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ORIGINAL RESEARCH

Classification of Fetal Congenital Heart Disease by Prenatal Ultrasound and Its Diagnostic Value

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Purpose: To evaluate diagnostic value of prenatal ultrasound in classifying fetal congenital heart disease (CHD) and to verify its diagnostic accuracy by comparing its results with postnatal pathological findings.

Methods: This retrospective study analyzed 372 pregnant women with fetal CHD, detected by ultrasound, who underwent interventional prenatal diagnosis. Prenatal CHD cases were classified at three levels. Pathological and anatomical examinations of CHD fetuses were performed in 305 pregnant women who terminated pregnancies; results were compared to those of prenatal ultrasonography.

Results: At first classification level, complex type accounted for 37.6% (140/372), predominated by double outlet right ventricle (DORV); severe 36.6% (136/372), represented by tetralogy of Fallot (TOF); and simple 25.8% (96/372), commonly ventricular septal defect (VSD). At second classification level, incidence of isolated was higher than that of syndromic [55.9% (212/372) vs 42.2% (160/372), $P<0.05$]. Facial dysplasia 24.2% (90/372) and skeletal system malformations 12.4% (46/372) were common. Incidence of simple CHD did not vary between isolated and syndromic [OR=1.017, 95% CI (0.636,1.626), $P=0.945$]. In contrast, incidence of severe [OR=2.126, 95% CI (1.366, 3.310), $P<0.001$] was high in isolated and that of complex [OR=0.478, 95% CI (0.312, 0.732), $P<0.001$] was high in syndromic. At third classification level, valvular disease accounted for 57.3% (213/372), and conotruncal defects (CTDs) 57.0% (212/372), were more prevalent in congenital cardiovascular anomalies. Incidences of VSD 70.4% (150/213) were high in all valvular diseases, with combined intracardiac and extracardiac malformations being 58% (87/150) and 42.7% (64/150), respectively. Among CTDs, TOF 25.5% (54/212) was common. Prenatal ultrasound and postnatal pathology revealed 92.5% (282/305) coincidence rate in CHD diagnoses.

Conclusion: Three-level classification method enables a comprehensive analysis of prenatal diagnosis and prognosis for fetal CHD, facilitating timely decision-making in clinical settings. Prenatal ultrasound plays an essential role in CHD diagnosis, facilitating implementation of clinical interventions tailored at halting this menace.

Keywords: fetal congenital heart disease, prenatal ultrasound, classification analysis, pathological anatomy, diagnostic value

Introduction

Fetal congenital heart disease (CHD) is a prevalent birth defect characterized by abnormal development of the fetus's heart and blood vessels, resulting in congenital malformation. Globally, its incidence rate ranges approximately between 8‰ and 12‰, presenting it as the most common severe congenital malformation in newborns.[1,2] The incidence rate of CHD differs across various global regions, with an estimated 8.2‰ in Europe and 6.9‰ in North America, further substantiating its significant prevalence worldwide.[3] Meanwhile, the birth rate of CHD in Asia is the highest among all continents, at approximately 9.3‰, with the incidence rate representing about 8‰ of live births in India in 2017,[4] which is comparable to the CHD incidence rate observed in China and other areas of Asia. From 2011 to 2013, the incidence rate of fetal CHD in China was 7.4‰.[1] Based on recent research, the prevalence of fetal CHD ranks highest among other types of birth defects in China.[5,6] Complex and severe cardiac malformations have emerged as the main cause of death in newborns and infants.[7,8] Specifically, among all infant and child mortalities related to congenital malformations, CHD accounts for 20–35% of infant deaths and 50% of childhood deaths.[9–11] In China, approximately 1.5 million children are

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living with CHD, with over 200,000 new cases identified among children, and about 20% of them being classified as complex, refractory, or at high risk of early postnatal mortality.[12] Most children endure prolonged illnesses that significantly diminish their quality of life, which hinders the improvement of the overall quality of the population in China and exerts a heavy burden on families and societies.

