Incidence and outcome of prenatally diagnosed, chromosomally normal congenital heart defects in Singapore

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INTRODUCTION Congenital heart defect (CHD) is a significant cause of neonatal and infant mortality. We aimed to evaluate the incidence and pregnancy outcome of foetuses diagnosed with chromosomally normal CHD in KK Women's and Children's Hospital (KKH), Singapore, in 2008–2009.

METHODS We reviewed the medical records of pregnant women who underwent first trimester screening and were diagnosed with foetal CHD at KKH. Additional information was obtained from the Birth Defect Registry for the period 2008–2009. Foetuses with abnormal karyotype or minor lesions not expected to be detected by ultrasonography were excluded.

RESULTS 38 out of 9,834 euploid foetuses were diagnosed with CHD. Major defects were found in 26 (68%) foetuses, while 12 (32%) had minor CHDs. Tetralogy of Fallot, atrioventricular septal defect, hypoplastic left heart syndrome, transposition of the great arteries and ventricular septal defect constituted the five most common major CHDs observed. In 14 (54%) foetuses with prenatally diagnosed major CHD, the outcome was termination of pregnancy, while 12 (46%) pregnancies continued to birth. Among the live-born babies with major CHD, eight (67%) underwent surgery.

CONCLUSION The incidence of non-chromosomal major CHD in Singapore was about 2.6 per 1,000 foetuses. A detection rate of 88.5% was achieved for major CHD during the study period. Advances in CHD management have thrown up new challenges for clinicians in the area of diagnosis, treatment and ethics. Therefore, it may be beneficial to constitute a regulatory entity as a fundamental guide to improve the future management of foetuses diagnosed with CHD.

Keywords: congenital heart defects, incidence, outcome, prenatal diagnosis, ultrasonography
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INTRODUCTION

Congenital heart defect (CHD) is a significant cause of neonatal and infant mortality.[1] In a non-chromosomal CHD European population, the total prevalence of CHD was estimated as 7.0 per 1,000 births, with severe defects occurring in 2.0 per 1,000 births.[1] Prenatal screening for cardiac defects is usually performed using ultrasonography at 16–20 weeks of gestation to assess the anatomical structure of the foetal heart, in particular, the four chambers and the outflow tract views. Earlier diagnosis of CHD allows for invasive testing of foetal karyotype as well as detailed ultrasonography to search for additional abnormalities.[2,3] Prenatal diagnosis of structural, rhythmic or functional abnormalities can be useful not only for appropriate patient counselling about expected prognosis but also for outlining the management plan to improve the care and support provided to the foetus, mother and family.

Recent developments in ultrasonography and neonatal cardiac surgery have led to higher detection rates and more favourable outcomes for CHD patients in terms of mortality and morbidity.[4-6] For instance, prenatal diagnosis of hypoplastic left heart syndrome (HLHS) has shown an improved early survival that is attributed to better preoperative clinical conditions. Identification of such lesions *in utero* provides caregivers with the ability to maintain ductal patency and haemodynamic stability with prostaglandin E1 therapy.[7] In this paper, we aimed to examine the incidence and pregnancy outcome of chromosomally normal CHD diagnosed in the largest maternity hospital in Singapore.

METHODS

A comprehensive review was conducted on the medical records of all women diagnosed with CHD pregnancies during their first trimester screening (FTS) at KK Women's and Children's Hospital, Singapore, between 2008 and 2009. Information gathered was compiled with data extracted from the Birth Defect Registry for the same period. The FTS was done from 11 to 13+6 weeks of gestation to screen for Down syndrome. Cytogenetic examinations were offered, including an assessment of 22q11 microdeletion for DiGeorge syndrome. The antenatal and post-natal management of these patients was noted. Only foetuses with normal karyotype were included for evaluation. Foetuses

