Prenatal Diagnosis of Shone's Syndrome by Fetal Echocardiography

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Research

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Abstract

Background Shone's syndrome is a rare complex with few data published on its prenatal diagnosis, this study aimed to compare the fetal echocardiographic features between Shone's syndrome fetuses and coarctation of the aorta (CoA) fetuses to improve the prenatal diagnosis of Shone's syndrome and identify the mitral valve obstruction associated with the anomaly.

Methods: Retrospective study was performed. Between January 2015 to December 2019, fourteen fetuses diagnosed with Shone's syndrome were enrolled and ten were analyzed in our final study, their clinical information and echocardiographic features were compared to normal controls (N=30) and CoA cases (N=10). The main points of identification were summarized.

Results: Comparing to normal controls, the PA/AO ratio was increased in both Shone's syndrome and CoA, but Shone's syndrome fetuses had higher PA/AO ratio than CoA fetuses ($P=0.006$). RV/LV and TVC/MVC ratios were only elevated in Shone's syndrome cases ($P<0.0001$, $P<0.0001$). Analysis revealed that the TVC/MVC ratio had the best capability in predicting Shone's syndrome and fetuses with TVC/MVC ratio over 1.290 were more likely to have Shone's syndrome rather than CoA. Meanwhile, the main points of identification in mitral valve obstruction included (1) restrictive opening of the mitral valve, thickened leaflets, echo-enhancement of chordae tendineae and single papillary muscle in short-axis section view; (2) decreased antegrade flow and abnormal flow pattern of mitral valve in color Doppler image. Chi-square test revealed that restrictive opening of the mitral valve and single papillary muscle were the most relevant features of mitral valve obstruction.

Conclusions: There are several parameters of prenatal diagnosis of Shone's syndrome by fetal echocardiography, including (1) echocardiographic measurements: elevated RV/LV ratio, PA/AO ratio and TVC/MVC ratio, of these, the TVC/MVC ratio has the best capability in predicting Shone's syndrome; (2) morphologic changes in short-axis section view: restrictive opening of the mitral valve and single papillary muscle are the most relevant features of Shone's syndrome.

Background

Shone's syndrome is a constellation of congenital abnormalities characterized by four lesions including parachute mitral valve, supra-ventricular mitral ring, subaortic stenosis and coarctation of aorta. It was first described in 1963 by Dr JD Shone^[1]. Incomplete Shone's syndrome, which consists of at least 1 left ventricular inflow tract lesion and at least 1 left ventricular outflow tract (LVOT) lesion, is more common than complete Shone's syndrome in clinical practice^[2]. Shone's syndrome is compromising approximately 0.6% of all cases of congenital cardiac abnormalities^[3]. The clinical setting is characterized by a congenital mitral valve anomaly resulting in stenosis, with resultant downstream underdevelopment of left heart outflow tract^[4].

Shone's syndrome is a rare complex with few data published on its prenatal diagnosis^[5] which could provide less help for fetal cardiologist to clinical determination. Shone et al.^[1] noted that mitral valve obstruction appeared to be the most critical problem associated with the anomaly. The severity of mitral valve obstruction correlates with poor long-term outcomes^[5, 6]. However, mitral stenosis is difficult to be accurately diagnosed and may go unnoticed in the fetus with coarctation of the aorta (CoA). Several Shone's syndrome cases were misdiagnosed with CoA and found mitral valve obstruction lesions not until adult^[7, 8]. So, evaluation of mitral valve is important in prenatal diagnosis of Shone's syndrome, especially in its differential diagnosis with isolated coarctation.

This study was conducted to improve the prenatal diagnosis of Shone's syndrome and summarize the main points of identification in mitral valve obstruction associated with the anomaly to provide actual help for fetal cardiologist to clinical determination.

Methods

This was a single-center retrospective study conducted by Pediatric Cardiology Department of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine between January 2015 to December 2019. Ethical approval was obtained from the Institutional Review Board of the Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine. Informed consent was obtained from each patient.

Population

Between January 2015 and December 2019, a total of 1500 fetuses were examined in our center and fourteen cases of Shone's syndrome were contained in the study. The study inclusion criteria were (1) with suspected Shone's syndrome (2) singleton fetus without aneuploidy (3) absence of extracardiac malformations (4) the size of the fetus is consistent with the gestational age.

