Echocardiographic and pathomorphological features in fetuses with ductal-dependent congenital heart diseases

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Abstract

Objective: To individually analyze echocardiographic features in fetuses with ductal-dependent congenital heart diseases (DDCHD) and to verify the anatomical characteristics corresponding to the echocardiogram scan views.

Background: Ductal-dependent congenital heart diseases depends on the ductus arteriosus (DA) remaining open to maintain suitable pulmonary or systemic circulation after birth. An accurate diagnosis using prenatal echocardiography has important clinical significance in evaluating disease prognosis and ensuring timely treatment.

Methods: Fetuses were followed in the prenatal and postpartum periods via echocardiography. The results of postpartum echocardiography or autopsy specimens were compared with the prenatal echocardiography findings.

Results: One hundred and eight fetuses displayed various types of DDCHD including 66 fetuses with ductal-dependent pulmonary circulation, and 42 fetuses with ductal-dependent systemic circulation. Prenatal echocardiography revealed the typical characteristics of no forward flow signal from right ventricular outflow tract to the pulmonary trunk proximally and a reverse flow in the DA in most fetuses for ductal-dependent pulmonary circulation, a reverse flow in the transverse aortic arch for aorta atresia, and a loss of continuity between aortic arch and descending aorta for interruption of the aortic arch (IAA). All 108 fetuses displayed various types of complex CHD, including right ventricular dysplasia with pulmonary atresia (PA), severe Ebstein anomaly, double outlet right ventricle with PA, tetralogy of fallot with PA, single ventricle with PA or aorta atresia, hypoplastic left heart syndrome, and IAA.

Conclusions: The identification of reverse flow in the aortic arch or DA aids in the subsequent accurate diagnosis of DDCHD associated with complex malformation of the heart.

Keywords
congenital heart disease, diagnosis, ductal-dependent, fetal echocardiography, pathomorphology
Ductal-dependent congenital heart diseases (DDCHD) are a group of complex congenital heart diseases (CHD) characterized by serious pulmonary circulatory or systemic circulatory abnormalities. These circulatory systems depend on the ductus arteriosus (DA) remaining open to maintain suitable pulmonary or systemic circulation after birth; sudden rapid deterioration of the neonate’s hemodynamic condition in the early neonatal period occurs in the case of the DA closure. DDCHD are classified into two types according to the role of the DA in the circulation: (a) CHD characterized by right heart system obstruction and pulmonary circulation, that is dependent on the patency of DA; and (b) CHD characterized by left heart system obstruction and systemic circulation, that is dependent on the patency of DA.

An accurate diagnosis using prenatal echocardiography has important clinical significance in evaluating disease prognosis and ensuring timely treatment. Prenatal echocardiographic diagnosis and surgical treatment of DDCHD after birth have been reported. Few studies have reported on the individual assessment of prenatal echocardiographic features and the anatomical study of the echocardiogram views. According to the results of a previous study, individual assessment is necessary because of the significant differences in the surgical methods, surgical difficulty, and outcomes in these patients. In recent years, integration of the prenatal diagnosis and postnatal treatment of fetal heart disease has become a trend. Detecting the pathological characteristics of DDCHD has important clinical significance in improving the accuracy of the prenatal diagnosis, evaluating diseases prognosis, optimizing the operative plan, and making surgical decisions. Therefore, the purpose of this study was to individually analyze the prenatal echocardiographic and anatomical features in fetuses with DDCHD.

METHODS

2.1 Patient population

We conducted a retrospective cohort study of fetuses at ≥17 weeks gestation that were transferred by subordinate hospitals to the Medical Ultrasound Center at Xinqiao Hospital, Chongqing, between May 1, 2011, and January 31, 2017. Fetuses with suspected DDCHD according to prenatal echocardiography were selected. The results of postpartum echocardiography or autopsy specimens were compared with prenatal echocardiography. Normal gestational age-matched controls were also evaluated. We did not include fetuses with isolated mild-to-moderate pulmonary or aortic stenosis because there is no ductal dependency. Follow-ups in the antenatal and postpartum periods were performed for live births and included clinical interventions and evaluation of changes in echocardiographic characteristics. This study was performed in accordance with a protocol that was approved by the Xinqiao Hospital Ethics Committee for Clinical Investigations.

