocardiographic studies performed at our institution between January 2011 and December 2015.

Data were collected from medical records, fetal echocardiographic reports, and fetal echocardiographic images. Pregnancy and post-natal outcomes were obtained from obstetric hospital records, post-natal medical records, and echocardiographic and/or electrocardiographic assessments of neonates and infants within the hospital system. For pregnancies that ended outside of our hospital, outcome data were collected by phone calls.

Pregnancy data reported included maternal age, maternal gravidity, number of fetuses, gestational age at the time of fetal echocardiography, and indication for referral for fetal echocardiography.

All fetal echocardiographic images and reports, performed by two paediatric cardiologists, were reviewed, and the fetal cardiac diagnosis was recorded.

Referral indications were either due to fetal, maternal, or familial indications. Fetal indications included the suspicion of CHD on the detailed obstetric ultrasound scan, fetal intracardiac masses, the presence of extracardiac anomalies, functional cardiac assessment including the presence of hydrops fetalis, twin–twin transfusion, and the presence of abnormal fetal rhythm including fetal tachycardia, bradycardia, or irregular rhythm. Maternal indication included advanced maternal age above 40 years as the sole indication for referral for fetal echocardiography. Familial indication included a family history of CHD whether in first- or second-degree relatives.

The results of fetal echocardiography were divided into five categories: normal, CHD, hydrops (including twin–twin transfusion syndrome), arrhythmias, and intracardiac masses.

Any discrepancies between prenatal and post-natal diagnoses were recorded. Post-natal diagnosis of a patent ductus arteriosus, a patent foramen ovale, or an ostium secundum atrial septal defect was not considered an error since they were considered part of normal fetal cardiac anatomy.

Mortality assessment included both prenatal mortality which included termination of pregnancy or intrauterine fetal death, and neonatal mortality within the first month after delivery.

The statistical analysis of continuous variables was expressed as the mean +/− standard deviation, and of categorical variables as ratio/percentage.

The analysis of data was done using GraphPad statistical software. The p value less than 0.05 was considered significant.

The study was approved by the Institutional Review Board at the Jordan University Hospital.

Results

There were 11,256 pregnant women who underwent a detailed fetal obstetric scan by feto-maternal obstetric specialist during the period 2011–2015. A total of 195 (1.7%) pregnant women and 208 fetuses were referred for fetal cardiac assessment at the paediatric cardiology department, including 182 singleton and 26 twins. The mean maternal age was 30.8 ± 6.3 years. The mean gestational age at fetal echocardiography assessment was 26.5 (± 5) weeks. Demographic data and referral indications for referral for fetal echocardiography are summarised in Table 1.

The most common referral indication was suspicion of CHD on fetal obstetric scan (92 fetuses, 44%); most of the referral reports indicated the suspicion of CHD based on actual visualisation of an abnormality such as “abnormal atrioventricular valve”, “abnormal outflow tract”, or abnormality in the size of the cardiac chambers. The second commonest indication was for functional cardiac assessment (36 fetuses, 17%), including 18 singleton and 9 pairs of twins with twin–twin transfusion syndrome. A family history of CHD was the cause of referral in 31 fetuses (14%), 20 had a sibling with a diagnosis of CHD, 3 had either parent with history of CHD, and 8 had other family members with CHD. Twenty-eight fetuses (13%) were referred due to the presence of extracardiac anomalies (lung anomaly in eight, CNS anomaly in seven, renal anomaly in three, oligo or polyhydramnios in three, and other miscellaneous in seven).

Table 1. Demographic data and referral indication for pregnant women who underwent fetal echocardiographic evaluation.

Age of mother	30.8 ± 6
Number of mothers/Number of fetuses	195/208 (13 pairs of twins)
Mothers older than 40 years	17
Gravida	3.4 ± 2.2
Gestational age at the time of study	26.5 ± 5 weeks
Indication for referral for fetal echocardiography	
Suspicion of CHD on obstetric scan	92
Functional assessment including suspicion of hydrops	36
Family history of CHD	31
Other fetal anomalies on obstetric scan	28
Abnormal rhythm on obstetric scan	13
High maternal age only	6
Intracardiac masses on obstetric scan	2

Fetal echocardiography revealed 100 fetuses with normal heart, 71 with CHD, 26 with heart failure, 9 with arrhythmia, and 2 with intracardiac masses and suspicion of tuberous sclerosis. Post-natal follow-up and outcome were determined in 177 fetuses (86%). Thirty-one fetuses had no follow-up data where no follow-up records were found for the mothers, and no phone contact was successful.