Measurements

A detailed fetal echocardiography was performed by at least 2 trained pediatric cardiology physicians with at least 3 years of experience in accordance with the 2013 guidelines of the American Institute of Ultrasound in Medicine^[9]. All fetal echocardiographic examinations were performed on GE Voluson E8 with a 4 to 8-MHz transabdominal probe. The following cardiac views were examined in each fetus: the abdominal view, the four chamber view, the left and right ventricular outflow tract view, the three vessel trachea view, the short-axis view of the great vessels, the short-axis view of the mitral valve, the vena cava view, and the long axis view of the aortic arch and the ductal arch. The following measurements were assessed:

- Inflow tracts: tricuspid valve circle (TVC) dimension, mitral valve circle (MVC) dimension and Z score
- Outflow tracts: aortic valve dimension and z score, ascending aorta diameter and z score, aortic isthmus (in sagittal) diameter and Z score, transverse aortic arch diameter, pulmonary valve dimension, main

pulmonary artery diameter, arterial duct diameter

- Ratios: Right ventricular diameter/left ventricular diameter (RV/LV), TVC/MVC, pulmonary valve dimension/aortic valve dimension (PA/AO)
- Doppler signs: mitral velocity (MV), aortic velocity (AoV), aortic isthmus peak systolic velocity, reversed or mixed flow at the aortic arch

RV and LV diameters were measured in the apical four-chamber view at end-diastole. TVC and MVC diameters were measured in diastole in the four-chamber view. We assigned z-scores for valve dimensions based on fetal biometry^[10].

Statistical analysis

All statistical analyses were performed with SPSS21.0 software, and p-values under 0.05 following two-tailed t test, one-way ANOVA and Pearson χ^2 were considered as statistically significant. Receiver-operating characteristic (ROC) curve and binary logistic regression analysis were used to detect the predictors of Shone's syndrome.

Results

General information

A total of ten fetuses diagnosed of Shone's syndrome were analyzed in our final study, after excluding four fetuses (two confirmed with only CoA, one confirmed with no CHD after birth and one lost to postnatal follow-up) Fig. 1. Eight (80%) fetuses underwent the termination of pregnancy and two (20%) were born alive and received operation in our center. Of these ten fetuses, five were diagnosed with mitral stenosis and CoA, three with mitral stenosis and aortic valve stenosis, two with mitral stenosis, CoA and aortic valve stenosis. Among all, two were combined with ventricular septal defect (VSD). None of the cases had extracardiac findings. Clinical information and echocardiographic data of Shone's syndrome cases were summarized at Table 1,2. Results of postmortem autopsy showed smaller mitral annulus and parachute mitral valve in two Shone's syndrome cases respectively Fig. 2a, b. The clinical information of ten Shone's syndrome cases were compared to normal controls (N = 30) and CoA (N = 10) cases then. No significance was detected in gestational weeks or ages between three groups Fig. 3. The clinical information and echocardiographic data of CoA cases were summarized at Table 1S, 2S.

Table 1
Clinical information of ten prenatally diagnosed Shone's syndrome cases.

Patient	Gestational Age	Age	Prenatal echocardiographic diagnosis	Extracardiac malformation
A	21 + 3	26	Mitral stenosis, aortic valve stenosis, COA, VSD	none
B	27 + 4	30	Mitral stenosis, COA, VSD	none
C	24 + 2	34	Mitral stenosis, aortic valve stenosis	none
D	35 + 2	35	mitral stenosis, COA	none
E	25 + 1	29	Mitral stenosis, aortic valve stenosis, COA	none
F	30 + 3	30	Mitral stenosis, COA	none
G	25 + 2	26	Mitral stenosis, aortic valve stenosis	none
H	26	21	Mitral stenosis, COA	none
I	23 + 5	25	Mitral stenosis, aortic valve stenosis	none
J	25 + 6	22	Mitral stenosis, COA	none

Table 2
Echocardiographic measurements of ten prenatally diagnosed Shone's syndrome cases.

Patient	RV/LV	TVC/MVC	PA/AO	MV (m/s)	Z score of MVC	Aortic valve diameter Z score	Ascending aorta diameter Z score	Aortic isthmus diameter Z scores (in sagittal)
A	1.71	1.54	2.33	0.7	-0.97	-3.22	-3.7	-2.77
B	1.37	2.44	1.63	0.8	-6.51	-1.5	-1.41	-1.96
C	1.8	2.1	2.0	0.41	-5.38	-3.09	/*	/*
D	1.02	1.33	1.07	0.9	-2.33	0.19	-1.97	-1.82
E	1.5	1.63	2.11	0.6	-4.12	-3.13	-2.89	-2.74
F	1.7	1.5	1.58	0.52	-2.12	-1.08	-3.12	-3.33
G	0.93	3.59	2.63	0.42	-7.71	-4.48	-4.94	-1.93
H	1.51	1.5	1.66	0.42	-2.15	-1.14	-0.5	-3.26
I	1.39	1.55	1.7	1	-2.93	-1.43	-1.39	-0.81
J	1.24	1.37	1.55	0.57	-1.23	-0.04	-1.18	-3.56
*The lost data were showed as /.								

