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Clinical investigation of congenital heart defects in prenatal life: a retrospective study on 198 cases

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Summary

Objective: The authors present a necropsy study of fetal congenital heart defects (CHD) collected retrospectively, to investigate the spectrum of CHD in prenatal life and the frequency of extracardiac malformations and the proportion of chromosome abnormalities among the fetuses. *Materials and Methods:* During a five-year period, necropsies were performed in 198 fetuses with congenital heart anomalies identified by prenatal ultrasound and for which prenatal cytogenetic analyses were performed on fetal cells obtained by amniocentesis and cordocentesis. Sequential segmental analysis was used to describe cardiac defects according to the prenatal ultrasound findings and postnatal necropsy results. The classification of these cases was referred to the grading suggested by Choi. *Results:* The 198 cases were divided into two groups: group 1 described fetuses with severe cardiac anomalies which contained 90 cases and group 2 described fetuses with complex cardiac anomalies which contained 108 cases. In the spectrum of heart malformations, complex cardiac anomalies comprised 54.5% of the malformations and severe cardiac anomalies comprised 45.5% in the present necropsy population. Extracardiac malformations accounted for 104 cases (52.5%), and chromosome abnormalities were diagnosed in 34 fetuses (17.2%). *Conclusion:* Fetal cardiac anomalies detected in the present study were more severe than those in previous cardiology surveys. The present data will provide an adequate basis for future genetic counseling and improvement of prenatal care for fetal congenital heart defects.

Key words: Congenital heart defects; Extracardiac malformations; Chromosomal abnormalities; Necropsy; Ultrasound.

Introduction

Congenital heart defects (CHD) are the most common congenital anomalies in fetuses, accounting for about 1% of human malformations [1, 2], with most cases occurring in low-risk populations [3]. With the development of screening pregnancies for fetal malformations by routine ultrasound imaging, there has been a recent increase in abnormal cardiac findings from obstetric ultrasonography screenings, suggesting prenatal diagnosis may significantly affect the incidence of complex or serious congenital cardiac malformations. Based on some published prenatal studies for CHD, there is a higher proportion of cases diagnosed in utero that have had severe malformations than cases presenting in infancy [4]. A detailed evaluation of the fetal heart not only optimizes the diagnosis of CHD, but also assists with appropriate prenatal and postnatal planning.

More specific classification of these cardiac lesions depends on a systematic approach to the diagnosis of congenital heart malformations [5]. In the present study, the authors systematically examined each heart by a sequential segmental approach and noted any abnormal connections or arrangements of the cardiac segments. They then retrospectively reviewed the spectrum of cardiac anomalies encountered in 198 fetuses with serious heart malformations, as identified by prenatal ultrasound screening and confirmed by postnatal necropsy, and they investigated the frequency and type of extracardiac malformations and the proportion of chromosome abnormalities among these fetuses. The authors hope these data can provide an adequate basis for genetic counseling and improve perinatal care of fetuses with CHD.

Materials and Methods

The Prenatal Diagnosis Center of Xiamen Maternal and Child Health Care Hospital is a regional tertiary referral center for expectant mothers whose fetuses have suspected anomalies and/or genetic syndromes. It provides prenatal services for a considerable percentage of suspected anomalous pregnancies in the southwest area of Fujian of mainland China. During a five-year period (2008 to 2013), necropsies were performed in the present center in 198 fetuses between 19 and 32 weeks of gestation. In these cases, pregnancy was terminated in case of complex or serious cardiac anomalies which were detected by prenatal obstetric ultrasonography screenings, among which some cases had severe extracardiac malformations. Maternal age of these cases was 19 to 44 years; there were only 11 cases with advanced maternal age. Among all cases, no parents had been diagnosed with CHD and there was no other maternal or familial risk, although three cases had a history of a previous child with CHD diagnosis. Prenatal cytogenetic analyses were performed in fetal cells obtained by amniocentesis and cordocentesis. In China, pregnancy can be terminated in any trimester if the fetus has severe malformations. The study was approved by the Ethics Committee of Xiamen Maternal and Child Health Care Hospital.

