

# Measurement of frontal lobe volume and thalamic volume in fetuses with congenital heart disease at different gestational weeks using three dimensional ultra sonography and its clinical value

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**Abstract:** Our study aimed to investigate the measurement of frontal lobe volume and thalamic volume in fetuses with congenital heart disease (CHD) at different gestational weeks using three dimensional (3-D) ultrasonography and its clinical value. Then, 238 pregnant women who received obstetric ultrasonography in ultrasound department of Internal Medicine of our hospital were enrolled between March 2013 to April 2014. In this study, 85 fetuses were diagnosed to develop CHD by prenatal fetal echocardiography, and the other 153 fetuses were normal. Frontal lobe volume, thalamic volume and cerebral blood flow was determined by color Doppler ultrasonic diagnostic apparatus (type: GE Voluson E8). The level of MCA-PI and CPR in CHD fetus group performed significantly lower than that in normal fetus group ( $P<0.05$ ), but the level of UA-PI performed significantly higher than that in normal fetus group ( $P<0.05$ ). When gestational age  $<30$  weeks, there was no significant difference in thalamic volume and frontal lobe volume between the two groups ( $P>0.05$ ); when gestational age  $\geq 30$  weeks, the level of CHD fetus group performed significantly lower thalamic volume and frontal lobe volume than that in normal fetus group ( $P<0.05$ ). When gestational age  $<30$  weeks, there was no significant difference in BPD, HC, and GA between the two groups ( $P>0.05$ ); when gestational age  $\geq 30$  weeks, the level of BPD, HC and GA in CHD fetus group performed significantly lower than that in normal fetus group ( $P<0.05$ ). If gestational age  $<30$  weeks, CHD performed a small impact on fetal frontal lobe volume and thalamic volume; if gestational age  $\geq 30$  weeks, the level of frontal lobe volume and thalamic volume in fetuses with CHD performed significantly lower than that in normal fetuses.

**Keywords:** 3-D ultrasonography, fetuses with congenital heart disease, frontal lobe volume, thalamic volume, clinical value.

## INTRODUCTION

Congenital heart disease (CHD) is one of congenital malformations with a relatively high incidence in neonates. Its incidence reaches approximately 8% in live births, and it is one of the main causes of the death of neonates (Liu, 2015; Zhu *et al.*, 2012). In recent years, various studies have indicated that neurodevelopmental and functional abnormalities are common in children with CHD, and they are important factors which reduce the survival of neonates with CHD. More and more radiographic evidence suggests that fetuses or neonates with CHD present functional abnormalities or deficiency of nervous system (Limperopoulos *et al.*, 2010; Berman *et al.*, 2011; Clouchoux *et al.*, 2013). More importantly, according to preoperative examination and prenatal diagnosis, intraoperative and postoperative factors have an impact on neurodevelopment of children with CHD or cause damage to them, and many children with CHD have already presented with structural and functional abnormalities before surgery. Currently, studies on neurodevelopmental abnormality caused by CHD mainly focus on the application of extracorporeal circulation in

cardiac surgery, or the damage of intraoperative cardiac arrest on the nervous system and the ways to take systematic and protective measures after surgery, etc., but prenatal neurodevelopmental status of fetuses is rare in concern (Yu and Li, 2011; Mao, et al., 2005). Therefore, if we can assess nervous system development of fetuses with CHD by effective means of examination during the period of prenatal examination, it will be of high clinical value. Frontal lobes and thalamus are important organs in the nervous system. Routine prenatal ultrasonography assessment of fetal craniocerebral development is mainly performed in two-dimensional (2-D) images, including the measurement of biparietal diameters, head circumference and transverse cerebellar diameter. In view of the irregularity of the human organs, 3-D volume values more accurately reflect the actual growth level of fetuses (Wu *et al.*, 2010). In recent years, automatic 3-D ultrasonography imaging technique, as a valuable and complementary approach to fetal assessment, has been applied more and more widely, which enables the measurement of fetal organ volume to be feasible, thus providing all fetal organs, such as growth and development evaluation of brain with more information. Additionally, compared with MRI and other diagnostic methods, 3-D ultrasonography is convenient and non-

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invasive, and it has advantages that can't be replaced by other diagnostic methods. Consequently, in this study, we aim to investigate the measurement of frontal lobe volume and thalamic volume in fetuses with CHD at different gestational weeks using 3-D ultrasonography and its clinical value.