Congenital heart disease

Seventy-one fetuses were diagnosed prenatally with CHD at a mean gestational age of 26.5 (±5.5) weeks. Table 2 describes the spectrum of CHD. Of the 71 fetuses, 12 were lost to follow-up, 3 had termination of pregnancy, 5 died in utero, and 51 were born alive at gestational age of 37.4 (±2.2) weeks. Two neonates had no confirmation of diagnosis after delivery due to early neonatal deaths within hours of birth. Forty-nine neonates had post-natal echocardiographic evaluation: 39 had concordant post-natal diagnosis while 10 were discordant with the prenatal diagnoses. The discordant diagnoses were four patients had small ventricular septal defects on prenatal echocardiography and were spontaneously closed at birth as anticipated; hence, this was not considered as diagnosis error. Five patients had normal post-natal echocardiograms despite prenatal diagnosis of CHD (abnormal pulmonary venous connections in two, borderline small right ventricle, mild aortic stenosis, and double outlet right ventricle in one each). One patient had a post-natal diagnosis of aortic valve stenosis with a ventricular septal defect while prenatally diagnosed with double outlet right ventricle. Exact concordance in our data was 43/49 (88%), Fig 1.

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Table 2. Spectrum of CHD diagnosed by fetal echocardiography at the Jordan University hospital between 2011 and 2015.

Diagnosis	Number (%)
VSD	18 (25)
DORV variants	11 (15)
Single-ventricle variants	8 (11)
HLHS	6 (8.5)
Atrioventricular canal defect	5 (7)
Tetralogy of Fallot	4 (5.5)
Transposition of great arteries	3 (4)
Pulmonary atresia	2 (3)
Truncus arteriosus	2 (3)
Ebstein anomaly	2 (3)
Abnormal pulmonary venous drainage	2 (3)
Aortic stenosis	2 (3)
Other miscellaneous conditions	6 (8.5)
Total	**71 (100)**

DORV = double outlet right ventricle; HLHS = hypoplastic left heart syndrome; VSD = ventricular septal defect

Four neonates were diagnosed postnatally with CHD despite having normal fetal echocardiographic report: two had small ventricular septal defect, one had coarctation of aorta with a ventricular septal defect, and one had mild Ebstein anomaly of tricuspid valve. The sensitivity of detecting CHD by fetal echocardiography in our institution was 44/48 (91.7%).

It is important to note that although majority of prenatal CHD diagnoses were in fetuses referred for suspicion of CHD by the obstetrician 49/59 (83%), CHD was diagnosed in four (6.8%) cases referred for functional cardiac assessment, three cases for a family history of CHD, two cases for the presence of fetal extracardiac anomalies, and one for a rhythm abnormality on the obstetric scan.

Fetal heart failure

Fetal heart failure was diagnosed in 26 fetuses. This was divided into two categories: non-immune hydrops fetalis (15) and fetal heart failure secondary to twin–twin transfusion (N = 11).

Of the 15 fetuses with signs of hydrops, 13 had structurally normal hearts, 2 had severe bradycardia due to complete heart block. Of note, there was one other patient with fetal hydrops and truncus arteriosus with truncal valve insufficiency; this was included in the CHD cohort. Two pregnancies had no follow-up data. Of the 13 with available follow-up data, 5 died in utero. Eight pregnancies were delivered at a median gestational age at delivery of 33 weeks (28–37). There were five deaths in the neonatal period, and only three were alive at 1 month of age. The overall perinatal mortality of non-immune hydrops in our series is 10/13 (77%).

As for fetuses diagnosed with fetal heart failure due to twin–twin transfusion (N = 11), signs of failure occurred in both twins in four pregnancies (eight fetuses), and in the recipient twin in three pregnancies (three fetuses) with normal donor counterparts. There were two intrauterine fetal deaths, and nine fetuses were born at median gestational age of 33 weeks (28–36). There were total of five neonatal deaths before the age of 1 month, all in recipient twins. The overall perinatal mortality of twin–twin transfusion in our series was 7/11 (64%).

Arrhythmias

Nine fetuses were diagnosed with abnormal rhythm on fetal echocardiography. Five with bradycardia (three complete heart block and two second degree heart block), two had irregular rhythm due to pre-mature atrial contractions, and two had documented supraventricular tachycardia.

