Int. J. Morphol.,
40(5):1308-1320, 2022.

Morphological Index of Fetal Cerebral Ventricular Development: A Diagnostic Ultrasound Study

Índice Morfológico del Desarrollo Ventricular Cerebral Fetal: Un Estudio Ecográfico Diagnóstico

Chen Yue[1]; Qian Ding[2]; Heng-Yang[3]; Sheng-Bo Yu[3]; Jin Gong[3]; Yi-Fei Wang[1]; Chan Li[3] & Hong-Jin Sui[3]

YUE, C.; DING, Q.; HENG, Y.; YU, S. B.; GONG, J.; WANG, Y. F.; LI, C. & SUI, H. J. Morphological index of fetal cerebral ventricular development: a diagnostic ultrasound study. *Int. J. Morphol., 40(5)*:1308-1320, 2022.

SUMMARY: To establish an unprovable diagnostic indicative index reference for ultrasound examination of the fetal cerebral ventricles, based on the morphological characteristics throughout fetal nervous system development. Key ultrasonic morphological indicators of fetal ventricular development, which includes frontal horn width (FHW), occipital horn width (OHW), width of 3rd ventricle, cavity of septum pellucidum (CSP), width and length of 4th ventricle and thalamo-occipital distance (TOD) had been measured and analyzed collectively. All data of the indicators was collected on singleton pregnant woman between 16-39 weeks of gestational age (GA), between November 2017 and June 2021 at the Second Hospital of Dalian Medical University. A total of 235 pregnant women were enrolled in the cross section study; another 36 pregnant women voluntarily joined a timeline-tracking follow-up study (cohort study) under the same examining criteria. A decrease of FHW and OHW of the lateral ventricles was observed as GA increased; while dimensional values of TOD, 3rd ventricle, CSP, as well as 4th ventricle increased with GA. Most of these indicators showed an enhanced variation tendency within a certain period of GA. Moreover, values of FHW and TOD showed asymmetry of the two hemispheres within the whole GA. Our findings revealed the morphological regularity of fetal ventricular development, which would instructively enhance the relative clinical ultrasound diagnosis; moreover, TOD also showed regularly changes as GA increased, suggesting that TOD should be considered as an additional routine ultrasonic indicator for fetal ventricular development.

KEY WORDS: Fetal ventricular development; Prenatal cranial ultrasound measurement index; Brain morphology.

INTRODUCTION

Human cerebral ventricular system consists of four ventricular chambers and one connective tube; fetal cerebral ventricular development is essential for the establishment of cerebrospinal fluid (CSF) circulation, which is critical for the physiology of central nervous system (CNS). In the morphological manner, the brain changes during the fetal development throughout the whole gestation. With the progress of brain development, the inner cavity of the brain expands to form the brain ventricle, choroid plexus, and CSF. Clinically, so far, the malformations specifically of the CNS are one of major causes of embryo death globally.

The possible mechanisms causing fetal cerebral development malformations may be: (1) obstruction of the cerebrospinal flow (CSF); (2) hypersecretion of the CSF; (3) defective filtration of the CSF; (4) and altered development of the intracranial architecture (D'Addario, 2004). Monitoring the changes during the development of the cerebral ventricles can further evaluate the development of the fetal brain. Nonetheless, to minimize diagnostic errors, it is essential to clarify the characteristic regularity of the ventricular morphological changes at different gestational ages (GA).

Generally, an increasing or reducing size of lateral cerebral ventricle implies a developmental anomaly. The lateral ventricles are one pair of largest chambers of ventricular system, thus the dimensional indicators of lateral ventricle, which includes frontal horn width (FHW), occipital horn width (OHW), have been considered the most common

[1] Department of Obstetrics and Gynecology, the Second Hospital of Dalian Medical University, Dalian, China.
[2] Department of the Ultrasound, the Second Hospital of Dalian Medical University, Dalian, China.
[3] Department of Anatomy, Dalian Medical University, Dalian, China.
This study was supported by Liaoning provincial department of education (507058); Natural Science Foundation of China (NSFC31871213, NSFC32071184).