## MATERIALS AND METHODS

### General data

Between March 2013 to April 2014, 238 pregnant women who received obstetric ultrasonography in Ultrasound Department of Internal Medicine of our hospital were enrolled, including 153 normal fetuses and 85 fetuses diagnosed as CHD by prenatal fetal echocardiography. In normal fetus group, pregnant women were aged from 20-37 years old with an average of (27.9±4.1) years; gestational weeks were 20-36 weeks with an average of (28.4±3.81) weeks, including 98 pregnant women with <30 gestational weeks and 55 ≥30 gestational weeks. In CHD fetus group, pregnant women were aged from 19-37 years old with an average of (28.3±3.9) years; gestational weeks were 20-37 weeks with an average of (28.1±3.65) weeks, including 57 pregnant women with <30 gestational weeks and 28 ≥30 gestational weeks. Sex, gestational weeks and other general data in the two groups were not statistically significant ( $P>0.05$ ), therefore, were comparable. All enrolled pregnant women in this study had signed information consent form after understanding and being informed the related projects of this study and this study had been reported to ethics committee of our hospital for approval of implementation.

### Inclusion and exclusion criteria

Inclusion criteria were as follows. (1) Inclusion criteria of normal fetus group: All were singleton gestation; fetuses had no abnormality in clinical and ultrasound examination; ultrasonic measurement values were within the normal range of the gestational age; pregnant women had no severe underlying diseases or pregnancy complications. (2) Inclusion criteria of CHD fetus group: all were singleton gestation; fetuses were diagnosis as fetal CHD in prenatal ultrasonography; Pregnant women had no severe underlying diseases or pregnancy complications. Exclusion criteria were as follows. (1) Exclusion criteria of normal fetus group: Those were twin gestation or multiple gestation; Presence of abnormality in chromosome; fetuses had persistent arrhythmia; there were placental dysfunction and other factors which were likely to lead to fetal intrauterine hypoxia. (2) Exclusion criteria of CHD fetus group: those were twin gestation or multiple gestation; Fetuses had abnormality in chromosome or other organs malformations; Fetuses had persistent arrhythmia; There were placental dysfunction and other factors which were likely to lead to fetal intrauterine hypoxia; fetuses were suspected to have intrauterine growth restriction; fetuses had simple small ventricular defects (<5mm).

### Methods

Prenatal diagnosis of CHD and 3-D data capture of fetal prenatal brain were performed using GE Voluson E8 type color Doppler ultrasonic diagnostic apparatus (U.S.A GE), and exploration of 3-D volume was performed using RAB4-8L type. Color Doppler ultrasonic diagnostic apparatus (Type: Phillip iE33) was used for postpartum neonatal echocardiography. The probe frequency was set at 4-12MHz.

### Acquisition of 3-D volume of fetal brain

In 3-D mode, 2-D image quality was adjusted to the best, and image quality was set to the highest with the section of biparietal diameter serving as a starting section. The size of the sampling frame was adjusted to fit for including the entire fetal head and scan angle for volume was set at 80°. Data collection was done when pregnant women held their breath and had no fetal movement. The obtained volumes were shown as axial section, coronal section and sagittal section (fig. 1). It should be noted that axial section and coronal section couldn't be blurred or distorted; otherwise, the data would be collected again.

### Measurement of frontal lobe volume and thalamic volume

Virtual organ computer-aided analysis (VOCAL) method was used for the measurement of fetal frontal lobe volume and thalamic volume. Manually painting was employed. Rotation angle was 15°. During measurement of frontal lobe volume, anterior and lateral margin were the inner surface of cranial bone. The bottom was skull base. Its posterior margin was separated by the connecting line of lateral fissure of bilateral cerebrums from temporal lobe. It should be noted that thalamus couldn't be included (fig. 2). During the measurement of thalamic volume, thalamus was manually painted along its contour (fig. 3).