Comparing and analyzing of echocardiographic measurements

Of the ten Shone's syndrome cases, mean PA/AO ratio was 1.796 ± 0.47 , mean RV/LV ratio was 1.391 ± 0.30 , mean TVC/MVC ratio was 1.855 ± 0.70 and mean MV was 0.634 ± 0.21 Table 3. By comparing the measurements with control groups, shared features between Shone's syndrome and CoA were detected, including (1) LVOT obstructions, with no significance in Z scores of ascending aorta and aortic isthmus between two groups Fig. 4a,b; (2) great vessel disproportion, with elevated PA/AO ratio in both diseases Table 3, which were in accord with other centers' results^[11, 12]. However, Shone's syndrome cases exhibited more evident signs of great vessel disproportion than CoA cases. The fetuses with Shone's syndrome had higher PA/AO ratio than those with CoA ($P = 0.006$) Fig. 4c. Significance was also detected in ventricular disproportion between two diseases. The ratios of RV/LV, TVC/MVC were increased in Shone's syndrome cases ($P < 0.0001$, $P < 0.0001$) but not CoA cases. The Shone's syndrome cases also seemed to get higher MV than control groups, although no statistical significance was detected ($P = 0.0714$). Binary logistic regression analysis was used to detect predictors of Shone's syndrome, which showed that the TVC/MVC ratio had the best capability in predicting the anomaly Table 4. ROC curve

indicated that the fetuses with TVC/MVC ratio over 1.290 were more likely to have Shone's syndrome rather than CoA with a sensitivity of 100% and a specificity of 89.5%. Analysis of ROC curve for the TVC/MVC ratio revealed an area under the curve of 0.988 Fig. 4d.

Table 3
Measurements were compared between three groups.

Measurements	Normal controls N = 30	Shone's syndrome N = 10	CoA N = 10	P value
PA/AO	1.069 ± 0.05	1.796 ± 0.47	1.471 ± 0.14	.000*
RV/LV	1.029 ± 0.05	1.391 ± 0.30	1.159 ± 0.16	.000*
TVC/MVC	1.070 ± 0.06	1.855 ± 0.70	1.160 ± 0.11	.000*
MV	0.554 ± 0.09	0.634 ± 0.21	0.506 ± 0.10	.071

Table 4
Binary logistic regression analysis showed
predictors of Shone's syndrome.

Variables	OR	95% CI	P Value
PA/AO	0.900	0.732–1.107	.640
RV/LV	1.750	0.740–4.139	.371
TVC/MVC	5.000	1.448–17.271	.000*

Table 5

Main points of identifying mitral valve obstruction in Shone's syndrome.

Features	Shone's syndrome	CoA	P value
	N (n%)	N (n%)	
Left ventricle short-axis section			
restrictive opening of the mitral valve	5 (50%)	0	.0098*
thickened leaflets	2 (20%)	0	.1360
echo-enhancement of chordae tendineae	1 (10%)	0	.3049
single papillary muscle	4 (40%)	0	.0253*
Color Doppler Image		0	
decreased antegrade flow	1 (10%)	0	.3049
abnormal flow pattern	1 (10%)	0	.3049

Unique echocardiographic features of mitral valve obstruction in Shone's syndrome

There were several unique sonographic features indicating mitral valve obstruction in Shone's syndrome fetuses, including (1) in two-dimension short-axis section view: 4 cases showed restrictive opening of the mitral valve with diastolic deformity **Video 1**, 2 cases showed thickened leaflets **Video 1**, 1 case showed echo-enhancement of chordae tendineae **Video 2** and 4 cases showed single papillary muscle **Video 3**; (2) in color Doppler image: decreased antegrade flow Fig. 5a and abnormal flow pattern Fig. 5b of mitral valve were cue of Shone's syndrome. None of these were found in CoA, on the contrast, developments of mitral valve and papillary muscle were normal in CoA cases **Video 4**. The main points of identification in mitral valve obstruction were summarized at Table 4. Chi-square test revealed that restrictive opening of the mitral valve and single papillary muscle seemed to be the most relevant features of mitral valve obstruction in Shone's syndrome.

Discussion

Shone's syndrome is a rare and under-recognized diagnostic entity, associated with substantial morbidity related to arrhythmias, heart failure, and interventions^[13]. The obstructive lesions in Shone's complex have a tendency to worsen over time as compared to other congenital heart defects^[14]. The antenatal recognition of Shone's syndrome is still challenging, the complex hemodynamic interactions between multiple levels of left-side obstructions challenge the clinical determination of prognoses^[15] and sometimes the diagnosis at mid-gestation is misleading, as both steady state and worsening by the end point are possible^[5].