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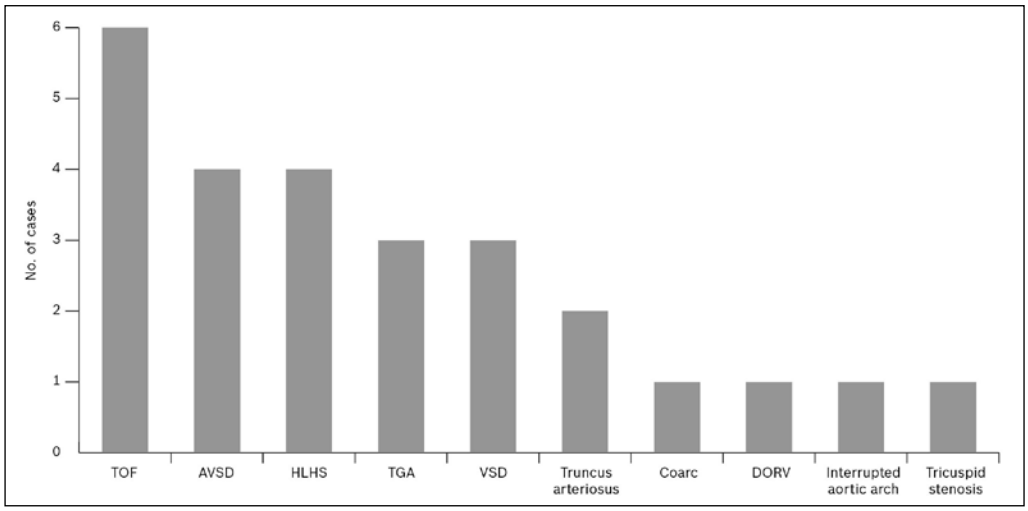

Fig. 1 Graph shows the spectrum of major congenital heart defects in 9,834 foetuses.
AVSD: atrioventricular septal defect; Coarc: coarctation of the aorta; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; TGA: transposition of the great arteries; TOF: Tetralogy of Fallot; VSD: ventricular septal defect

with minor lesions that were not expected to be detected by ultrasonography (such as patent ductus arteriosus [PDA], functional arrhythmias and other non-structural lesions) were excluded from the study.

Women at high risk of foetal abnormality due to thickened nuchal translucency at FTS and/or maternal medical or past obstetric histories were referred for early cardiac imaging at 15 weeks. For other patients, cardiac imaging was arranged for the first time at 18–20 weeks of gestation. Imaging typically included evaluation of the four-chamber heart, great arteries and venous return to look for intra- or extra-cardiac malformations. Women whose foetuses were diagnosed with CHD were referred to a cardiologist for foetal echocardiography. During delivery, a neonatologist was present to examine the condition of the newborn and postnatal echocardiography was requested in high-risk patients. The intensive care unit was prepared and emergency management strategies decided upon based on the antenatal findings and the recommendations of the perinatal team.

As termination of pregnancy is legal in Singapore prior to 24 weeks of gestation, postmortem examination was offered to parents to confirm the prenatal diagnosis of CHD. All live-born CHD infants were followed up in the paediatric clinics. At three months of age, echocardiography was performed to assess the extent of disease progression. Any clinical impairment and management beyond this period were recorded in the outpatient follow-up notes. All foetuses with CHD were categorised according to the International Classification of Diseases version 9 or 10 with British Paediatric Association one-digit extensions. CHD defects were classified as major or minor based on the likelihood of infants requiring surgical repair. Major defects included HLHS, transposition of the great arteries (TGA), atrioventricular septal defect (AVSD), coarctation of the aorta and large ventricular septal defect (VSD). Minor defects included mild pulmonary stenosis, mild aortic stenosis, small VSDs and small atrial septal defects (ASDs). Retrospective classification was performed after the final diagnosis, either by postmortem examination or postnatal echocardiography. Defects were additionally subclassified as associated malformation, if additional major extracardiac abnormality was present, or isolated.

RESULTS

Among 9,834 euploid foetuses that underwent FTS in 2008 and 2009, 38 were diagnosed with CHD, including 26 foetuses with major defects and 12 with minor defects. The incidence of CHD in our cohort was 3.9 per 1,000 foetuses, while that of major CHD was 2.6 per 1,000 foetuses. Of the 38 foetuses with CHD, 12 (32%) were female and 19 (50%) were male. In seven (18%) foetuses, karyotyping was not performed because the mother had declined to have invasive testing or chosen to terminate the pregnancy before chorionic villous sampling or amniocentesis. The karyotypes of these foetuses were regarded as normal. There was no DiGeorge syndrome (22q11 microdeletion) among the foetuses for whom cytogenetic examinations were performed.