Follow-up data demonstrated one intrauterine death in a fetus with complete heart block, and one termination in a fetus with supraventricular tachycardia resistant to all therapy resulting in severe hydrops. Two cases were lost to follow-up. Overall, five were delivered at median gestational age of 38 weeks (28–40). There was one neonatal mortality due to complete heart block and pre-maturity.

Intracardiac masses

There were two patients in our series with intracardiac masses diagnosed prenatally as rhabdomyomas and postnatally confirmed. Both patients underwent tuberous sclerosis workup and were well and alive at 1 month of age.

Normal fetal echocardiography

Fetal echocardiography showed normal fetal heart in 100 fetuses. Referral indications were 31 (31%) with suspected structural heart disease where most referral were due to the suspicion of septal defects or due to the suspicion of abnormal size of chambers, 28 (28%) referrals were due to a family history of CHD, 24 (24%) due to the presence of extracardiac fetal anomalies (7 lung anomalies, 6 brain anomalies, 2 renal anomalies, and 9 other miscellaneous findings), 6 (6%) referred due to the suspicion of abnormal rhythm on obstetric scan, 6 due to the advanced maternal age of >40 years, **and 5 (5%) were referred for functional assessment of heart failure.**

Of the 24 fetuses with other extracardiac anomalies, 23 had follow-up data. Three died in utero, and one underwent termination of pregnancy (hydrocephalous). Nineteen were delivered at a median gestational age of 38.5 weeks (35–40). Seven had neonatal deaths within days of delivery (three with brain anomalies, two with congenital diaphragmatic hernia, and two with respiratory failure). Overall, perinatal mortality for fetuses with non-cardiac anomalies **was 11/23 (48%).**

Of the 76 fetuses with normal fetal echocardiography and no other congenital anomalies, 14 had no follow-up data, 2 died in utero (twins with family history of early neonatal deaths of unclear aetiology), and 60 were born with a mean gestational age of 37.3 (±2) weeks. There were four neonatal deaths: two due to prematurity and lung disease, one was born to a 54-year-old mother with diabetes, and one with family history of unexplained neonatal deaths. As mentioned previously, post-natal evaluation revealed a small ventricular septal defect in two patients, coarctation of the aorta with a ventricular septal defect in one patient and mild Ebstein anomaly of the tricuspid vale in one patient. **The total number of normal documented post-natal echocardiography was 83 (60 otherwise normal fetuses and 23 with extracardiac anomalies).** Therefore, specificity of prenatal diagnosis of CHD in our series is **83/87 (95.4%)**.

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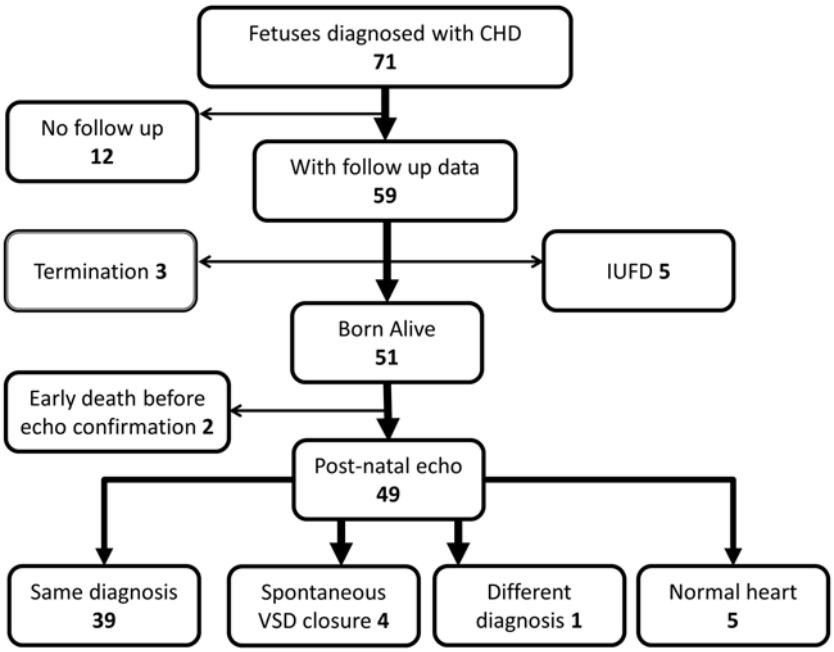

Figure 1. Number of fetuses diagnosed with CHD and their follow up data. IUFD: Intrauterine fetal death.

