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The vital role the ductus arteriosus plays in the fetal diagnosis of congenital heart disease: Evaluation by fetal echocardiography in combination with an innovative cardiovascular cast technology

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ABSTRACT

Background: The ductus arteriosus (DA) is one of the most important vessels of the fetal circulation. A variety of fetal congenital heart disease (CHD) may greatly influence the structure and flow patterns of the DA. This study was to investigate the structural characteristics of the DA and its value in the diagnosis of fetal CHD using fetal echocardiography combined with cardiovascular casting technology.

Methods: Twenty-six cases of a normal fetus and 20 cases of a fetus with CHD (10 cases of right-sided obstructive CHD and 10 cases of left-sided obstructive CHD) were enrolled in this study. The three-vessel view and the long axis view of the DA arch were chosen to observe the fetal DA. The diameters of the ascending aorta (AO) and the pulmonary artery trunk (PA) were measured on the left ventricular outflow tract view and the three-vessel view separately, and AO/DA and PA/DA values were calculated separately. The flow direction of the DA was recorded, and the blood flow peak velocity was measured using color and spectral Doppler technology. Cardiovascular cast specimens were made for fetuses secured from induced labor to facilitate further observations of the true form and connections of the DA. At the same time, heart and great vessel deformities were also recorded through careful observation of the cardiovascular cast.

Results: The following DA anomalies were observed: ① abnormal diameter (6 cases of stenosis and 9 cases of dilatation); ② abnormal blood flow direction (reverse flow in 5 cases); ③ abnormal blood flow speed (12 cases); ④ abnormal connection site (right-sided DA in 2 cases and a DA connection between the left pulmonary artery and the left subclavian artery in one case); and ⑤ absence of the DA in 2 cases. Compared with the control group, the DA diameter in the right-sided obstructive group was obviously narrowed; by contrast, the diameter of the DA in the left-sided obstructive group was obviously dilated. These differences were statistically significant ($p < 0.05$). Compared with the control group, the AO/DA values in the right- and left-sided obstructive groups were significantly increased and decreased, respectively. Finally, relative to the control group, the PA/DA values of the right- and left-sided obstructive groups were significantly reduced.

Conclusions: DA enlargement was often associated with left-sided obstructive CHD, whereas a small DA and reverse blood flow often indicated the presence of right-sided obstructive CHD. DA connections can manifest with multiple anatomical variations. During fetal echocardiography, evaluation of the DA is very important; such analyses may help search for associated cardiac defects whenever a diagnosis of CHD is made.

1. Introduction

Congenital heart disease is a leading cause of birth defect-associated infant morbidity and mortality, with an estimated incidence of 6 per 1000 live births and presentation in moderate to severe forms [1,2]. Accurate prenatal diagnosis offers potential clinical benefits with regard to infant outcomes. Fetal echocardiography is broadly defined as a detailed sonographic evaluation used to identify and characterize fetal heart anomalies before delivery. Previous studies [3,4] have shown that the prenatal detection of major forms of CHD may not only reduce neonatal morbidity and mortality but also improve preoperative conditions, survival after surgery, and surgical outcomes.

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Prenatal routine ultrasonic screening allows physicians to detect most fetal heart malformations; however, due to the complex structure of the organ and the high degree of expertise required for a thorough examination, there still remain some conditions that are difficult to diagnose. Therefore, it is necessary to identify new sensitive technology for the diagnosis of fetal CHD and to improve diagnostic accuracy.

The DA is a great vessel with muscular walls that connects the pulmonary trunk and aorta. The systolic flow within the DA has the highest velocity of the entire fetal cardiovascular system, and the velocity increases with increasing gestational age [5]. The human DA shunts an estimated 78% of the right ventricular output, or 46% of the combined cardiac output, away from the lungs to join the descending aorta and perfuse the lower body [6]. Several studies [7,8] have shown that fetuses with CHD often present dramatic changes in the DA. Therefore, the current study is an attempt to use echocardiography in combination with cardiovascular cast technology to investigate the various forms of the DA and its value in the fetal diagnosis of CHD.

2. Materials and methods

2.1. Study subjects

From September 2013 to December 2014, 256 women with uncomplicated singleton pregnancies came to our hospital for routine fetal echocardiography. The exclusion criteria included gestational diabetes mellitus, gestational hypertension, pregnancy-associated heart disease and intrauterine growth restriction. Among these women, 51 had a fetus with CHD. The age of the pregnant women in the CHD group was 28.36 ± 5.31 years, and the fetal gestational age determined by sonography was 26.57 ± 3.62 weeks. The echocardiographic findings were normal in the remaining 205 cases; among them, 35 cases with appropriate gestational ages and good ultrasound images were selected for follow-up examination two months postpartum. The age of the pregnant women in the control group was 28.76 ± 4.61 years, and the fetal gestational age determined by sonography was 26.62 ± 3.62 weeks.

All of the patients had been enrolled in research protocols approved by the ethics committee of Tongji Medical College of Huazhong University of Science and Technology. All of the women provided written informed consent for this study.

2.2. Apparatus

A Voluson E8 Expert (GE Medical Systems) equipped with C4-8, C4-8D and RM6C probes was used with a probe frequency from 4.0 to 8.0 MHz.