Fig. 1 shows the spectrum of major CHD detected prenatally in our cohort. Tetralogy of Fallot (TOF) was the most commonly observed major CHD, accounting for six (23%) foetuses. AVSD and HLHS were the second most common, with four (15%) foetuses each, followed by TGA and VSD, with three (12%) foetuses each. Coarctation of the aorta, double outlet right ventricle (DORV), interrupted aortic arch and tricuspid valve stenosis were observed in one foetus each. Although three foetuses had a right aortic arch, postnatal findings revealed only small-to-moderate PDA, and these were thus excluded from the study.

Discrepancies were noticed between prenatal diagnosis and postnatal confirmation in two foetuses with TOF. At routine imaging, one foetus was diagnosed with an overriding aorta while the other had a DORV. There was one other foetus with an interrupted aortic arch that was previously diagnosed as coarctation of the aorta during routine imaging. Accordingly, only 23 (88.5%) foetuses with major CHD were found to have been accurately detected prenatally in our study. Of the 12 foetuses with minor heart defects, two small ASDs and one moderate ASD

Table I. Major congenital heart defects detected in the foetuses.

Defect	Total	Type of CHD	
		Isolated CHD	Associated malformation
Tetralogy of Fallot	6 (23)	4 (67)	2 (33)
Atrioventricular septal defect	4 (15)	-	4 (100)
Hypoplastic left heart syndrome	4 (15)	3 (75)	1 (25)
Transposition of the great arteries	3 (12)	3 (100)	-
Ventricular septal defect	3 (12)	2 (67)	1 (33)
Truncus arteriosus	2 (8)	1 (50)	1 (50)
Coarctation of the aorta	1 (4)	-	1 (100)
Double outlet right ventricle	1 (4)	1 (100)	-
Interrupted aortic arch	1 (4)	1 (100)	-
Tricuspid valve stenosis	1 (4)	1 (100)	-
Total	26 (100)	16 (62)	10 (38)

Note: Data is presented as number (%).

Table II. Outcomes of foetuses with major congenital heart defects.

Defect	Total	Outcome		Surgery	Age at last hospital visit
		Pregnancy terminated	Born alive		
Tetralogy of Fallot	6 (23)	2 (33)	4 (67)	3 (75)	2, 5, 11 and 12 mths
Atrioventricular septal defect	4 (15)	4 (100)	-	-	-
Hypoplastic left heart syndrome	4 (15)	4 (100)	-	-	-
Transposition of the great arteries	3 (12)	1 (33)	2 (67)	2 (100)	3 and 12 mths
Ventricular septal defect	3 (12)	-	3 (100)	2 (67)	2, 12 and 24 mths
Truncus arteriosus	2 (8)	1 (50)	1 (50)	-	Died at 34 days
Coarctation of the aorta	1 (4)	-	1 (100)	1 (100)	Died at 70 days
Double outlet right ventricle	1 (4)	1 (100)	-	-	-
Interrupted aortic arch	1 (4)	-	1 (100)	1 (100)	Died at 17 days
Tricuspid valve stenosis	1 (4)	1 (100)	-	-	-
Total	26 (100)	14 (54)	12 (46)	8 (67)	-

Note: Data is presented as number (%); unless otherwise stated.

were previously thought to have been a VSD at routine imaging. The remaining nine foetuses were confirmed postnatally. This accounted for an antenatal detection rate of 75% for minor CHDs.

Table I lists the major isolated and associated malformation CHDs detected among the foetuses in our study. Of the 26 (68%) foetuses with major CHDs, 62% had isolated defects. The remaining 38% of defects were associated malformations, which included hydrops foetalis, absent nasal bone, cystic hygroma, choroid plexus cyst, echogenic bowel, abdominal organ dilatation, isomerism, diaphragmatic hernia, anomaly of the gallbladder, cleft and abnormalities of the limbs. All foetuses with AVSD and coarctation of the aorta had associated extracardiac malformations.