The incidence of Shone's syndrome in our center is about 0.66%, which is close to the reported 0.67%. A key point in diagnosis of Shone's syndrome is a comprehensive evaluation of mitral valve. In our study, we found out that the TVC/MVC ratio had the best capability in predicting Shone's syndrome. Besides, restrictive opening of the mitral valve and single papillary muscle were the most relevant factors of mitral valve obstruction which provided important clues for prenatal diagnosis of Shone's syndrome. These findings could provide some information for fetal cardiologist to determine those with Shone's syndrome from those with just an isolated coarctation to help better counsel the family.

However, misdiagnosis is inevitable as the difficulty of distinguishing Shone's syndrome from other LVOT obstruction lesions. In this study, there were still three cases who had been misdiagnosed with Shone's syndrome prenatally but were confirmed other diagnosis postnatally, among whom two were confirmed only CoA, including one manifested as thickened leaflets **Video 5** and one manifested as single papillary muscle **Video 6** prenatally. In addition, another two cases in our center who were not enrolled in this study, had been diagnosed with isolated CoA prenatally but found to be combined with mitral stenosis after birth. Thus, the sensitivity and specificity of prenatal diagnosis of Shone's syndrome still need to be improved.

Mitral stenosis is a progressive process which could be missed occasionally if obstruction is mild in early stage of pregnancy or overlapped by signs of severe LVOT obstruction. In these patients, prenatal echocardiography diagnosis is less satisfactory and serial assessment after initial diagnosis is needed for evaluating progress of multiple-level obstructions. Fetal echocardiograms may be performed every 4 weeks based on the gestational age at the time of initial suspicion. In addition, prenatal echocardiography diagnosis relies on the quality of image extremely^[16]. Sometimes suboptimal imaging of fetal heart could interfere the clinical determination by physicians.

Referring to a Fetal Medicine Unit is required in order to obtain a better monitor and management for Shone's syndrome patients after birth, especially for those who may require special intervention at birth or within the first days of life. The patient outcome of Shone's syndrome is widely variable because of the diversity and complex nature of cardiac anomalies itself. It is reported that operative outcome is excellent in Shone's syndrome patients^[17] and surgical intervention is recommended to be undertaken early before the onset of pulmonary hypertension^[18].

Limitations

This was a retrospective study with its inherent limitations. In addition, our study population was limited to fetuses who were suspected with congenital heart defects and referred to our hospital for further diagnosis and treatment. Our results reflected a single center's experience. Larger sample sizes are needed to validate the result we got from this study.

Conclusion

There are several parameters of prenatal diagnosis of Shone's syndrome by fetal echocardiography which could provide actual help for fetal cardiologist to clinical determination, including (1) echocardiographic measurements: elevated RV/LV ratio, PA/AO ratio and TVC/MVC ratio, of these, the TVC/MVC ratio has the best capability in predicting Shone's syndrome; (2) morphologic changes in short-axis section view: restrictive opening of the mitral valve and single papillary muscle are the most relevant features of mitral valve obstruction which provide important clues for prenatal diagnosis of Shone's syndrome.

Declarations

Ethical approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consents were obtained from all individual participants included in the study.

Consent for publication: Consents for publication were obtained from all individual participants included in the study.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

Zhuoyan Li drafted the manuscript and was responsible for collecting and analyzing patient data. Yurong Wu was in charge of informed consents of patients. Sun Chen designed this study. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of fetuses with suspected Shone's syndrome. The study group contained fourteen fetuses referred to our center during the study period. In the final study, four of fourteen were excluded, including three confirmed other diagnosis after birth and one lost follow-up.

Figure 2

Postmortem autopsy of two Shone's syndrome cases. (a) Autopsy showed smaller mitral annulus in patient B and (b) parachute mitral valve in patient E. Yellow arrow indicated mitral valve, red arrow indicated tricuspid valve, white arrow indicated parachute mitral valve.

Figure 3

Basic characteristics of three groups. Gestation weeks and ages of three groups were no difference ($P=0.1007$, $P=0.0510$).

Figure 4

Echocardiographic features of three groups. (a) LVOT obstructions in Shone's syndrome and CoA respectively. (b) Z scores of ascending aorta and aortic isthmus showed no difference between Shone's syndrome and CoA. (c) Compared to normal controls, the ratio of PA/AO was increased in both Shone's syndrome ($P<0.0001$) and CoA ($P<0.0001$). However, RV/LV ($P<0.0001$) ratio and TVC/MVC ($P<0.0001$) ratio were increased only in Shone's syndrome cases. (d) Receiver-operating characteristic curve of TVC/MVC ratio for the predictor of Shone's syndrome.

Figure 5

Unique sonographic features of mitral valve obstruction in Shone's syndrome cases. (a) Decreased antegrade flow and (b) abnormal mitral flow pattern (single peak) of two Shone's syndrome cases respectively.

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