Mortality

The total perinatal mortality in our series was 59/177 (33%). In five cases, termination of pregnancy was elected by the parents (three with CHD, one with hydrocephalus, and one with intractable supraventricular tachycardia resulting in hydrops fetalis). Termination of pregnancy was performed outside of our institution. In utero death occurred in 18 fetuses, and post-natal death during the first month of life occurred in 36 cases. Details of the perinatal mortality cases are outlined in Table 3.

The perinatal mortality of prenatally diagnosed CHD (24/59, 41%) was significantly higher than cases with normal heart and no other anomalies (4/62, 6.5%, $p = 0.0001$), and significantly lower than cases with non-immune hydrops (10/13, 77%, $p = 0.03$), but not significantly different from cases with extracardiac anomalies (11/23, 48%, $p = 0.62$) or from cases with twin–twin transfusion (7/11, 64%, $p = 0.20$).

Pre-term delivery

There were 154 fetuses who completed pregnancy till delivery. There was no difference between the gestational age at delivery between fetuses with a diagnosis of CHD (37.4 ±2.2) and those with normal hearts (37.1 ± 2.4) ($p = 0.5$). Fetuses with hydrops had a significantly lower gestational age (32 ± 3.6) at delivery compared to fetuses with normal hearts and those with CHD ($p = 0.0001$).

Overall, 52 (34%) were born prematurely with gestational age of less than 37 weeks (mean 33.3 weeks, range 28–36). Premature delivery occurred in 22/85 (26%) fetuses with normal fetal echocardiography, 13/58 (22%) with CHD, 14/24 (58%) with hydrops, and 3/7 (42%) with arrhythmia. As expected, risk of pre-mature delivery is highest in fetuses with hydrops (14 out of 24 (58%)) when compared to fetuses with normal hearts (22 out of 85 (26%)) ($p = 0.006$), and when compared to fetuses with CHD (13 out of 58 (23%) ($p = 0.004$).

Discussion

Fetal echocardiography has become a standard practice in developed countries, and is becoming common practice in developing countries as well, provided expertise in the field is available, particularly in the obstetric/fetal as well as paediatric cardiac specialties.

The applications of prenatal diagnosis of heart disease has increased in recent years from the early detection of disease that allows for preparation and counselling, to becoming vital in creating multidisciplinary approach for management, including prenatal treatment of the fetus by either medical management of problems like arrhythmia and fetal heart failure, to even surgical and catheter interventions for the fetus in utero.[13]

The Jordan University Hospital is a tertiary academic institution in Amman, Jordan, catering for a significant public population. The fetal echocardiography service started in 2007 and became a regular service with a dedicated clinic in 2011. Our initial experience is presented in this report, reflecting the first 5 years of establishment.

CHD at our institution has an incidence of 12.3 per 1000 live births as described by Al-Ammouri, et al.[7] During the 5-year study period, there were 21,180 live births with estimated 260 newborns expected to have CHD. Our cohort detected 51 patients (live born), which puts the rate of prenatal detection at our institution at 19.6%. This low prenatal detection rate is due to a multitude of factors, including lack of awareness of prenatal diagnosis of CHD by the general public and primary care providers and relatively lower rates of performing routine obstetric ultrasound scans during pregnancy. It may also reflect lower rates of referral for fetal cardiac evaluation.

In our institution, there were 11,256 detailed fetal scans performed during the study period, with an unknown number of these pregnancies delivering outside of our institution. Detailed fetal obstetric scans were performed for 53% or less of pregnancies and 195 of which were referred for fetal cardiac assessment (1.7%). These findings emphasise the importance of referral guidelines that include: maternal causes, such as maternal pre-gestational or first trimester diabetes mellitus, lupus, and exposure to teratogenic medications; familial factors

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Table 3. Perinatal mortality in a cohort of patients who underwent fetal echocardiography at the Jordan University Hospital during 2011–1015.