Among the foetuses with major CHD, 14 (54%) pregnancies were terminated, including those with TOF, AVSD, HLHS, TGA, DORV, truncus arteriosus and tricuspid valve stenosis (Table II). In the remaining 12 pregnancies that proceeded to delivery, surgery was performed for eight foetuses. Three infants were confirmed to have died before the end of the study period. One infant with an interrupted aortic arch was unable to survive beyond one month due to the complexity of his condition and intrauterine growth restriction. The baby died on Day 17, although repair of the interrupted aortic arch was performed. The second infant with coarctation of the aorta died on Day 70. This patient also had a large PDA and congenital hernia diaphragm. Thoracotomy to repair the coarctation and hernia was performed. The third infant had truncus arteriosus and died on Day 34. Postnatal echocardiography showed type II truncus arteriosus with moderate truncal valve stenosis (Doppler gradient 55 mmHg). The truncal valve overrode the aorta about 5% across a large VSD that was approximately 8.96 mm wide. There was also hypertrophy of the ventricular septum and left ventricular free wall.

Table III shows the number and outcome of foetuses diagnosed with minor CHD in our study. Defects included small and moderate ASDs, small VSD and muscular VSD. Two (17%) foetuses that had minor CHD with complex associated malformations were terminated, while the other 10 (83%) survived. Perinatal management was outlined by the perinatal team for all foetuses who were born alive with major CHD. Administration of prostaglandin E, diuretics and invasive treatment (such as

Table III. Minor congenital heart defects (CHD) detected and outcomes of the foetuses.

Defect	Total	Type of CHD		Outcome	
		Isolated CHD	Associated malformation	Pregnancy terminated	Born alive
Atrial septal defect					
Small	5 (42)	5 (100)	-	-	5 (100)
Moderate	1 (8)	-	1 (100)	-	1 (100)
Ventricular septal defect					
Small	5 (42)	1 (20)	4 (80)	1 (20)	4 (80)
Muscular	1 (8)	-	1 (100)	1 (100)	-
Total	12 (100)	6 (50)	6 (50)	2 (17)	10 (83)

Note: Data is presented as number (%).

Table IV. Major congenital heart defects detected during first trimester screening and outcomes of the foetuses.

Gestational age at detection	Risk	1st trimester screening result	Defect	Associated finding	Outcome
12^{+2}	G4P3, previous pregnancy with hypoplastic left heart syndrome	Nuchal translucency, 1.8 mm	Hypoplastic left heart syndrome	Very small left ventricle, mild tricuspid regurgitation, very small aortic arch	Mid-trimester pregnancy terminated at 15 weeks
12^{+2}	G4P0, triplet pregnancy	Nuchal translucency, 1.9 mm, absent nasal bone	Hypoplastic left heart syndrome	Absent nasal bone, cystic hygroma, absent left ventricle, very small left atrium, absent mitral valve flow, very small aorta, echogenic bowel, hypoplastic left heart	Mid-trimester pregnancy terminated at 18 weeks

catheterisation or balloon arterial septostomy) were among the procedures performed for patients in this study. Among the foetuses examined, two (7.7%) were detected with HLHS early in the first trimester of pregnancy (Table IV). The first patient was a G4P3 who had a higher risk due to a history of previous pregnancy with HLHS. The second patient was a G4P0, with a triplet pregnancy where the affected foetus had an absent nasal bone and cystic hygroma. The pregnancies were terminated at 15 and 18 weeks, respectively, for these two women prior to the routine scan at 18–20 weeks.

DISCUSSION

Our results indicate that the overall incidence of non-chromosomal CHD in Singapore during 2008 and 2009 was 3.9 per 1,000 foetuses, while that of major CHD was 2.6 per 1,000 foetuses, which is comparable to reports by other authors.[8,9] The five major CHDs – TOF, AVSD, HLHS, TGA and VSD – observed in our cohort were also the most common in many other studies.[8,10-12] However, our study differs from earlier reports in that only euploid CHD foetuses were included for examination.