Received: 2022-07-05 Accepted: 2022-07-26

measurement indicator in diagnosis for fetal brain developmental malformation; furthermore, 3rd ventricle develops from the embryonic midline cavities of the telencephalon and diencephalon, thus the width of 3rd ventricle is essential in distinguishing CNS abnormalities; CSP bridges two hemispheres of the telencephalon near midline that from thickening of the upper end of the lamina terminalis around 7-week GA (Nagaraj *et al*., 2018), as a result, the width of CSP could be a key factor to reflect the development of the whole fetal neural system; 4th ventricle connects the aqueduct of midbrain (aqueduct of Sylvius) and myelocoele, therefore the dimensions of 4th ventricle is a critical morphological indicator of the CNS development as well. 3rd ventricle, thalami, aqueduct of midbrain and cerebellum were associated with pathologies of the diencephalon, mesencephalon or rhombencephalon (Cagneaux *et al*., 2013). TOD is defined as the distance between the outermost point of the thalamus at its junction with the choroid plexus and the outermost part of the occipital horn in the parasagittal plane (Brouwer *et al*., 2012); additionally, as the occipital horn of the lateral ventricle is one of the most important indicators of fetal ventricular development (Davies *et al*., 2000); although it is currently only used for CNS ultrasonography in neonates, TOD has a strong potential to become a routine morphological indicator of fetal ventricular development.

Cranial ultrasound (CUS) is a safe and economical method with high sensitivity to monitor the neural developmental abnormalities of fetuses. Clinically, ultrasound has been the preferable method to monitor the key morphological changes of fetal cerebral ventricular development. Progressive ventricular dilation determined by ultrasonography was signs of disturbed CSF dynamic (Schulz *et al*., 2014).In the present study, we determined to use these sonographic dimensional indicators as reference values for the CUS during the whole pregnancy.

Due to the insufficient detectability of sizes, the cerebral ventricles are normally not suitable for ultrasound examination before 16-week GA. As a result, the ventricular dimensional indicators of 16-39 weeks of GA are considered to be more reliable and detectable, therefore the anomaly scan of fetuses is usually undertaken during second trimester ultrasound evaluations (Wyldes & Watkinson, 2004).

In general, the sources and accumulation of data of fetal ventricular development are limited worldwide and there is no consensus on the ultrasound dimensional indicators of the fetal brain development.

We introduced the reference data based on fetuses for clinical ultrasound examination. Accurate reference values are of importance for local fetuses with cerebral ventricular developmental disorders, a change in ventricular measurements as minor as a few millimeters can result in poor outcomes.

Moreover, each of the fetal cerebral ventricles morphs with different speed at different GA stages, although the current ultrasound diagnosis of fetal ventricular development has basically determined the routine examination indicators, the regularities of the morphological changes of these indicators during the whole pregnancy remain unclear; in the present study, we also aim to analyze the regularity these changes to improve the current diagnostic reference.

Ethics Statement. This study was permitted under the ethical approval of the Second Hospital of Dalian Medical University on 18.9.2017. The number of the ethical approval document is No.134 of 2017. All of the examinees had read the consent form carefully beforehand, and voluntarily participated in the present study under the premise of being affirmative with the purpose, process, potential risks and benefits of the present study.

MATERIAL AND METHOD

Study design and setting. In the present study, GA was stated in weeks, fractions of weeks were rounded to the nearest week, with fraction ≤4days and>5days being assigned to the lower and higher weeks, respectively. All pregnant women examined in this study were divided into two groups.

For group one (cross section study), all data was collected on 235 pregnant women between 16-39 weeks of GA. GA was determined by the date of the last menstrual period (LMP). The local ethics authority and research committee approved the study protocol. All pregnant women were admitted in the Second Hospital of Dalian Medical University.

For group two (cohort study), another 36 pregnant women voluntarily joined a timeline follow-up study. Every single fetus of the 36 women was examined every 4 weeks between the GA of 16-39 weeks.

Participants. All of the participants engaged in this study were recruited during November 2017 to June 2021; amongst the authors, only Dr. Chen Yue and Dr. Qian Ding, the operators who participated in the ultrasound examination, had access to information that could identify individual participant during or after data collection. Data of Age, LMP and parity of the mothers were obtained.