Fetal diagnosis	Number	Termination	IUFD	Neonatal death	Alive at 1 month
CHD	59	3	5	16	35 (59%)
Normal heart					
With no fetal anomalies	62	0	2	2	58/62 (93.5%)
With extracardiac fetal anomalies	23	1	3	7	12/23 (52%)
Non-immune hydrops	13	0	5	5	3/13 (23%)
Twin–twin transfusion	11	0	2	5	4/11 (36%)
Arrhythmia	7	1	1	1	4/7
Intracardiac masses (tuberous sclerosis)	2	0	0	0	2

IUFD = intrauterine fetal death

including parents or siblings with structural heart disease; and fetal factors including the suspicion of CHD, chromosomal anomalies, non-cardiac anomalies, hydrops, and umbilical or placental venous anomalies.[13,14]

The sensitivity and specificity of diagnosis of CHD were 92 and 96%, respectively. This is comparable to global results.[13] The advancement of ultrasound imaging technology as well as thorough evaluation of fetuses at dedicated fetal cardiac clinics and adherence to international guidelines play a significant role in improving the accuracy of fetal diagnosis. While our results in terms of specificity and sensitivity are comparable to global results, it is of note that there are significant differences in terms of significantly lower rate of referral and later timing of referral for fetal cardiac assessment.

The overall perinatal mortality rate in our cohort, including termination of pregnancy, intrauterine deaths, and neonatal deaths, was highest in fetuses with hydrops fetalis. In fact, the only survivors of this group of patients were the ones with mild hydrops. Since then, more intense measures were taken and the threshold for starting in utero therapy was lowered.

Fetuses with CHD, arrhythmias, or fetuses with non-cardiac malformations also had a high rate of perinatal mortality (40–50%). As expected, mortality was related to the severity of the malformation, for example, all patients with hypoplastic left heart syndrome were offered comfort care and passed away during the neonatal period, and most fetuses with diaphragmatic hernia and severe brain anomalies also succumbed to neonatal deaths. In addition to the severity of malformations, high total mortality in our cohort may be attributed to other factors: pregnancies that are considered "high risk" are more likely to be thoroughly assessed by obstetric services, thence more likely to be referred for cardiac assessment. In addition, more severe malformations are more likely to be detected by obstetric services and referred for assessment, and those will have higher perinatal mortality rates than simpler lesion are less likely to be detected or referred.

The limited availability of advanced surgical options for critical CHD as well as the lack of facilities for extracorporeal membrane oxygenation following complex cardiac surgeries make the neonatal mortality for infants with CHD relatively high in developing countries. Although there are no reports on mortality rates of CHD in Jordan, there are some reports from other developing countries.[15]

The positive impact of early detection of heart disease in the fetus has been demonstrated in the literature in terms of counselling, planning, and early neonatal management.[10–12] However, prenatal detection of significant heart disease in the fetus has led to increased incidence of termination of pregnancy that may reach >50% of affected fetuses.[16]

In Jordan, although termination of fetuses with congenital anomalies is not a common practice due to legal and religious reasons, our cohort demonstrated that there have been five cases of termination of pregnancy. Termination is done outside of our institution and is chosen by the parents of the fetus that had severe disease and expected to have significant morbidity or mortality after birth. The low termination rate may also be partially attributed to the relatively late detection of heart disease, where neonates may have already reached to viable gestational age at the time of diagnosis.

Apart from fetuses with hydrops fetalis, there was no increase in the rates of pre-maturity in fetuses with heart disease as compared to fetuses with no heart disease. The approach in our institution is to avoid pre-maturity as much as possible in order not to compound the CHD pathology with added morbidities due to pre-maturity. In cases of fetuses with severe hydrops, the decision to deliver the fetus prematurely is a multidisciplinary one weighing the risks versus benefit.

The mean gestational age of our fetal echocardiograms was 26.5 (±5) weeks. This relatively late evaluation is due to late referrals and/or late presentation of the pregnant woman to obstetric care. This raises the importance of more public awareness as well as earlier performance of the obstetric scans and more coverage; as in many cases, earlier diagnosis can result in a significant outcome improvement due to early initiation of fetal therapeutic interventions, such as the early initiation of treatment for fetal arrhythmias, hydrops, and twin–twin transfusion.

Conclusion

The prenatal diagnosis of heart disease is highly important for both fetal management and prognosis, family counselling, and to optimise post-natal management. Fetal echocardiography service at the Jordan University Hospital is a valuable and a reliable tool in the diagnosis and management of fetal heart disease.

Moving from the first years of inception, we are undergoing more team building, standardisation of fetal ultrasound scanning, stricter adherence to the latest guidelines including more comprehensive and earlier referrals, as well as improving counselling services for expecting parents via training and dedication.

In addition, we recommend having a nation-wide registry for both CHD and other congenital malformation to be able to

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measure the change of outcome, and the impact of prenatal detection on outcome.

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Ethical Standards. The authors assert that all procedures contributing to this work comply with the global and local ethical standards and guidelines and have been approved by the institutional review board at the Jordan University Hospital and the University of Jordan.

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