### Pulsatility index (PI) and cerebroplacental doppler ratio (CPR)

Willims ring was displayed in the section of skull base. In view of the fact that variation of blood flow index in proximal middle cerebral artery (MCA) was the smallest, the sample volume was placed at the beginning point of MCA to obtain MCA-PI. UI-RI was obtained from umbilical artery near placenta, the sample volume was placed on central parts of blood vessel, with width of 2-3 mm and measurement angle of <20°. When fetal heart rate (FHR) was 120-120bpm and there was no fetal movement, pulse Doppler was used for the acquisition of three consecutive cardiac cycles. Make sure that the waveform was homogeneous with a well-defined margin. Then PI and CPR were calculated.  $PI=(S-D/A)$ . S stands for the peak systolic flow velocity, D for late diastolic peak flow velocity and A for time mean highest flow velocity.  $CPR=MCA-PI/UA-PI$ .

### Evaluation indices

Obtained fetal craniocerebral 3-D volume, 2-D growth parameters and cerebral blood flow parameters of two

**Table 1:** Comparison of two dimensional parameters at different gestational weeks between two groups of fetuses

Groups	BPD (cm)		HC (cm)		GA	
	<30 weeks	≥30 weeks	<30 weeks	≥30 weeks	<30 weeks	≥30 weeks
Normal fetus	6.28±1.03	8.83±1.24	23.17±1.09	29.98±1.62	25.31±2.12	30.13±1.94
Congenital heart disease fetus	6.37±0.93	8.09±1.03	23.22±1.13	27.06±1.43	25.92±2.17	28.01±1.79
t	0.541	2.751	0.269	8.067	1.693	4.828
P	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

**Table 2:** Comparison of volume of thalamus and frontal lobe in normal fetuses and fetuses with CHD

Groups	Thalamic volume (cm <sup>3</sup> )		Frontal lobe volume (cm <sup>3</sup> )	
	<30 weeks	≥30 weeks	<30 weeks	≥30 weeks
Normal fetus		4.23±0.64	33.41±6.09	78.49±8.61
Congenital heart disease fetus	1.54±0.81	3.84±0.59	32.42±5.13	61.46±7.74
T	0.632	2.693	1.032	8.806
P	>0.05	<0.05	>0.05	<0.05

**Table 3:** Comparison of fetal cerebral blood flow parameters between two groups

Groups	MCA-PI	UA-PI	CPR
Normal fetus (n=153)	1.78±0.41	1.03±0.32	1.84±0.47
Congenital heart disease fetus (n=85)	1.65±0.39	1.18±0.31	1.61±0.38
T	2.385	3.504	4.103
P	<0.05	<0.05	<0.05

groups of fetuses were taken as observation indices. Correlation analysis was performed between cerebral blood flow parameters and craniocerebral 3-D volume.

## STATISTICAL ANALYSIS

SPSS version 19.0 software was used for data processing. Measurement data were expressed as  $\bar{x} \pm s$ . Inter-group comparison was performed using *t*-test.  $P < 0.05$  indicated the difference was significant.

## RESULTS

### *Comparison of two dimensional parameters between normal fetuses and fetuses with CHD*

When gestational age <30 weeks, there was no significant difference in BPD, HC and GA between the two groups ( $P > 0.05$ ); when gestational age ≥30 weeks, CHD fetus group had significantly lower BPD, HC and GA than normal fetus group ( $P < 0.05$ ) (table 1).

### *Comparison of thalamic volume and frontal lobe volume between normal fetuses and fetuses with CHD*

When gestational age <30 weeks, there was no significant difference in thalamic volume and frontal lobe volume between the two groups ( $P > 0.05$ ); When gestational age ≥30 weeks, CHD fetus group had significantly lower thalamic volume and frontal lobe volume than normal fetus group ( $P < 0.05$ ) (table 2).

### *Comparison of fetal cerebral blood flow parameters between two groups*

CHD fetus group had significantly lower MCA-PI and CPR ( $P < 0.05$ ), but significantly higher UA-PI than normal fetus group ( $t = 3.504$ ,  $P < 0.05$ ) (table 3).