2.2 Echocardiographic diagnosis and follow-up

All fetal patients underwent at least one detailed prenatal echocardiogram, and neonates received echocardiographic examinations following birth. Echocardiography was performed using a Philips IE33 unit (Philips Healthcare) with an S8-3 and C5-1 probe. The views of the left ventricular outflow tract (LVOT), right ventricular outflow tract (RVOT), three-vessel, three-vessel trachea (3VT), long axis of the pulmonary artery-DA arch, and long axis of the transverse aortic arch were scanned. Multiple parameters including cardiovascular anatomical structures and Doppler blood flow were assessed. Specifically, the anatomical assessment included the measurement of the following structures in accordance with the cardiac segmental approach: the size of the fetal LVOT and RVOT, the diameters of ascending aorta (AAO), pulmonary trunk (PT), left ventricular (LV), and right ventricular (RV). The tricuspid valve (TV) and mitral valve (MV) were described as either anatomically normal or abnormal. Pulmonary or aortic atresia (AA) was defined as a lack of blood flow from the RVOT or LVOT into the pulmonary atresia (PA) or aorta (AO), including primary atresia and secondary functional atresia. The flow directions of the foramen ovale (FO), transverse aortic arch, and DA were also recorded. All direct measurements were performed by a single experienced investigator who was blinded to the patient information when measuring these parameters.

2.3 Pathomorphological analyzes

When performing autopsies, the RV was opened along the coronal plane from the apex to the base, and the PA was opened along the long axis of the PA. The left side of the heart was opened according to the path of blood flow. Each investigator was blinded to the patient information when analyzing the pathomorphology.

2.4 Statistical analysis

The data are primarily presented in a descriptive manner and as the medians (range), mean ± SD, and percentages. Statistical analyzes were performed using Student’s t test to compare parameters between echocardiographic results and normal reference standards. The correlation between echocardiographic findings and autopsy results of the diameter ratio of the AAO to the PT was assessed using Pearson’s analysis via SAS 9.3 (SAS Institute Inc), and a P-value of <.05 was considered statistically significant.

RESULTS

3.1 Patients and follow-up

During the study period, 13 141 fetuses were referred for enrollment in the study. A total of 108 fetuses with DDCHD in the pulmonary or systemic circulation combined with other complex cardiac malformations were diagnosed by prenatal echocardiography (Figure 1). Gestational age-matched normal fetuses served as controls. During the follow-up,
76 parents elected to terminate the pregnancy after considering the poor prognosis associated with a fetal heart condition. Through the kind efforts of the dedicated families who signed the donation agreements, 22 formalin-fixed heart specimens from DDCHD fetuses (gestational age 17.7–34.9 weeks) were obtained from the Department of Pathology at Xinqiao Hospital including 10 cases with DDCHD in the pulmonary circulation, and 12 cases with DDCHD in the systemic circulation. Follow-ups in the antenatal and postpartum periods were performed for eight live births. Of these subjects, one boy with HLHS died at 126 days of age, 1 day after selective angiocardiography catheterization during hospitalization. One boy with HLHS died at 89 days of age, 1 week after computed-tomography angiography. A pair of twin brothers with HLHS died (one twin at 18 days of age and the other twin at 135 days of age). One boy with PA and RV dysplasia died at 136 days of age. One girl with severe Ebstein anomaly and functional PA died at 59 days of age. Two infants with PA were alive after cardiac surgery over a median of follow-up period of 6 months. Twenty-four fetuses were lost to follow-up and were not included in statistical analysis.