Epidemiological studies have shown that early diagnosis and administration of CHD therapeutic interventions can significantly improve the prognosis of this disease in newborns.[13,14] Moreover, prenatal diagnosis facilitates the implementation of targeted medical care interventions immediately after birth, thereby reducing the incidence of various complications. Since the late 1970s, prenatal diagnosis of CHD has been gradually implemented.[10] The ongoing improvements in the resolution of ultrasonic diagnosis have significantly enhanced prenatal ultrasonic diagnosis of fetal heart malformations. Fetal echocardiography is regarded as the main tool for diagnosis, prognosis formulation, and management of CHD, which can accurately detect approximately 85% of fetal heart abnormalities.[15] By using systematic and reliable fetal echocardiography, the structural and hemodynamic characteristics of the fetal heart can be presented, which facilitates accurate diagnosis of congenital heart malformations.[16] This approach enables the prediction of disease prognosis, the assessment of risk levels, and enhances accurate differentiation of various types and the severity of heart malformations, including fatal and non-fatal conditions.[17] In the late 1980s, fetal echocardiography technology was introduced and widely promoted in China, enabling basic hospitals to screen for CHD in fetuses.[18] With the progressive advancements in surgical techniques, most children with CHD who undergo surgical intervention can have their heart functions restored to normal or near normal levels.[19] Fetal birth defects associated with CHD are recognized for their complexity and diversity in anatomical malformations.[20] Moreover, most cardiac birth defects are often combined with various intracardiac and extracardiac malformations, posing significant challenges for accurate clinical evaluations.[21] Despite the progression of research tailored at determining the suitable diagnostic technique and treatment of fetal CHD, some challenges remain to be addressed. Currently, prenatal echocardiography still relies on two-dimensional (2D) ultrasound and Doppler ultrasound as the primary examination methods to obtain planar images of the heart structure and basic hemodynamic parameters.[22] However, these techniques are still limited to one-dimensional or local assessment and are difficult to meet clinical requirements for a comprehensive diagnosis of fetal CHD.[23] Advanced technologies, such as three-dimensional (3D)/four-dimensional (4D) echocardiography, have significantly improved diagnostic capabilities. They can achieve the reconstruction of the heart's spatial structure or the precise estimation of cardiac volume.[24] However, due to the complexity of technical operation and the high requirements for equipment and personnel, they have not been extensively adopted in clinical practice.[25] Furthermore, recent classification methods rely solely on pathological anatomic features and fail to adequately incorporate hemodynamic changes, leading to inaccurate assessment of the severity and prognosis of fetal CHD.[26,27] Meanwhile, there are two fundamental issues in the clinical diagnosis and treatment of fetal heart birth defects.[17] Firstly, there is a lack of nationally standardized guidelines for diagnosis and clinical evaluation. Secondly, standardized diagnostic criteria and an individualized evaluation system based on diseases' classification and their severity have not been established.

This study employs a three-level classification method to examine the prenatal ultrasound results of 379 cases of fetal CHD, conduct an in-depth analysis of the characteristics of fetal CHD, and systematically determine the prevalence of various cardiac structural abnormalities. It also aims to comprehensively evaluate the value of ultrasound in diagnosing fetal CHD via comparisons of the results of prenatal ultrasound and postnatal pathological examinations. Moreover, this research will provide novel insights and a robust clinical foundation for developing clinical evaluation systems, including consultations and guidance on the mechanisms of fetal CHD.

Materials and Methods

Subjects

This study retrospectively enrolled 372 pregnant women who were admitted to the Department of Prenatal Diagnosis of Women and Children's Hospital, Xiamen University, from January 1, 2017, to December 31, 2023. These women received interventional prenatal diagnosis due to fetal CHD identified by Doppler ultrasound. Inclusion criteria: (1) Regularly received prenatal check-ups; (2) Women who had a singleton pregnancy; (3) Women who had no

complications such as gestational hypertension or diabetes. Exclusion criteria: (1) The presence of coagulation dysfunction; (2) Combined with malignant tumors; (3) Patients whose clinical records were missing. The data collected from pregnant women included their age, the results of prenatal examination based on the findings of color ultrasound and fetal echocardiogram, follow-up outcomes of the pregnancies, and autopsy results. Pregnant women and their families were informed about the indications and potential risks of interventional puncture before they could sign an informed consent for the surgery. This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Women and Children's Hospital, Xiamen University (Approval Number: KY-2024-147-H01).

Ultrasonic Examination

GE Voluson E8, Philips iU22, and Siemens ACUSON Sequoia512 color Doppler ultrasonic diagnostic instruments were used to conduct ultrasound examinations, and a probe frequency of 2.0~6.0 MHz was recorded. The examination was performed according to an established fetal system and cardiac examination. Firstly, a routine obstetrical examination was performed to determine fetal position, the location of the fetus' heart in the chest and alignment with the internal organs, and to determine the apex of the heart. Conventional imaging views such as the apical 4-chamber (4C), apical 5-chamber (5C), left ventricular outflow tract (LVOT), right ventricular outflow tract (RVOT), three-vessel, and aortic arch were displayed. The size of each ventricle was measured, and the location and dimensions of the identified ventricular septal defect (VSD) were described. Ultrasonic Color Doppler imaging was used to measure and characterize the directions of intracardiac shunt and flow rates at different levels.

Fetal CHD Classification Standard

First Classification Level

According to the prognosis of the fetus, cardiac malformations were categorized into four types: simple, severe, complex, and special.[28] Simple CHD primarily encompasses conditions such as VSD, atrial septal defect (ASD), and abnormal position and direction of the aortic arch. Patients with these conditions typically experience mild symptoms at birth, accompanied by minor or no significant hemodynamic alterations. They can be followed up for a certain period, undergo spontaneous healing, or require elective surgical interventions.[29] In contrast, severe CHD is a defect that can be resolved by surgical interventions, with minimal risk of reoperation, such as tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), and complete transposition of the great arteries (TGA).[30] Complex CHD is a defect that can be surgically corrected in terms of anatomy, likely to result in sequelae or require Fontan surgery, such as single atrial single ventricle (SV), double outlet right ventricle (DORV), TGA with pulmonary stenosis, and hypoplastic left heart syndrome (HLHS).[31,32]

Second Classification Level

Cardiac malformations are characterized into isolated and syndromic types based on their association with congenital defects in other systems. Notably, isolated CHD occurs independently, without any associated anomalies in other systems. On the other hand, syndromic CHD involves the presence of CHD along with congenital defects in other organs, including abnormal kidney development, limb deformity, cleft lip and palate, and special facial features.