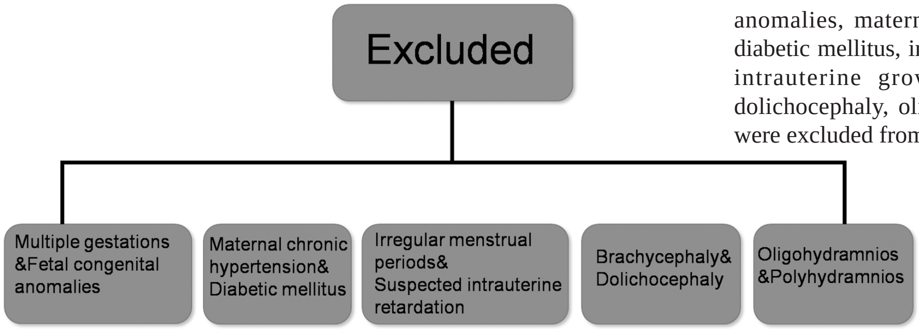

Fig. 1. Exclusion flowchart of the present study. Pregnant women with multiple gestations, fetal congenital anomalies, maternal chronic hypertension, maternal diabetic mellitus, irregular menstrual periods, suspected intrauterine growth retardation, brachycephaly, dolichocephaly, oligohydramnios and polyhydramnios were excluded from this study.

The flowchart of the exclusion criteria of the present study was shown in Figure 1. Pregnant women with multiple gestations, fetal congenital anomalies, maternal chronic hypertension, maternal diabetic mellitus, irregular menstrual periods, suspected intrauterine growth retardation, brachycephaly, dolichocephaly, oligohydramnios and polyhydramnios were excluded from this study.

Sonographic evaluation. For all examined fetuses, CUS was performed by two observers separately who have more than 10-year experience in Obstetrics sonography. The measurements were repeated by two observers, who were unaware of each other`s data. For each examined woman, routine obstetric sonography was performed beforehand to determine the number of fetuses, gestational age and fetal weight to detect and exclude fetal malformation and placental abnormalities. To enhance the reliability and the validity, all the measurements were performed at least two times followed ISUOG practice guideline (Malinger *et al*., 2020). FHW, OHW, CSP, width of 3rd ventricle, length and width of 4th ventricle and TOD were performed. Followed ISUOG practice guideline, measurement data was obtained via transabdominal ultrasound (GE company Voluson E8 ultrasound machine C1-5-D equipped with 2-d 2-5MHz; or RAB6-D equipped with 3-d 6-8MHz probe respectively). This study was approved by the local ethics committee of the Second Hospital of Dalian Medical University. All parents were informed about all the details of this study and consent was obtained verbally before the ultrasound examination.

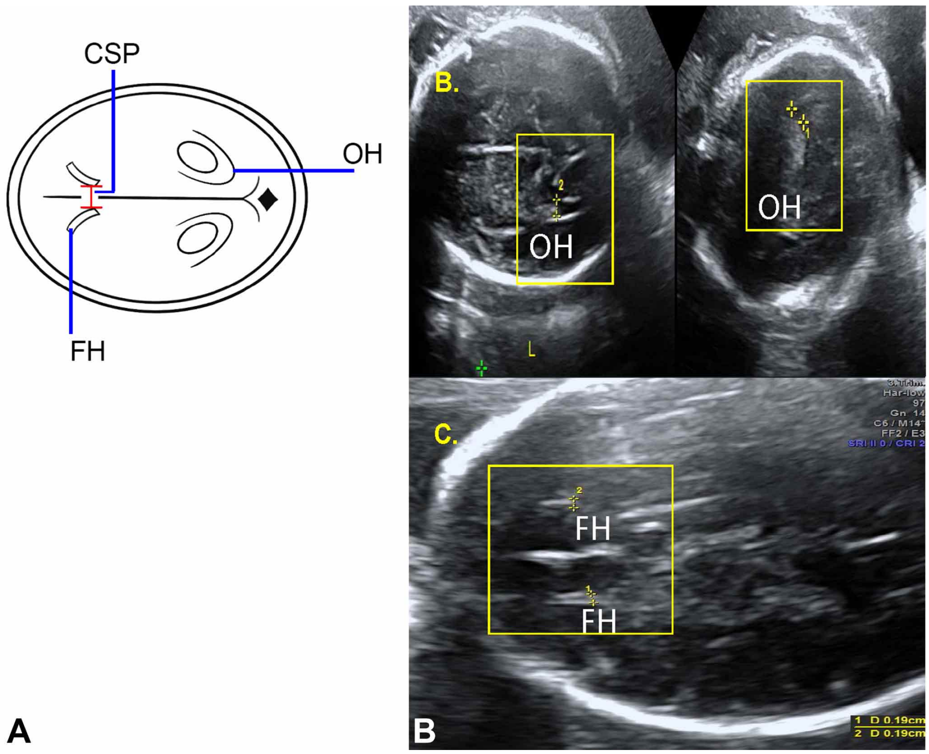

Fig. 2. Measurement diagram of lateral ventricle. A. The sketch of the lateral ventricle; B. the ultrasound measurement of the OHW; C. the ultrasound measurement of the FHW. OH: occipital horn; FH: frontal horn; CSP: cavity of septum pellucidum.