3.2 | Echocardiographic examinations and Pathomorphological findings

Echocardiographic reference parameters of normal fetuses with different gestational weeks were displayed in Table 1 (n = 899). A total of 66 fetuses with DDCHD involving the pulmonary circulation caused by PA included the following cases: 38 right ventricular dysplasia (RVD), 11 severe Ebstein anomalies, eight DORV, three Fallot’s tetralogy, and six SV. A total of 42 fetuses with DDCHD involving obstruction of the systemic circulation caused by AA or interruption included the following cases: 15 HLHS, nine SV with AA, and 18 interruption of aortic arch (IAA). Detail was displayed in Figure 1. Histomorphological examinations of the fetuses with DDCHD were performed in 22 cases. All the morphological results confirmed the prenatal echocardiography diagnosis.

Prenatal echocardiography of 66 fetuses with ductal-dependent pulmonary circulation displayed the typical characteristics as that the PT and its branches were visible by two-dimensional echocardiography, but no forward flow signal from RVOT was detected in the PT proximally. The diameter of the PT was normal or hypoplastic. Most fetuses displayed a reverse flow in the DA. The perfusion order was displayed from the DA to the PT and then to the right and left PA (Figure 2A,B). This pulmonary artery-DA dependence persists after birth (Figure 2C,D). Very tortuous DA was detected in some fetuses and also the attachment of DA to PA’s was varies. Two cases with PA atresia displayed atresia or dysplasia of the PT with normal branches of the pulmonary artery and a ductus attached to the left anomalous artery, and right aortic arch with mirror branches (Figures 3 and 4). Premature constriction of DA occurred in one fetus with PA

### TABLE 1

| Gestational age (wk) | n  | Left ventricular out-flow tract (mm) | Right ventricular out-flow tract (mm) | Left ventricular (mm) | Right ventricular (mm) | Aorta (mm) | Pulmonary trunk (mm) |
|---------------------|----|------------------------------------|--------------------------------------|-----------------------|------------------------|-----------|---------------------|
| 20°0–23°6           | 251| 4.69 ± 0.61                        | 5.26 ± 0.92                          | 9.58 ± 1.03           | 9.81 ± 1.13            | 4.41 ± 0.54 | 4.96 ± 0.65         |
| 24°0–27°6           | 235| 5.18 ± 0.52                        | 6.28 ± 0.64                          | 11.05 ± 1.16          | 11.43 ± 1.27           | 4.97 ± 0.53 | 5.85 ± 0.93         |
| 28°0–31°6           | 206| 5.73 ± 0.75                        | 6.62 ± 0.49                          | 11.95 ± 1.35          | 12.28 ± 1.43           | 5.46 ± 0.63 | 6.36 ± 0.96         |
| 32°0–35°6           | 128| 6.58 ± 0.56                        | 7.49 ± 0.76                          | 13.84 ± 1.40          | 14.17 ± 1.30           | 6.20 ± 0.70 | 7.37 ± 0.81         |
| 36°0–38°6           | 79 | 7.22 ± 0.46                        | 8.57 ± 0.79                          | 15.24 ± 2.64          | 15.89 ± 2.91           | 7.11 ± 0.89 | 8.13 ± 0.95         |
and single ventricular. The overall morphology of DA was displayed in Figure 5.

The lack of a continuous flow signal between the aortic arch and the descending AO was detected in fetuses with Type A IAA (Figure 6). The aortic branches go up straight along the head and neck instead of curved trend in fetuses with type B IAA (Figure 7A, B), and that the descending AO relies on the DA to receive blood flow from the pulmonary artery, and with aberrant left subclavian arteries (Figure 7C, D). Prenatal echocardiography revealed the typical characteristics as a reverse flow in the transverse aortic arch in the fetuses with AA, which looks similar to a cockscob (Figure 8). Autopsy specimens from fetuses with AO atresia displayed a severely underdeveloped transverse aortic arch (Figure 8B), a blind end of the AAO, and absence of the aortic valve (Figure 8C). Compared with the gestational age-matched normal fetuses, the AAO and aortic arch of the fetuses with IAA, AO atresia, and HLHS exhibited significant dysplasia (Figures 7A, 8B, and 9A–E). Restrictive atrial septum was detected in fetus with HLHS (Figure 9F). The ratio of the AAO diameter to the PT diameter decreased significantly between the two groups (median: 0.46, range: 0.37–0.63 in the DDCHD group with the systemic circulation obstruction vs median 0.84, range 0.78–1.02 in the control group, \( P < .01 \)). In the DDCHD in the systemic circulation group (\( n = 12 \)), the average diameter ratio of AAO to PT measured by echocardiography vs autopsy was 0.44 ± 0.11 vs 0.46 ± 0.12, respectively (\( r = .98 \), \( P < .001 \)).