Third Classification Level

Sequential segmental analysis[33] was used to classify cardiac malformation into: (1) Valvular diseases including VSD, endocardial cushion defect (ECD), tricuspid valve disease, mitral valve disease, pulmonary valve disease, and aortic valve disease; (2) Conotruncal defects (CTDs) including DORV, TOF, TGA, persistent truncus arteriosus (PTA), aortic valve atresia, pulmonary atresia, coarctation of aorta and aortic arch, and interruption of the aorta and aortic arch; (3) Ventricular dysplasia including left ventricular dysplasia, and right ventricular dysplasia; (4) Vascular diseases involving persistent left superior vena cava (PLSVC), anomalous pulmonary venous return (APVR), pulmonary stenosis, aorta and aortic arch hypoplasia, anomalies in the position, number, and branches of the aortic arch, inferior vena cava atresia (IVC), and interrupted IVC; (5) Single atrium (SA) and SV; (6) Cardiac malposition.

Local Pathological Anatomical Examination of the Heart

In 305 cases of pregnancy termination resulting from fetal CHD, a pathologic and anatomic examination of the fetal heart was performed 24 hours after the procedure. Due to the characteristics of the fetal heart, such as smaller size, complexity of internal structure, and variable blood vessels, the primary techniques employed involve the integration of in-situ observation and post-mortem examination after ex vivo fixation.[13] This process was conducted in five steps: thoracic cardiovascular exposure, in-situ cardiac assessment, cardiopulmonary tissue sampling, cardiac autopsy, and recording of the specimen.

Thoracic Cardiovascular Exposure

This procedure commenced with the right anterior axillary approach to resect the chest wall, isolate and remove the thymus tissue, and provide complete visibility of the major vessels located at the base of the heart and pericardium. Parallel bilateral incisions were made at the base of the pericardium, extending to the head end to cut the pericardium; the pericardium tissue at the connection between the heart and blood vessels was completely incised.

In-situ Cardiac Assessment

This process involved observing the in-situ cardiac, yielding important information that can be used to design more appropriate autopsy methods to determine the hearts exhibiting complex CHD. This investigation revealed the following key anatomic traits: (1) characteristics of the heart such as its position, axis, volume and shape; (2) atrial arrangement and anatomical characteristics of the auricle; (3) The relationship between the vein, pulmonary vein and the atrium; (4) the spatial position and the diameter of large arteries; (5) external morphological characteristics of atrial ventricle; (6) distribution and branching patterns of the coronary artery; (7) examination of the continuity between the aortic arch and descending aorta through pulmonary displacement.

Cardiopulmonary Tissue Sampling

In a sterile environment, large cervical vascular branches, including the common carotid artery and internal jugular vein, along with the tracheoesophagus, were first ligated and severed. The mediastinal connective tissue was transected in the plane of the diaphragm and cardiopulmonary complex comprising the heart, two lungs, and connected great vessels. This complex was promptly placed in a 10% neutral formalin fixation solution, where it was allowed to fix for 48 hours at room temperature.

Cardiac Autopsy

Multiple techniques were integrated to select a suitable autopsy strategy. The first method employed was blood flow direction autopsy performed in 6 steps: 1) conducting a longitudinal incision along the line connecting the superior vena cava and inferior vena cava on the anterior wall of the right atrium, followed by a transverse cut at the base of the right auricle. The morphology of the vena cava entrance, the opening position of the coronary sinus, and the closure of the foramen ovale were evaluated; (2) to observe the continuity of the atrioventricular septum and the development of trabecular structures in the right ventricular muscle, a tricuspid valve septum was incised. Alternatively, longitudinal incision was made along the anterior wall of the RVOT while preserving the intactness of the tricuspid valve; (3) the main pulmonary artery was cut along the funnel of the right ventricle to assess the number of lobes in the pulmonary valve and the development of the branches on the left and right pulmonary arteries; (4) annular incision was conducted at the posterior wall of the left atrium at the junction of the pulmonary vein, and the mode of pulmonary vein confluence was recorded; (5) the anterior lobe of mitral valve was cut from the left atrium to the left ventricle, and the diameter of the AVSD and the size of the left ventricular cavity were measured; (6) the ascending aorta was cut from the LVOT to observe the morphology of the aortic valve, the opening position of the coronary artery and the development of the ascending aorta. A window dissection method suitable for infants with low weight (<2500 g) or those exhibiting complex cyanotic CHD specimens was employed. Subsequently, a 5–8 mm tissue window was removed by microshear in non-diseased areas such as the free wall of the right atrium to examine the relationship between the spatial adjacency of cardiac malformations. Some cases were examined directly in the body, and the general principle was that specified conditions of the deformity could be accurately displayed.