Tegnander et al found that AVSD was the most common major CHD diagnosed antenatally,[8] unlike in our study where TOF was the most common diagnosis, followed by AVSD and HLHS. Although cardiac failure is rarely seen in the foetal or postnatal life of patients with TOF, infants with severe pulmonary stenosis may experience cyanosis immediately after delivery. Two women with foetuses diagnosed with TOF in our study terminated their pregnancy, and in both cases the foetuses had additional malformation. The other four foetuses diagnosed with TOF in our cohort survived till birth, with three of them undergoing invasive management. Full repair of the defect was successfully performed in two infants within one year of birth, underscoring the relative good prognosis of the condition.

Additional intra- or extra-cardiac malformations (such as right isomerism, cystic hygroma, congenital diaphragmatic hernia, polyhydramnios) were noted in all patients with AVSD and coarctation of the aorta. As AVSD is known to be associated with chromosomal aberrations and extracardiac anomalies,[12-14] our finding is not particularly surprising. Coarctation of the aorta, a potentially fatal condition especially when the ductus arteriosus closes after birth, was previously shown to benefit from early diagnosis.[15] However, we found that the only patient with coarctation of the aorta in our study survived just until 70 days after birth. It is likely that extracardiac abnormalities (such as right lung agenesis and right diaphragmatic hernia) may have required additional care and contributed to the poor outcome in this infant.

HLHS and AVSD were the second most common major CHDs detected in our series. The prognosis of HLHS is usually poor and the patient is unlikely to survive beyond the first week of life.[16] Nonetheless, it has been suggested that prenatally diagnosed HLHS patients have a favourable advantage, possibly because it may improve long-term neurological outcome.[5,17] A study by Tworetzky et al also showed improved preoperative clinical status as well as improved survival in prenatally diagnosed HLHS patients.[7] In our study, the parents of all four HLHS foetuses opted to terminate the pregnancy following diagnosis. Two of

these foetuses were detected prior to routine second-trimester imaging, and the diagnosis in one of these was confirmed by postmortem examination.

It has been suggested that prenatal diagnosis may improve pre- and postoperative mortality in foetuses with TGA.[18] In our study, two pregnancies detected with TGA continued to delivery, and the babies were born alive and surviving at three and 12 months after birth. Both infants required either prostaglandin therapy or urgent balloon septostomy on the first day of life, following which TGA was repaired by arterial switch at a later stage. The early recognition of such defects during the prenatal period may support better postnatal management of infants and improve outcome.

Major VSDs were noted in three (12%) foetuses, of which two infants had a large perimembranous VSD with an additional intracardiac lesion. Both infants needed diuretic therapy during early life and subsequent closure of the defect. VSDs (including small and muscular VSDs) also accounted for six (50%) of the minor CHDs detected in our study. The other less common CHDs found were truncus arteriosus, DORV, interrupted aortic arch and tricuspid valve stenosis. The three foetuses detected prenatally with right aortic arch were excluded from the study, as postnatal findings indicated small-to-moderate PDA instead. As right aortic arches are known to be associated with intracardiac anomalies, postnatal evaluation should be carried out to confirm the diagnosis.[19]

Prenatal diagnosis of CHDs has made the management of such foetuses more challenging. Regular monitoring of the foetal cardiac status during pregnancy may offer additional information on the development of the foetus *in utero*[20] as well as provide insights regarding the expected perinatal outcome, so that appropriate management strategies can be instituted. Accurate prenatal diagnosis could not only influence the decision to terminate a pregnancy but also help in planning the delivery and treatment of the newborn.

This study had its share of limitations. The short duration of the period of study (two years) may have adversely affected the sample size. Then again, some diagnoses where the pregnancies were terminated following prenatal examinations could not be confirmed, as postmortem reports were unavailable. A more comprehensive study with a larger sample size is required to confirm the findings of our study. It would also be worthwhile to consider the constitution of a regulatory entity that could function as a fundamental guide for improving the future management of foetuses diagnosed with CHD.

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