4 | DISCUSSION

Clinical signs are absent in newborns with DDCHD with no obvious symptoms after birth. Therefore, the clinical misdiagnosis rate of newborns with DDCHD can be as high as 25%. However, symptoms gradually appear following the sudden decrease in pulmonary vascular resistance and the marked increase in pulmonary blood flow. Severe cyanosis, shock, or circulatory failure will occur in DDCHD neonates with DA contraction occurring hours or days after birth. Up to 40% of the children who do not receive treatment have significant symptoms or die prior to the 6-week follow-up visit. Therefore, a definitive
diagnosis during the fetal period is important for timely postpartum treatment and prevention of fatal injury of the newborn. This study focused on the prenatal echocardiographic and pathomorphological features of fetuses with DDCHD. Clarifying the pathological features of this complex of CHD is important for improving the accuracy of prenatal diagnosis, evaluating the prognosis of the disease, clarifying the surgical path, and making the appropriate surgical decisions.

4.1 | Role of the patency of DA during pregnancy and for newborn with DDCHD

The DA is one of the main physiological shunt pathways in the fetal blood circulation. During the fetal period, 90% of the blood in the pulmonary artery enters the descending AO sequentially through the DA, and most of the blood then passes through the umbilical artery into the placenta to exchange nutrients and oxygen. In most newborns, the DA is functionally closed at approximately 20 hours after birth and begins to form anatomical occlusion within 2–3 days, then ultimately becoming an arterial ligament. Due to the obstruction of the large vessels, the supply of blood through the DA is required. If the DA is physiologically closed, survival will be difficult for children with DDCHD.

The clinical application of prostaglandin E1 (PGE1) has been used to maintain the opening of the DA in neonates for the purpose of cardiac surgery or heart transplantation. However, PGE1 may produce unwanted side effects. Lewis et al. observed side effects in 20% of infants treated with PGE1, 12% of whom developed respiratory depression. Therefore, stratified and refined diagnosis of fetus with DDCHD is very important for further management during the pregnancy, delivery plans, management, and prognosis after birth. For fetuses with signs of premature constriction of DA, regular prenatal echocardiography is necessary. If necessary, terminate the pregnancy in time by choosing a cesarean birth to give birth to a fetus. For newborns, it is also important to closely observe the opening of the DA and ensure the patency of DA before surgery.

4.2 | Prenatal echocardiographic characteristics and hemodynamic changes in DDCHD

Currently, fetal echocardiography is the best way to diagnose DDCHD. The views of the LVOT, RVOT, three vessels, 3VT, long axis of the pulmonary artery-DA, and long axis of the transverse aortic arch are important in the diagnosis of fetal DDCHD. The contrast of the same segments between the systemic and pulmonary circulation is helpful for detecting abnormalities and avoiding missed diagnoses.

4.2.1 | Ductal-dependent pulmonary circulation

In fetuses with PA and IVS, blood in the right ventricle cannot be injected into the PA and refluxes into the right atrium (RA) through
the TV. This condition is usually accompanied by hypoplasia of the RV and enlargement of the RA. The blood in the RA then flows through the FO to the left heart. Due to PA, the pulmonary circulation depends on the reversed flow from the AO through the DA. The main PA trunk can manifest as atresia, hypoplasia, or dilatation. The branches of the pulmonary artery can be poorly developed or normal. In fetuses with PA and ventricular septal defect (VSD), blood in the right ventricle can be injected into the AO through the VSD. Therefore, the sizes of the left and right heart are still symmetric.