Recoding of the Specimen

Imaging records were made throughout the anatomy, including preoperative in-situ morphology, intraoperative anatomical details, and postoperative pathological features, and standardized graphic files were established.

Pregnancy Outcome Follow-Up

All enrolled pregnant women received outpatient care, and follow-ups were conducted through the telephone. Detailed information about pregnancy outcomes, neonatal birth defects, and prognosis was recorded.

Statistical Analysis

SPSS version 25.0 was used for data analysis. The data was expressed as percentages (%) and numbers (n). The χ^2 test was used to compare data across the groups. $P<0.05$ was considered statistically significant.

Results

Classifications of Fetal CHD Based on Prenatal Ultrasound

First Classification Level

The 372 pregnant women with fetal CHD included in this study had an average age of 29.9±3.7 (range, 20–44) years, and were classified in the following CHD types: simple, 96 (25.8%); severe, 136 (36.6%); and complex, 140 (37.6%) (Table 1). The results revealed that severe and complex types of CHD were the most prevalent, accounting for 74.2% (276/372). Within the simple CHD category, VSD 70.8% (68/96) was predominant, while TOF 39.7% (54/136) was most common in severe CHD classification. DORV 30.0% (42/140) was most common in the complex type.

Second Classification Level

Among 372 cases of fetal CHD, 212 (55.9%) were isolated CHD without exhibiting combined extracardiac malformations, while 160 (42.2%) were categorized as syndromic CHD with combined extracardiac malformations. The results showed that the incidence of isolated CHD in the fetal period was significantly higher than that of syndromic CHD ($P<0.05$). These were further categorized into facial dysplasia according to the frequency of extracardiac malformations, they were divided into 24.2% (90/372, malformation of the skeletal system 12.4% (46/372), heterotaxy (HTX) 8.3% (31/372), cervix hygroma 7.3% (27/372), digestive system malformation 7.0% (26/372), hydrops foetalis 4.8% (18/372), renal and urogenital system malformation 4.3% (16/372), central nervous system malformation (CNSM) 3.5% (13/372) and abdominal wall defect 3.0% (11/372) (Table 2). Among them, facial dysplasia and skeletal system malformations were the most frequent extracardiac malformations. By combining the results of the first level classification, the study found that there were no significant variations between the incidence of simple CHD in isolated and syndromic CHD [OR=1.017, 95% CI (0.636,1.626), $P=0.945$]; the incidence of severe CHD was significantly higher in the isolated CHD cases than those in syndromic CHD [OR=2.126, 95% CI (1.366, 3.310), $P<0.001$] while the incidence of complex CHD

Table 1 First Classification Level of Cardiac Malformations in 372 Fetuses with CHD

CHD Type n(%)	Cardiac Malformations n(%)
Simple 96(25.8)	VSD 68(70.8), right aortic arch 16(16.7), pulmonary stenosis 11(11.5), PLSVC 5(5.2), double aortic arch 3(3.1), IIVC-AC 2 (2.1), aortic valve stenosis 1(1.0)
Severe 136(36.6)	TOF 54(39.7), TGA 21(15.4), ECD 18(13.2), coarctation of aorta 17(12.5), aortic stenosis 10(7.4), Ebstein's anomaly 4 (2.9), IAA 3(2.2), PA/IVS 2(1.5), TS 2(1.5), TR 2(1.5), absent aortic valve 2(1.5), aortic dysplasia 2(1.5), TA 1(0.7), tricuspid valve dysplasia 1(0.7)
Complex 140(37.6)	DORV 42(30.0), HLHS 35(25.0), SV 31(22.1), PTA 27(19.3), SA 15(10.7), ARVD 14(10.0), APVR 14(10.0), DOLV 1(0.7)

Abbreviations: CHD, congenital heart disease; VSD, ventricular septal defect; PLSVC, persistent left superior vena cava; IIVC-AC, interrupted inferior vena cava with azygous continuation; TOF, tetralogy of Fallot; TGA, transposition of the great arteries; ECD, endocardial cushion defect; IAA, interrupted aortic arch; PA/IVS, pulmonary atresia with intact ventricular septum; TS, tricuspid stenosis; TR, tricuspid regurgitation; TA, tricuspid atresia; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; SV, single ventricle; PTA, persistent truncus arteriosus; SA, single atrium; ARVD, arrhythmogenic right ventricular dysplasia; APVR, anomalous pulmonary venous return; DOLV, double outlet left ventricle.