## DISCUSSION

Brain and heart have numerous same foundation, and are closely related to each other during embryonic development period. Many same genes and signaling pathways, such as sonic hedgehog signaling pathway and notch/jagged signaling pathway, were involved in. And signaling pathways related to cell proliferation, cell qualification, transformation growth factors and other aspects play similar roles in human embryonic and cardiac development. In addition, Down's syndrome, DiGeorge syndrome, Williams-Beuren syndrome and Noonan all have symptoms of cardiac malformations and nervous system abnormalities. The above factors illustrate the close relationship between fetal CHD and fetal nervous system dysfunction. CHD, as one of common fetal congenital malformations, has a relatively high incidence and can cause big damage. And at present, surgery is the most common option for treatment of CHD, and studies on the relationship between CHD and functions of nervous system mainly focus on the possible impairment of nervous system function due to intraoperative or postoperative temporary cardiac arrest. Nevertheless, congenital fetal prenatal functional and

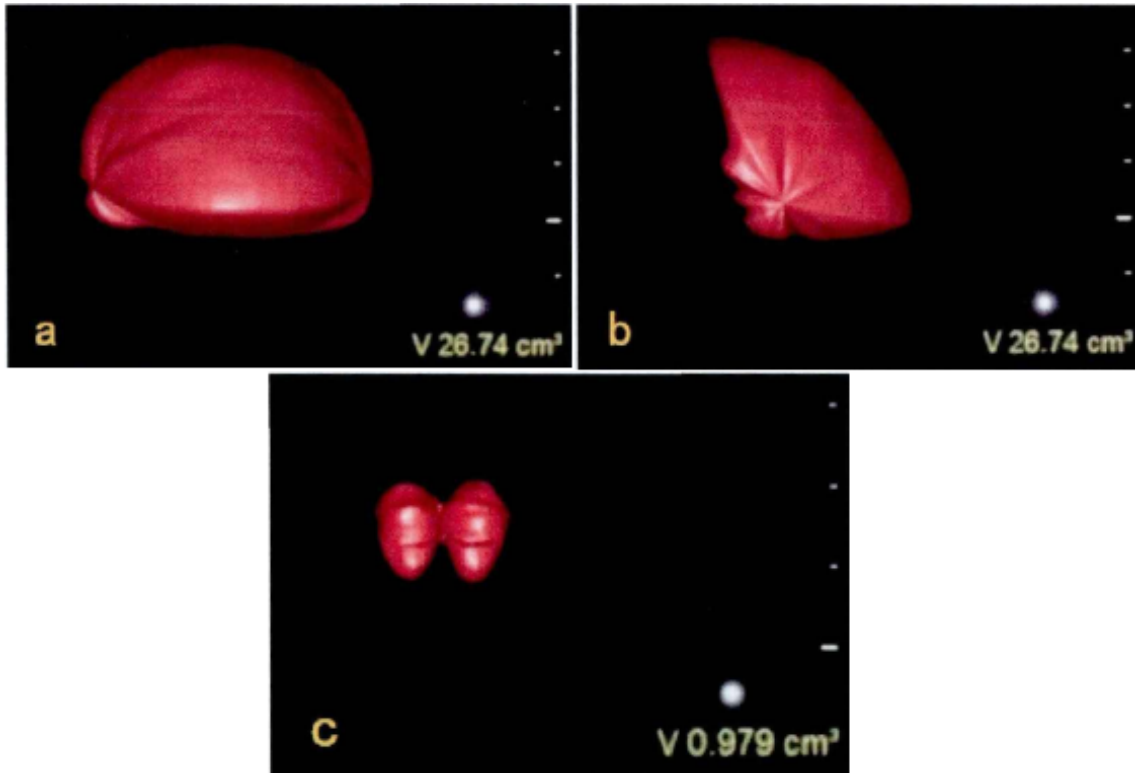


Fig. 1: Three dimensional effect of fetal brain structure (a: Axial plane; b: Coronal section; c: Sagittal section)