4.2.2 Ductal-dependent systemic circulation

When LVOT obstruction occurs, the LV blood flow is blocked, and the LV pressure overload leads to LV wall thickening or LV dysplasia. The blood flow from the FO to the right heart increases, the volume of the right heart increases, and the right heart becomes enlarged. When AA occurs, the AAO is dysplastic, and the blood flow in the aortic arch comes from the DA, which presents as a reversed flow. When interruption of the aortic arch occurs, the blood flow direction of the aortic arch is normal, but the descending AO receives the blood flow from the PA through the DA. The diameter of the AAO is narrowed in the three-vessel and trachea view. No signs of continuity between the aortic arch and the descending AO are observed in the transverse aortic arch view. In the view of the pulmonary artery-DA arch, the pulmonary artery extends to the descending AO through the DA.

5 CONCLUSION

In conclusion, although fetal heart disease complicates only a small percentage of pregnancies, CHD causes more neonatal morbidity and mortality than any other congenital malformation. Unfortunately, screening approaches for fetal heart disease continue to miss a large percentage of cases. This weakness in fetal screening has important clinical implications because the prenatal detection and diagnosis of CHD may improve the outcome for many of these fetal patients. In fact, the detection of major heart disease prenatally can improve neonatal outcomes by avoiding discharge to home of neonates with DDCHD. Education and training regarding the fetal heart are an important part of this process to ensure that sonographers are taught and can maintain the skills of the fetal heart examination. Fortunately, recent advances in screening techniques, an increased ability to change the prenatal natural history of many forms of fetal heart disease,
and an increasing recognition of the importance of a multidisciplinary, team approach to the management of pregnancies complicated with fetal heart disease increase, and the potential for improvements in the outcomes of fetuses with CHD. Cardiac morphogenesis changes significantly during the fetal period and in the first few years after birth in patients with complicated DDCHD. With the support of the patients and Xinqiao Hospital, we were able to observe pathomorphological features in these patients. However, our case series contains only a limited number of patients.

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FIGURE 8 A couple of diagnosis of aortic atresia where compare pathology specimen and prenatal echocardiography findings. Prenatal echocardiography at 34.3 wk of gestation revealed the typical characteristics as a reverse flow in the transverse aortic arch in the fetuses with aortic atresia, which looks similar to a cockscomb (A, red arrow). Autopsy specimens at 34.7 wk of gestation from fetuses with AO atresia displayed a severely underdeveloped transverse aortic arch (B, red arrow), a blind end of the ascending aorta, and absence of the aortic valve (C, yellow arrow). AO = aorta; DA = ductus arteriosus; DAO = descending aorta; PA = pulmonary atresia

FIGURE 9 A couple of diagnosis of restrictive atrial septum in fetus with HLHS where compare pathology specimen and prenatal echocardiography findings. Prenatal echocardiography at 17.7 wk of gestation displayed the typical characteristics of HLHS as a severe underdevelopment of the LV, obvious hypoplasia of mitral valve, aortic valve, ascending aorta (red arrow), and aortic arch (A, B and D). Autopsy specimens at 17.9 wk of gestation from fetuses with HLHS displayed obvious hypoplasia of left atrium (F), mitral valve (F), left ventricle (E), ascending aorta (C, red arrow), aortic arch (E), and a restrictive atrial septum (F, yellow arrow). AAO = ascending aorta; AOA = aortic arch; DA = ductus arteriosus; DAO = descending aorta; LA = left atrium; LV = left ventricle; MV = mitral valve; OS = ostium secundum; PA = pulmonary artery; RAA = right atrial appendage; RV = right ventricle; T = trachea

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CONFLICT OF INTEREST

No conflicts of interest.

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