Table 2 Second Classification Level of Cardiac Malformations in 372 Fetuses with CHD

Types of Extracardiac Malformations n(%)	Symptoms n(%)
Facial dysmorfism 90(24.2)	Wide interocular distance+low-set ears+micrognathia 70(77.8), cleft lip and palate 15(16.7), otodysplasia 2 (2.2), ocular anomalies 1(1.1)
Skeletal system malformation 46 (12.4)	Finger dysplasia 26(56.5), talipes equinovarus 5(10.9), abnormal posture 3(6.5), spinal deformities 3(6.5), cranial dysplasia 3(6.5), upper limb mesomelic dysplasia 2(4.4), shortness of the extremities 1(2.2), occipital bone defect 1(2.2), achondroplasia 1(2.2)
HTX 31(8.3)	/
Cervix hygroma 27(7.3)	/
Digestive system malformation 26(7.0)	Asplenia 16(61.5), pancreatic hypoplasia 4(15.4), esophageal atresia 2(7.7), anal atresia 2(7.7), polysplenia 2 (7.7), gallbladder hypoplasia 2(7.7), diaphragmatic hernia 1(3.9)
Hydrops foetalis 18(4.8)	/
Renal and urogenital system malformation 16(4.3)	Renal dysplasia 9(56.3), reproductive system dysplasia 6(37.5), ureteral malformation 4(25.0)
CNSM 13(3.5)	Cerebral hypoplasia 7(53.9), holoprosencephaly 3(23.1), exencephaly 2(15.4), cerebellar hypoplasia 2(15.4)
Abdominal wall defect 11(3.0)	Omphalocele 9(81.8), thoracoceloschisis 2(18.2)

Abbreviations: CHD, congenital heart disease; HTX, heterotaxy; CNSM, central nervous system malformation.

was significantly higher in syndromic CHD than in isolated CHD [OR=0.478, 95% CI (0.312, 0.732), $P<0.001$] (Table 3).

Third Classification Level

According to the "Atlas of Prenatal Ultrasonography and Pathological Anatomy of Fetal Malformations",[30] a continuous segmental analysis was used to classify 372 fetal CHD cardiac malformations at the third classification level. These malformations were divided into six categories of congenital cardiovascular malformations, including 213 (57.3%) cases of valvular diseases, 212 (57.0%) cases of CTDs, 130 (34.9%) cases of vascular diseases, 49 (13.2%) cases of ventricle dysplasia, 34 (9.1%) cases of SA and SV, and 18 (4.8%) cases of cardiac malposition (Table 4). The results showed that the prevalence of congenital cardiovascular malformations in fetal CHD was valvular diseases and CTDs. Among valvular diseases, VSD was the most common, accounting for 70.4% (150/213), while TOF was the most common, 25.5% (54/212), in the CTDs. VSD alongside other intracardiac malformations 58% (87/150) and extracardiac malformations 42.7% (64/150) was prevalent.

Comparative Analysis of Prenatal Ultrasound and Postnatal Pathological Examination Results

Among 372 pregnant women with fetal CHD, 305 pregnancies were terminated due to factors such as severe or complex fetal CHD, and multiple or severe fetal extracardiac malformations. Further pathological and anatomical examinations were performed on the fetus after delivery. The results showed that the prenatal ultrasound findings for 282 women aligned with the postnatal pathological findings, with a diagnosis coincidence rate of 92.5%. However, 23 cases had inconsistent results (Table 5). Prenatal ultrasonography indicated the presence of simple cardiac malformations, while

Table 3 Prognostic Typing of Cardiac Malformations in Isolated and Syndromic CHD

First Classification Level	Second Classification Level		OR (95% CI)	*P*
	Isolated CHD (n=160)	Syndromic CHD (n=212)		
Simple CHD	41	55	1.017 (0.636, 1.626)	*P*=0.945
Severe CHD	43	93	2.126 (1.366, 3.310)	*P*<0.001
Complex CHD	76	64	0.478 (0.312, 0.732)	*P*<0.001

Abbreviations: CHD, congenital heart disease; OR, odds ratio; CI, confidence interval.

Table 4 Third Classification Level of Cardiac Malformations in 372 Fetuses with CHD

Classification	Numbers	Combined with Intracardiac Malformation	Combined with Extracardiac Malformation
Valvular diseases	213	130	93
VSD	150	87	64
ECD	32	18	23
Tricuspid valve lesion	17	17	4
Mitral valve lesion	13	13	3
Pulmonary valve lesion	13	7	3
Aortic valvular lesion	7	7	3
CTDs	212	154	82
TOF	54	16	14
DORV	42	42	27
Coarctation of aortic arch	39	33	15
PTA	27	26	14
TGA	26	14	8
COA	20	19	6
Aortic valve atresia	7	7	1
IAA	5	5	2
Pulmonary atresia	2	2	1
DOLV	1	1	1
Ventricular dysplasia	49	44	23
Left ventricular	35	31	19
Right ventricular	14	13	4
Vascular diseases	130	107	60
Pulmonary stenosis	51	47	31
Right aortic arch	38	25	16
PLSVC	36	36	11
APVR	14	12	12
Aortic dysplasia	5	5	2
Double aortic arch	4	2	1
AAH	2	2	0
IVC	2	2	2
LAA	1	0	1
Atretic IVC	1	1	1
SA and SV	34	28	21
Cardiac malposition	24	24	20

Abbreviations: CHD, congenital heart disease; VSD, ventricular septal defect; ECD, endocardial cushion defect; CTDs, conotruncal defects; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; PTA, persistent truncus arteriosus; TGA, transposition of the great arteries; COA, coarctation of aorta; IAA, interruption of the aortic arch; DOLV, double outlet left ventricle; PLSVC, persistent left superior vena cava; APVR, anomalous pulmonary venous return; AAH, aortic arch hypoplasia; IVC, interrupted inferior vena cava; LAA, left-sided aortic arch; IVC, inferior vena cava; SA, single atrium; SV, single ventricle.