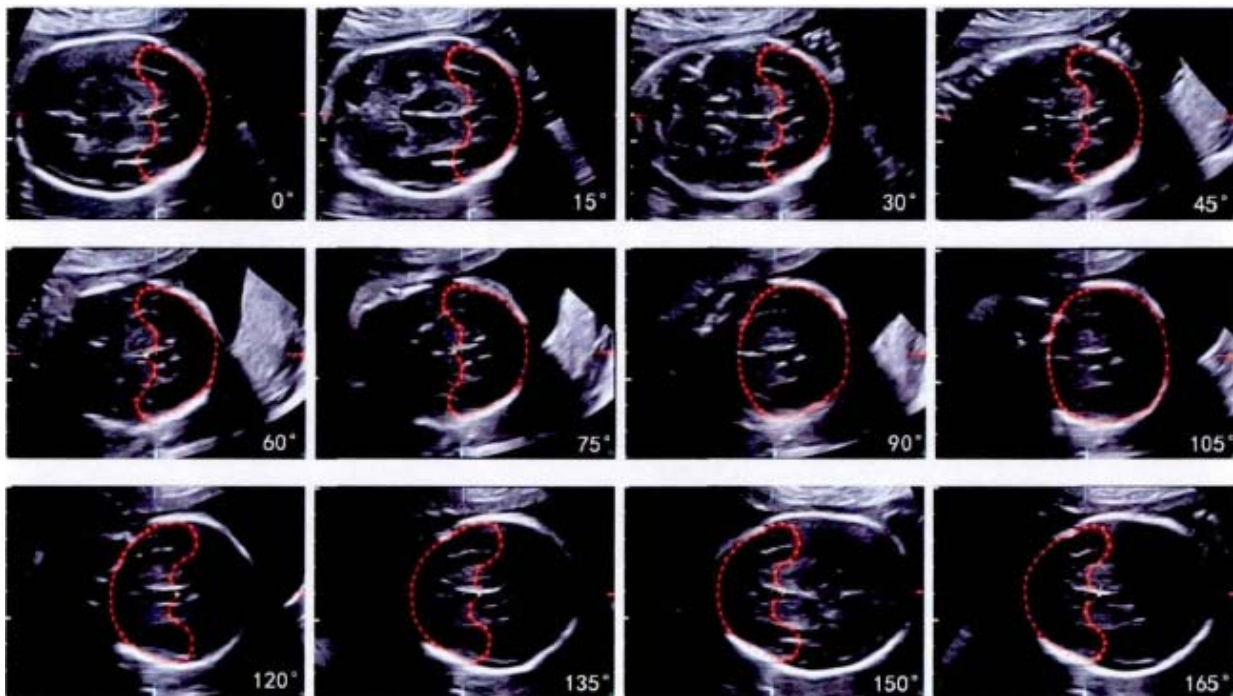
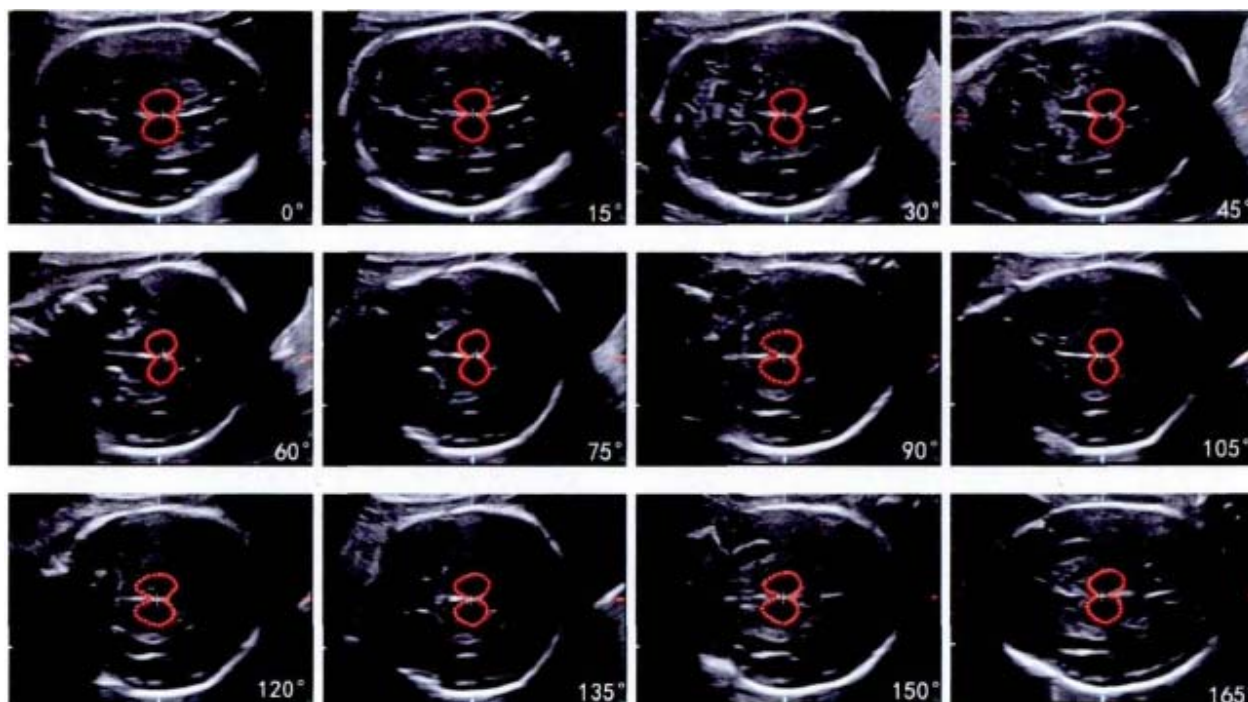