All the examined ventricular dimensions were diagramed in Figures 2 to 5. Followed the ISUOG practice guideline, width of the lateral ventricles measured in transventricular plane (Farrell *et al*., 1994) (Figs. 2 A-C). Additionally, TOD is defined as the distance between the outermost point of the thalamus at its junction with the choroid plexus and the outermost part of the occipital horn in the parasagittal plane (Brouwer *et al*., 2012), it was measured from its junction with the choroid plexus (the distance was marked by the symbol + + in Figures 3 A-B). The measurement for width of 3rd ventricle was taken from one inner edge to the other inner edge of the thalamus. Width of 3rd ventricle and CSP were measured in the transthalamic plane (Figs. 4 A-C). For the cerebellar ultrasound; 4th ventricle is triangular in shape (Figs. 5A); width of 4th ventricle is the distance between the lateral recesses, it also means the left and right diameter line of 4th ventricle(the distance was marked by the symbol ** in Figure 5B).The length of 4th ventricle is the distance from the apex to the base (Davies *et al*., 2000), which means the front and rear diameter line of 4th ventricle (the distance was marked by the symbol # # in Figure 5B). Dimensions of 4th ventricle were measured in the trans-cerebellar plane.

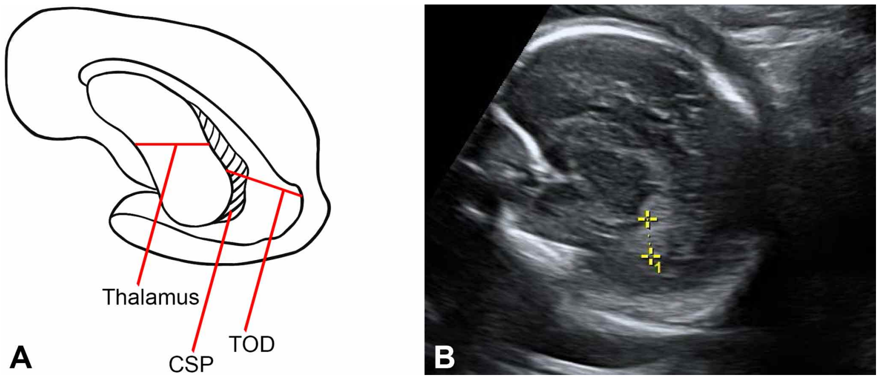

Fig. 3. Measurement diagram of the TOD. A. The sketch of the TOD of human fetus; B. the ultrasound picture of TOD, the distance was marked by the symbol + +. TOD: thalamo-occipital distance; CSP: choroid plexus.

Statistical Methods. Pearson's coefficient of correlation(r) was used to examine the relationship between each dimension of the ventricles and GA. The strength of the relationship was weak when the absolute value of correlation coefficient was less than 0.2; moderate when between 0.21 and 0.4; fair when between 0.41 and 0.6; good when between 0.61 and 0.8 and very good when ≥0.81. To evaluate the differences between the left and right ventricle, Wilcoxon test was performed, p≤0.05 was considered statistically significant.

Statistical calculations were performed using Graph Pad Prism software (version 7.0 for Mac Os X, GraphPad Software). All data was analyzed to determine by the coefficient of correlation(r), regression equations and plotted against GA.