Table 5 Inconsistent Results of Cardiac Malformations in 23 Cases of Prenatal Ultrasound and Postpartum Autopsy

Types of Cardiac Malformations by Prenatal Ultrasound	Types of Cardiac Malformations in Postpartum Autopsy	Number
Simple	Complex	1
Severe	Simple	1
	Complex	7
Complex	Simple	4
	Severe	10

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postnatal pathologic examination revealed complex cardiac malformations in 1 case. Additionally, prenatal ultrasonography detected multiple malformations with VSD, while postnatal pathologic examinations indicated DORV with VSD. Prenatal ultrasonography indicated severe or complex cardiac malformations, while postnatal pathologic examination indicated simple cardiac malformations in 5 cases. Among these, 3 cases were incorrectly diagnosed as DORV, 1 case as SV, and 1 case as severe TR, which was not validated in postnatal pathologic examination. Prenatal ultrasonography revealed the presence of severe cardiac malformations while the subsequent postnatal pathologic examinations showed complex cardiac malformations in 7 cases, among which 4 of them were undetected by DORV examinations; the ultrasonography assessment of 3 cases exhibited endocardial cushion defect and postnatal pathologic examinations confirmed SV. Prenatal ultrasonography findings indicated the presence of complex cardiac malformations, while postpartum pathological examinations identified 10 cases of severe cardiac malformations, which were reflected by the inconsistencies in the diagnosis of valvular diseases and CTDs. Valvular diseases showed inconsistent diagnoses, involving endocardial cushion defect, SA, and SV. Similarly, CTDs showed inconsistent diagnoses of DORV, single arterial trunk, and TGA. The results of this study also indicated that CTDs, particularly DORV, are more likely to be missed and misdiagnosed during prenatal ultrasonography.

Discussion

Classification of Cardiac Malformations in Fetal CHD

The cardiovascular system of the fetus differs significantly from that of newborns due to the unique features of placental and umbilical circulation, high resistance in pulmonary circulation, and the absence of a fully developed respiratory function.[34] Consequently, pulmonary vascular abnormalities do not significantly affect fetal intrauterine development, which considerably complicates the diagnosis of fetal CHD. Our study systematically classified fetal CHD to improve the accuracy of prenatal diagnosis and facilitate the implementation of subsequent interventions.

At present, pregnant women seeking prenatal diagnosis for fetal CHD are advised to consult with obstetricians, cardiac surgeons, and pediatricians for prenatal counseling.[35,36] Based on the outcomes and prognosis of CHD, fetal CHD has been divided into simple, severe, and complex types. The first classification level of 372 cases of fetal CHD revealed a notably high proportion of severe and complex CHD, accounting for 74.2%, a value that is significantly higher than that of infants. Among them, severe CHD accounted for 36.6% of all cases, with TOF being the most prevalent, while complex CHD represented 37.6%, with DORV being the most common. This classification prevents inappropriate induction of labor or retention of fetuses, thereby reducing the rate of birth defects in newborns. By categorizing the severity of CHD, the parents of the fetuses and the healthcare providers can make more informed decisions regarding the fate of the fetuses, ensuring that medical decisions are based on robust scientific principles.

According to the latest research, 25–50% of CHD patients exhibit at least one or more extrinsic malformations, essential for disease prognosis at birth, long-term quality of life, and the evaluation of chromosomal abnormalities.[37–40] In our study, 372 cases of fetal CHD were classified into isolated CHD (55.9%) and syndromic CHD (42.2%). Consistent with the results reported by Karatza et al[41] the incidence of isolated CHD was higher than that of syndromic CHD. Moreover, the incidence of simple CHD did not differ significantly from isolated CHD and syndromic CHD when combined with the results of the first-level classification. The incidence of severe CHD was significantly higher than that of isolated CHD. The incidence of complex CHD in syndromic CHD was substantially higher than that of isolated CHD, indicating that the incidence of isolated CHD in severe CHD is higher than that of extracardiac malformations in complex CHD. Furthermore, our study also found that facial dysmorphisms and malformations of the skeletal system occurred more frequently in extracardiac malformations. This differed from the results reported by previous research, which indicated that CNSM, urogenital system malformations, and digestive system malformations accounted for relatively high proportions.[42–44] The intricate development of the embryonic heart has resulted in incomplete elucidation of the disease's pathogenesis, causing considerable variability in congenital cardiovascular malformations, which revealed a significant heterogeneity. Complex CHD often involves multiple anatomic malformations, and a clear clinical diagnosis can typically be made when an atrioventricular structure is in a normal position. However, in cases of complex

malformations such as TGA, SV, and dextrocardia, the potential for missed or incorrect diagnoses is heightened by spatial relationship disorders.[45]