Fig. 2: Fetal frontal lobe volume description section by VOCAL method

structural abnormalities of nervous system haven't gained enough attention: Therefore, the treatment might be delayed as a result of not taking targeted measures in the subsequent clinical treatment (Xiang *et al.*, 2011; Zhu and Mo, 2015). Thus, the study on neurodevelopmental status

of fetuses with CHD is of great significance. In this study, we aim to investigate 3-D ultrasound measurement of frontal lobe volume and thalamic volume in fetuses with CHD at different gestational weeks and to analyze its clinical value.



**Fig. 3:** Fetal thalamic volume description section by VOCAL method

Our findings demonstrate that, when gestational age <30 weeks, there is no significant difference in BPD, HC, and GA between the two groups ( $P>0.05$ ); when gestational age  $\geq 30$  weeks, CHD fetus group have significantly lower BPD, HC and GA than normal fetus group ( $P<0.05$ ). When gestational age <30 weeks, there is no significant difference in thalamic volume and frontal lobe volume between the two groups ( $P>0.05$ ); when gestational age  $\geq 30$  weeks, CHD fetus group have significantly lower thalamic volume and frontal lobe volume than normal fetus group ( $P<0.05$ ). These findings demonstrate that, when gestational weeks is small (< 30 weeks), CHD produces little impact on fetal neurodevelopment, but with the increase of gestational weeks, neurodevelopmental abnormalities present gradually in fetuses with CHD. Fetuses with CHD have significantly lower frontal lobe volume and thalamic volume than normal fetuses in 3-D ultrasonography and have significantly lower BPD, HC and other indices than normal fetuses even in conventional 2-D ultrasonography indices. These findings are basically consistent with the opinion of Limperopoulos C *et al.* (Limperopoulos, et al., 2000). that with the increase of gestational age, clinical examination indices of fetuses with encephalodysplasia gradually present. The reason may be that though fetal brain tissue begins developing in early and mid gestation, with the increase of gestational weeks, in late gestation, brain volume increases rapidly, a large number of nerve synapse are formed, synaptic connections are widely established and brain metabolism increases significantly. These all inevitably lead to the rapidly increased needs of brain tissue for nutrients. If fetal cardiovascular system is

not complete, it will be difficult to meet the needs of brain tissue for nutrients. This contradiction will be more and more obvious with the increase of gestational weeks. Therefore, normal cardiac structure in late gestation is an important foundation for guaranteeing the growth and development of brain. This is also consistent with our findings that CHD fetus group has significantly lower MCA-PI and CPR ( $P<0.05$ ), but significantly higher UA-PI than normal fetus group ( $P<0.05$ ).

Based on the above analysis, we conclude that, if gestational age  $\leq 30$  weeks, CHD has little effect on fetal frontal lobe volume and thalamic volume, but if gestational age > 30 weeks, fetuses with CHD have significantly lower frontal lobe volume and thalamic volume than normal fetuses.

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