2.3. Fetal echocardiography

During the echocardiography, the pregnant woman assumed a supine position. The echocardiographic machine was adjusted to the fetal heart model while optimizing the imaging quality to the best conditions throughout the examination. According to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) for the performance of routine mid-trimester fetal ultrasound scans (2011) [9], fetal biometry and well-being should be evaluated to determine the ultrasonic gestational age of the fetus. According to the ISUOG Practice Guidelines (2013, updated) [10], the fetal heart can be scanned as follows: the basic four-chamber view, the left ventricular outflow tract view, the right ventricular outflow tract view, the three-vessel view and the three-vessel and tracheal views, and the DA and aortic arch view. The diameters of the ascending aorta (AO), the main pulmonary artery (PA) and the ductus arteriosus (DA) were measured. All measurements were recorded as averages of three cardiac cycles. PA/DA and AO/DA values were calculated. Color flow and Spectral Doppler interrogation was used to reveal the flow direction of the DA and the blood flow peak velocity.

2.4. Cardiovascular cast

Counseling took place immediately after the diagnosis of any serious CHD. For families who decided to terminate the pregnancy, given the approval of the ethics committee of Tongji Medical College of Huazhong University of Science and Technology and the agreement of the family, the fetal body was donated to our institution after induced labor. The fetal body was later made into a cast specimen by the following steps: ① The abdominal wall of the body was cut open, and the umbilical vein was separated and intubated with a small tube. The umbilical artery was separated, and the left side cut off. Heparin (5–10 ml) and acetone (20–50 ml) were injected in turn through the small tube inside the umbilical vein. The blood and blood clots inside the cardiovascular system were flushed until no more blood or blood clot flowed out. ② The body was perfused with ABS gel (30–60 ml) at the appropriate pressure and a constant speed for approximately 10 h. ③ After 24 h, the fetal specimen filled with ABS gel was soaked in 30% hydrochloric acid. ④ After 2 weeks, the specimen was carefully removed from the hydrochloric acid and completely flushed until the surface of the cardiovascular cast had no residual tissue adhesions. ⑤ The fetal cardiovascular cast was then marked, displayed and analyzed.

2.5. Statistical analysis

Continuous variables are reported as the mean ± SD. The 95% confidence intervals were calculated. The indexes for the three groups were compared using one-way ANOVA. Given the influence of gestational age on the parameters, a covariance model was used to compare variables between groups. Fisher's exact probability method was used to compare the classification dataset. All values were considered significantly different at $p < 0.05$. Statistical analyses were performed using SPSS Inc. (version 18.0; Chicago, IL).

3. Results

Twenty-two of 51 cases were diagnosed with serious CHD by fetal echocardiography, and the family opted for termination of the pregnancy. After an informed consent was obtained, all fetuses delivered by induced labor were made into cast specimens. Twenty casts were successfully made, and these specimens were enrolled into the next phase of the study. This group included 10 cases with right-sided obstructive CHD (age of the pregnant women = 27.57 ± 5.08 years; fetal ultrasound gestational age = 27.28 ± 4.62 weeks) and 10 cases with left-sided obstructive CHD (age of the pregnant women = 26.44 ± 3.64 years; fetal ultrasound gestational age = 25.63 ± 2.30 weeks). Among the normal fetuses, 26 cases were successfully followed up at 2 months postpartum and were confirmed by neonatal echocardiography as normal. For this group, the age of the pregnant women was 27.96 ± 4.61 years, and the fetal ultrasound gestational age was 25.47 ± 3.32 weeks. All of these characteristics are described in Table 1.

The ages of the pregnant woman and their fetuses were not significantly different between the CHD and control groups ($p > 0.05$; Table 2). The DA abnormalities were as follows: ① reduced DA diameter in 6 cases, associated with significant right-sided obstructive cardiovascular anomalies such as pulmonary artery stenosis or atresia (Fig. 1); ② increased DA diameter in 9 cases, associated with significant left-sided obstructive cardiovascular anomalies such as aortic stenosis or interruption of the aortic arch (Fig. 2); ③ reversed blood flow across the DA in 5 cases, all of which had right-sided obstructive CHD (Fig. 3); ④ increased DA flow velocity in 12 cases, 7 with right-sided obstructive CHD and 5 with left-sided obstructive CHD; ⑤ abnormal DA connection point in 3 cases: 2 with a right-sided position, and one with the DA connection between the left subclavian artery and the left pulmonary artery (Fig. 4); and ⑥ absence of the DA in 2 cases — one with associated pulmonic stenosis and the other with a common arterial trunk. The prenatal echocardiographic and cardiovascular cast findings of 20 fetuses with CHD are shown in Table 1.

Compared with the control group (3.00 ± 0.75 mm), fetuses in the right-sided obstructive CHD group had a smaller DA diameter (2.27 ± 1.16 mm), whereas fetuses in the left-sided obstructive CHD group had a larger DA diameter (4.50 ± 0.91 mm). These differences were statistically significant ($p < 0.05$). Compared with the control group (1.81 ± 0.33), the AO/DA values of the right-sided (2.98 ± 1.63) and left-sided (0.65 ± 0.29) obstructive groups were significantly increased and decreased, respectively ($p < 0.05$). Compared with the control group (2.04 ± 0.39), the PA/DA values of the two CHD groups (1.56 ± 1.32 and 1.43 ± 0.34 for the right- and left-sided obstructive groups, respectively) were significantly reduced. Compared with the control group (70.96 ± 12.94 cm/s), the blood flow velocities within the DA were increased significantly in the CHD groups (95.54 ± 18.99 cm/s; 74.28 ± 7.33 cm/s; Table 2). Finally, compared with the control group, the right-sided obstructive CHD group showed a significant trend toward a reversed flow across the DA (Table 3).