Sequential segmental analysis was initially employed to conduct pathological and anatomical diagnoses of CHD, focusing on potential changes found at the atrioventricular and ventricular artery junctions, therefore, to solve heterogeneous diagnoses of congenital cardiovascular malformations, our study used continuous segmental analysis to classify cardiac malformations in 372 fetal CHD cases at the third level. These malformations were further classified into six categories: valvular diseases, CTDs, ventricular dysplasia, SA, SV, and cardiac malposition. The results showed that valvular diseases and CTDs were prevalent in fetal CHD cases. Among them, VSD emerged as the most common in valvular diseases and TOF was identified as the most predominant in CTDs. VSD has a high incidence rate represented by 58% incidence rate when combined with other intracardiac malformations and has a 42.7% incidence rate when combined with extracardiac malformations. Our study revealed that employing segmental analysis to examine complex CHD enables classification based on the segmental system from the large veins to the large arteries. All congenital cardiovascular malformation lesions can be classified and described in the segmental system, significantly enhancing the accuracy of CHD diagnosis and serving as a reliable method for determining congenital heart malformations.

In summary, the three-level classification approach adopted in this study facilitated a thorough analysis of fetal CHD from various dimensions, such as the severity of cardiac malformations, the state of complicated extracardiac malformations, and specific cardiac lesions. This multifaceted approach is crucial for making informed decisions about whether to proceed with fetal removal or retention, which consequently influences the timing of postnatal treatment, the formulation of surgical strategies, and the evaluation of the prognosis.

Value of Prenatal Ultrasound in the Diagnosis of Fetal CHD

The guidelines for fetal heart ultrasound screening established by the International Society of Ultrasound in Obstetrics and Gynecology (IUSOG) indicate that the optimal period for assessing fetal heart structure is between 18 and 22 weeks of gestation.[46] Domestic guidelines recommend prenatal ultrasound examinations during pregnancy be conducted in three essential timeframes, first trimester ($11–13^{+6}$ weeks), second trimester (20–24 weeks), and third trimester (28–34 weeks).[47] Fetal echocardiography conducted during the second trimester is the optimal method for evaluating the structure and function of the fetal heart during prenatal assessments. It demonstrated a sensitivity of 85%, a specificity of 97.28%, and an accuracy of 97.03% in the diagnosis of fetal CHD.[48,49] In our study, 305 cases were terminated due to fetal CHD. The results from postnatal pathological and anatomical examinations indicated that the diagnostic coincidence rate of prenatal ultrasound and postnatal pathological diagnoses was 92.5%, closely aligned with the existing literature.[50] This demonstrates that fetal cardiac ultrasound screening serves as the primary technology for the prenatal visual diagnosis of fetal heart defects and plays a crucial role in reducing perinatal mortality associated with CHD and neonatal CHD incidence.

At present, two-dimensional fetal cardiac ultrasound screening remains the primary method for evaluating fetal cardiac structure during prenatal examinations.[51] It involves a rich system of standard section detections, including the apical 4C view, LVOT view, RVOT view, epigastric transection view, three-vessel view, three vessels and trachea (3VT) view, aortic arch long-axis view, ductus arteriosus arch long-axis view, superior and inferior vena cava long-axis view, aortic isthmus and ductus arteriosus-descending aorta oblique and coronary view, and tracheobronchial coronary view. Many studies[48,52–54] on fetal heart ultrasound screening have been carried out at home and abroad, and the results show that its sensitivity fluctuates greatly and its specificity remains at a high level. Studies indicated a notable disparity in the sensitivity of a single 4C view screening in low-risk and high-risk pregnancy groups.[55,56] However, the integrated application of 4C+LVOT+RVOT views demonstrates vital advantages in the efficiency of CHD detection. Its convenient application, short inspection time, and high sensitivity have led to its adoption as a standard screening process in clinical practice.[57] Shengli Li, an expert in domestic ultrasound, emphasized that the number of sections examined for assessing fetal heart structure influences the accuracy of prenatal diagnosis, and a high number of sections necessitates high technical proficiency and elongates the duration of the examination. When irregularities in cardiac structures are identified, conducting multiple-section evaluations of these improves the sensitivity and specificity of prenatal ultrasound diagnoses for CHD, thereby minimizing the probability of missed and incorrect diagnoses.