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Table 1. — *Classification and subclassification of lesions found at necropsy in group 1.*

Type of defect	Number
Atrioventricular septal defect (AVSD)	13
Tetralogy of Fallot (TOF)	30
Transposition of the great arteries (TGA)	20
Coarctation of the aortic arch	3
AVSD + PS	2
AVSD + TGA	2
Aortic stenosis + PS	9
PS + VSD + tricuspid dysplasia	5
Mitral and tricuspid stenosis	1
Ebstein's anomaly and tricuspid dysplasia	5
Total	90

Group 1 describes fetuses with severe cardiac anomalies; the most frequent malformations were TOF, TGA, and AVSD.

Table 2. — *Classification and subclassification of lesions found at necropsy in group 2.*

Type of defect	Number
Heart with univentricular atrioventricular connection (UVH)	10
Truncus arteriosus communis (TAC)	12
UVH + TAC	12
UVH + PS	8
UVH + PS + tricuspid atresia	1
UVH + Aortic atresia	2
UVH + TAC + PS	1
TAC + AVSD	6
TAC + AVSD + PS	2
TGA + PS + AVSD	3
TGA + PS + VSD	7
Double outlet right ventricle (DORV) + PS + VSD	10
DORV + VSD	6
DORV + AVSD + PS	5
DORV + aortic atresia	1
Hypoplastic left heart	
+ mitral and aortic atresia	3
+ TAC + mitral atresia	2
+ DORV+ Mitral atresia	2
+ coarctation of the aorta	3
+ TAC	1
+ TAC + AVSD	1
+ TAC + VSD	1
+ DORV	1
+ TGA	1
Hypoplastic right heart	
+ PS and tricuspid atresia	3
+ PS +tricuspid atresia + AVSD	1
+ TAC + tricuspid atresia	1
+ PS + VSD	1
+ Tricuspid atresia	1
Total	108

Group 2 describes fetuses with complex cardiac anomalies which constitute 54.5% (108/198) of the malformations in the present necropsy population.

Cardiac anomalies encountered in 198 fetuses were identified by prenatal ultrasound screening. Prenatal ultrasound screening for fetal cardiac malformation is part of routine obstetric ultrasound screening at 18–26 weeks in China. According to scanning protocols, prenatal ultrasound screening is based on the combination of the four-chamber and outflow-tract views, potentially assisted by color Doppler ultrasonography [6].

In the present study, the diagnosis of each heart was made by using sequential segmental analysis based on the prenatal ultrasound findings and the postnatal necropsy results. The sequential segmental analysis as proposed by Van Praagh, which concentrates on the potential variations found across the atrioventricular and ventriculoarterial junctions, which describes the atrioventricular junction, including connections, mode of connection, ventricular morphology, and relation of chambers with ventricular mass, and describes the ventriculoarterial junction, including connections, relation of arterial valves and great arteries, and morphology of outflow tracts [7].

The prognosis of the fetus was evaluated mainly on the diagnosis of CHD and referred to the grading suggested by Choi *et al.* [8]. Severe cardiac anomalies were defined as defects able to be corrected surgically with a low risk for reoperation, such as tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), and complete transposition of the great arteries (TGA). Complex cardiac anomalies were defined as defects able to be corrected anatomically by surgery but with a high risk for sequelae or a Fontan operation candidate, such as double outlet right ventricle, transposition of the great arteries with pulmonary stenosis, and hypoplastic left heart syndrome. According to the prognosis of the fetus, 198 cases were divided into two groups: fetuses with severe cardiac anomalies were classified into group 1 and fetuses with complex cardiac anomalies were classified into group 2.

Upon autopsy, extracardiac malformations were classified into deformities involving the kidney, urinary tract, and genital system; central nervous system; gastrointestinal system; respiratory system; cleft lips/palate; limb anomalies; facial anomalies (retrognathia, low set ears); asplenia; situs inversus viscerum (complete/partial); and fetal hydrops.