Although prenatal ultrasound plays a vital role in the diagnosis of fetal CHD, there are still some limitations. Various factors, including the constraints of the ultrasound technique, the position of the fetus, frequency of fetal movements, anatomical structure of a fetal cardiovascular system, small blood flows, and a poor acoustic window in pregnant women, may lead to missed or inaccurate diagnoses of fetal cardiac malformations. As gestational age increases, some diseases may progress or regress. In addition, the unique characteristics of fetal circulation, with variations in fetal cardiac structure and hemodynamics before and after birth, will also introduce uncertainties in the evaluation of prenatal ultrasound.[52] Ma et al[58] analyzed 94 fetal CHD cases and identified 8 cases of misdiagnosis (8.51%) and 6 cases of misdiagnosis (6.38%). The majority of cardiac malformations that were either missed or misdiagnosed were CTDs. These misdiagnoses and missed diagnoses are attributed to various factors, including maternal age >35 years, number of prenatal examinations <3, oligohydramnios, presence of abdominal wall scars, and higher body mass index. In our study, we identified 4 (1.42%) cases of missed diagnoses and 19 (6.74%) cases of incorrect diagnoses of cardiac malformations, mainly caused by CTDs, particularly DORV. This may be attributed to the dynamic changes in the morphology of the conotruncal region and the relationship among the great vessels during the fetal period, resulting in a subtle or unclear presentation during the first or second trimester of the pregnancy. Therefore, in cases where there are risk factors for inaccurate diagnosis and missed diagnosis, it is essential to conduct systematic examinations, raise awareness, and lower the rates of missed diagnosis and misdiagnosis.

Ultrasound is currently the preferred non-invasive diagnostic technique for fetal CHD. Its clinical application is limited by factors such as the tiny anatomical structure of the fetal heart, the complex hemodynamics, the difficulty in obtaining standard sections due to variable fetal positions, and the inherent limitations of ultrasound. As a result, not all fetal CHD cases can be diagnosed through prenatal ultrasound. The application of spatiotemporal image correlation (STIC) technology enables dynamic analysis of 3D volumetric data of the fetal heart, thereby improving the efficiency of prenatal diagnosis in fetal CHD. Research indicates that this technique offers considerable benefits in terms of accuracy, sensitivity, and specificity in diagnosing fetal CHD.[59] Nevertheless, despite the swift advancements in medical imaging, molecular biogenetics, and related fields, the prenatal diagnosis of fetal CHD continues to encounter significant obstacles. Future developments and extensive adoption of standardized screening and diagnostic techniques, along with the establishment of collaborative multi-disciplinary approaches in diagnosis, treatment, and consultation, will enhance the precision of prenatal diagnosis for fetal CHD.

Limitations

This study is a retrospective study, which inevitably has selection bias. Additionally, postnatal pathologic autopsy was not performed on some cases, which may affect the assessment of diagnostic accuracy. Future research can expand the sample size and improve the reliability of the research through prospective cohort studies. With the progressive advancement of ultrasound technology, including the application of 3D ultrasound and fetal echocardiography, the diagnostic potential for complex CHD is anticipated to improve. Additionally, many fetal CHDs are closely related to genetic factors, and genetic testing can clarify the pathogenesis, assess the severity, and predict the prognosis. Since our study did not investigate the impact of genetic factors on fetal CHD, the findings of this study did not provide comprehensive and accurate diagnosis and treatment recommendations. Subsequent research can incorporate genetic testing, which complements prenatal ultrasound technology, to provide extensive, in-depth information for the classification and diagnosis of fetal CHD to improve the clinical diagnosis and treatment levels.

Conclusion

This study employed a three-level classification method to conduct a systematic analysis of fetal CHD from multiple dimensions, including types of cardiac structural abnormalities, severity of lesions, and combined malformations, providing an important reference for the selection of intervention timing and the formulation of treatment plans in clinical practice. Additionally, our findings revealed that the concordance rate between prenatal ultrasound diagnosis and postnatal pathological diagnosis was 92.5%, confirming the high clinical value of ultrasound screening in the diagnosis of fetal CHD. However, this approach is limited by many factors, and not all cases can be definitively diagnosed. There are also cases of missed diagnosis and misdiagnosis. Given that prenatal diagnosis of fetal CHD still has some challenges, it

is necessary to establish standardized screening and diagnostic methods in the future and construct a multidisciplinary collaborative model (such as ultrasound combined with genetic testing) to improve diagnostic accuracy.

Abbreviations

APVR, pulmonary venous return; ASD, atrial septal defect; AVSD, trioventricular septal defect; CHD, congenital heart disease; COA, Coarctation of aorta; CTDs, conotruncal defects; 2D, two-dimensional; 3D, three-dimensional; 4D, four-dimensional; DOLV, Double outlet left ventricle; DORV, double outlet right ventricle; ECD, endocardial cushion defect; HLHS, hypoplastic left heart syndrome; IAA, Interruption of the aortic arch; IVC, inferior vena cava atresia; LVOT, left ventricular outflow tract; PTA, persistent truncus arteriosus, PLSVC, persistent left superior vena cava; RVOT, right ventricular outflow tract; RVOT, right ventricular outflow tract; SA, Single atrium; SV, Single ventricle; TOF, tetralogy of Fallot; TGA, transposition of great arteries; VSD, Ventricular septal defect.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics Approval and Consent to Participate

All the patients signed an informed consent before they participated in this study. This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Women and Children's Hospital, Xiamen University (Approval Number: KY-2024-147-H01).

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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