Results

By sequential segmental analysis, the present authors ascribed a detailed diagnosis to each heart according to the necropsy result. The classification and subclassification of lesions found at necropsy among the 198 cases are summarized in Tables 1 and 2. In the study, the 198 cases were divided into two groups according to the prognosis of the fetus: group 1 described fetuses with severe cardiac anomalies which contained 90 cases and group 2 described fetuses with complex cardiac anomalies which contained 108 cases. Table 1 shows the spectrum of severe cardiac defects identified in necropsy of group 1. The most frequent malformations in group 1 were TOF, TGA, and AVSD. Table 2 shows the spectrum of complex cardiac defects identified in necropsy of group 2. The malformations such as heart with univentricular atrioventricular connection (UVH), truncus arteriosus communis (TAC), double outlet right ventricle (DORV), hypoplastic left heart, hypoplastic right heart and TGA with pulmonary stenosis (PS) were present in the spectrum of group 2, which constituted 54.5% (108/198)

Table 3. — *Classification and frequency of extracardiac malformations associated with congenital heart defects.*

Type of defect	Total
Kidney, urinary tract, and genital system	32
Central nervous system	18
Cleft lips/palate	17
Limb anomalies	20
Facial anomalies	11
Gastrointestinal system	8
Respiratory system	4
Fetal hydrops	4
Asplenia	28
Situs inversus viscerum	27

In the study, there were 104 cases (52.5%) associated with severe and/or multiple extracardiac anomalies. The most frequent extracardiac malformations involved the kidneys and urinary tract and genital system.

Table 4. — *Chromosome anomalies in fetuses with congenital heart defects.*

Chromosome anomaly	Total	Type of cardiac defects (number)
Trisomy 18	14	UVH (2), TOF (4), HLH + coarctation of the aorta (1), AVSD + TAC (1) VSD + DORV (2), TGA + VSD (2) TGA + VSD + PS (1), Coarctation of the aortic arch (1)
Trisomy 13	8	AVSD (1), TOF (1), HLH + Aortic atresia (1) UVH + TAC (1), TAC (3), DORV + VSD (1)
Trisomy 21	6	AVSD (5), TOF (1)
Chromosome structural anomalies	6	TOF (4), TGA (1), UVH + aortic atresia (1)
Total	34	

AVSD: atrioventricular septal defect; DORV: double outlet right ventricle; HLH: hypoplastic left heart; PS: pulmonary stenosis; TAC: truncus arteriosus communis; TOF: tetralogy of Fallot; UVH: heart with univentricular atrioventricular connection; VSD: ventricular septal defect.

of the malformations in the present necropsy population.

CHDs were associated with severe and/or multiple extracardiac anomalies in 104 cases (52.5%), which were detected and confirmed at necropsy. The classification and frequency of extracardiac malformations associated with CHD among the 198 cases are summarized in Table 3. The most frequent extracardiac malformations involved the kidneys and urinary tract and genital system.

Chromosome abnormalities were diagnosed in 34 of the fetuses (17.2%). Trisomy 18 was the most frequent abnormality associated with CHD (Table 4). The type of heart malformations including UVH, TOF, TGA, and DORV were identified in trisomy 18. AVSD were more frequent with trisomy 21.

Discussion

CHDs are the most common congenital anomalies in fetuses; the incidence of CHD with intrauterine diagnosis range from 2.4% to 50% in different countries [9]. In prenatal ultrasound investigations, the four-chamber view, incorporating visualization of the outflow tracts and the great arteries into the scanning protocol, increased the detection rate from 65–70% [10]. In China, ultrasound imaging in the second trimester is now widely used for routine screening of pregnancies for fetal malformations. There has been a recent increase in abnormal cardiac findings during obstetric ultrasonography screenings, with most congenital anomalies found among fetuses from pregnancies with no risk factors. Prenatal diagnosis of CHD leads to several options, such as termination of pregnancy, planning the timing, mode, and site of delivery to perform surgery on the neonate in the best conditions to improve the surgical outcome. Therefore, there is an increasing interest in improving evaluation of CHDs in prenatal life.

In the present study, the authors found that sequential segmental analysis is an effective method for determining congenital heart malformations and may improve understanding of cardiovascular anatomy. Understanding cardiovascular anatomy in cases of severe or complex CHD not only diagnoses CHD, but also can help predict prenatal prognosis and assess postnatal surgical effects for patients according to grading suggested by Choi *et al.* [8]. The sequential segmental analysis is logical and convenient, and because of its stepwise structure, ensures a thorough investigation [11]. The sequential segmental analysis of CHD has been proposed more than three decades ago [12]. It was introduced into fetal cardiac screening more than a decade ago [13] and has become a key requirement of current guides [14]. Although there was considerable discussion about some cases, none was unclassifiable by this analysis. Indeed, the approach provides a means of cataloguing and describing all congenital cardiac malformations, even if the combination of lesions has never previously been encountered. The present authors' experience suggests that sequential segmental analysis is an important requirement in the evaluation of congenital cardiac defects in prenatal life, combined with the grading suggested by Choi *et al.*, assist to make decisions regarding termination or continuation of the pregnancy. Accumulating experience on how to evaluate the prognosis of fetal CHD is not only beneficial to genetic counselling, but can also facilitate appropriate clinical management.

The present study showed the spectrum of CHD in fetuses which were detected by prenatal ultrasound screening and confirmed by postnatal necropsy. The 198 cases were divided into two groups: group 1 described fetuses with severe heart defects, TOF, TGA, and AVSD were the most frequent malformations in the group. Group 2 described fetuses with complex cardiac anomalies, heart with UVH, TAC, DORV, hypoplastic left heart, hypoplastic right

heart, and TGA with PS that are usually lethal, constituted 54.5% (108/198) of the malformations in the present necropsy population. The present results indicated that the cardiac defects in the study were more severe than those in previous pediatric cardiology surveys [4, 15]. There were two explanations for this: first, patients whose fetus presents with complex or serious congenital cardiac malformations were referred to the present tertiary center; second, the composition of the case population, which included only cases whose pregnancy was terminated in the event of complex or serious cardiac anomalies.

Prenatal investigations have shown that heart defects often accompany defects in other organ systems [16]. In the present study, over half of the cases (52.5%) with CHD also had extracardiac malformations. These findings point to the need to investigate the heart in cases of extracardiac anomaly and to look for extracardiac anomalies when cardiovascular malformations have been diagnosed. The most frequent extracardiac malformations in the study were anomalies involving kidney, urinary tract, and genital system. Among all the extracardiac malformations, cleft lips/palate, limb anomalies, and facial anomalies were quite frequent. These characteristic anomalies often occur in combination with CHD in some hereditary syndrome, such as heart-hand syndrome or velo-cardio-facial syndrome. The necropsy results confirmed that CHD not only occurred as an isolated defect in prenatal life, but also as a component part of a hereditary syndrome. The association between CHD and extracardiac malformations needs to be investigated, and this would improve the understanding of CHD etiology and would help in genetic counseling.

The frequency of chromosome abnormalities identified subsequent to discovery of a CHD varies between 16% [17] and 50% [18]. Among liveborn infants with heart defects, around 5% have chromosome abnormalities [19]. The incidence of CHD and fetal chromosome abnormalities is higher than in liveborn infants or stillbirths, as the fetuses often do not survive until birth and are therefore not included in statistical data collected by paediatric cardiologists. Trisomy 18 was the most frequent abnormality detected in the present study, suggesting that cardiac malformations are universal in trisomy 18; moreover, the types of CHD seen with trisomy 18 are more varied than other associated chromosome abnormalities. It is well recognized that the types of CHD seen in trisomy 18 are more varied than those associated trisomy 21 [19]. Different abnormal chromosome karyotypes contribute to different types of CHD. This supports the viewpoint that chromosome abnormalities are associated with CHD, but are not a major component of its etiology. Cardiac development is regulated by complex mechanisms involving interaction between genetic and environmental factors [20]. The etiology of CHDs may be associated with extracardiac malformations and chromosome anomalies, but it deserves to be investigated further. The present authors' future investigations will be devoted to identifying the genes and modifying factors contributing to congenital heart malformations.

In summary, the systemic collection of data regarding fetal CHDs, including necropsy investigation, extracardiac malformations, and chromosome abnormalities, will provide an adequate basis for future genetic counseling and improvement of prenatal care for fetal CHDs in China.

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