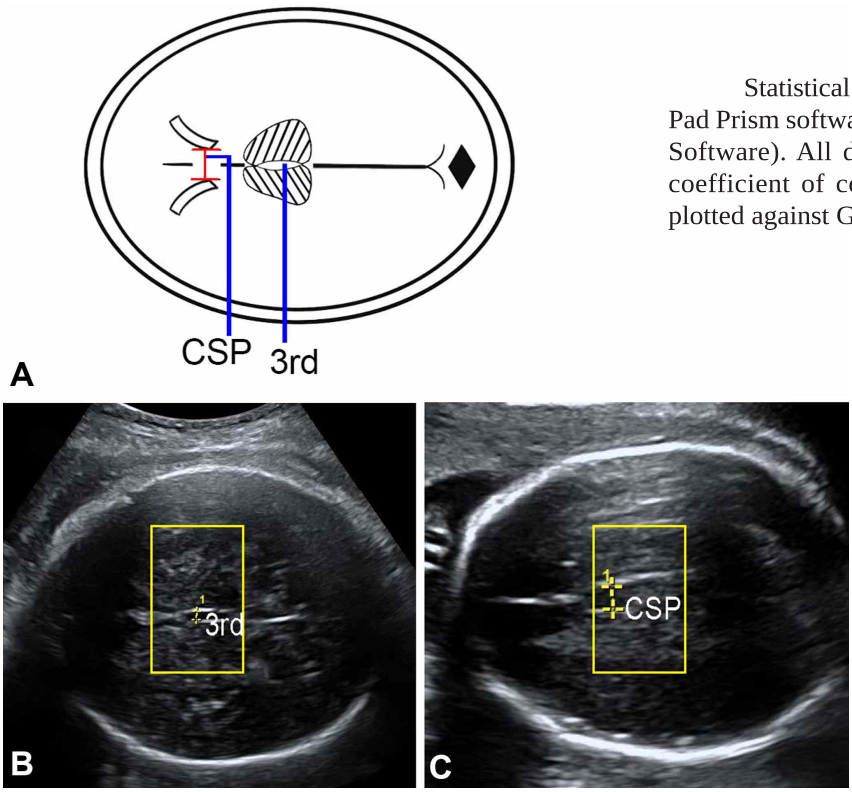

Fig. 4. Measurement diagram of 3rd ventricle and CSP. A. The sketch of the 3rd ventricle and CSP; B. the ultrasound measurement of 3rd ventricle, the distance was marked by the symbol + +; C. the ultrasound picture of the CSP, the distance was marked by the symbol + +. 3rd: the third ventricle; CSP: cavity of septum pellucidum.

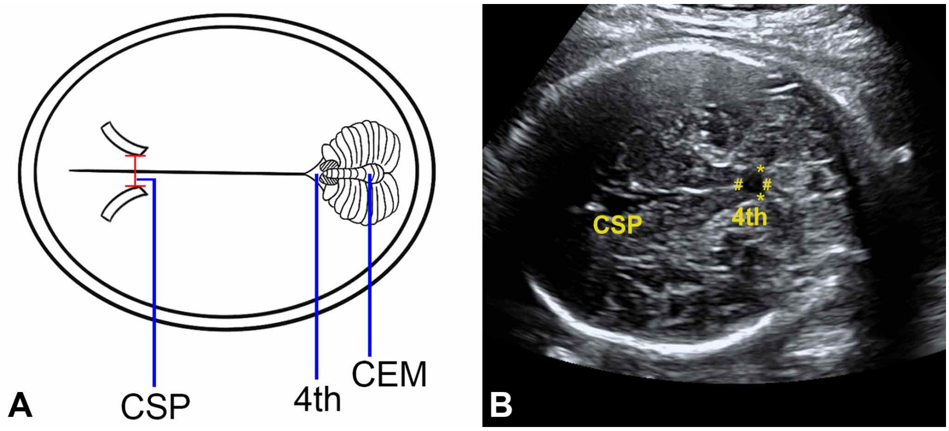

Fig. 5. Measurement diagram of 4th ventricle A. The sketch of the 4th ventricle, CSP and CEM; B. the ultrasound measurement of 4th ventricle. 4th: the fourth ventricle; CSP: cavity of septum pellucidum; CEM: cerebellum. The distance between * * means the width of 4th ventricle (left and right diameter line of the 4th ventricle). The distance between # # means the length of 4th ventricle (front and rear diameter line of the 4th ventricle).

RESULTS

In the present study, we collected the ventricular developmental data from two experimental groups. In cross section study, 235 pregnant women (between 16-week to 39-week GA) with healthy singleton pregnancies were recruited. Another 36 pregnant women (between 16-week to 39-week GA) voluntarily joined in a timeline follow-up ultrasound measurement in order to enhance the reliability and to control the data from cross section study; for each fetus in cohort study, the ventricular dimensions were examined every 4 weeks.

Owing to unqualified data or unsuccessful scan and such, some collected data was excluded for final evaluation. As a result, for cross section study, a total of 470 scans (235 pregnancies) of OHW, 420 scans (210 pregnancies) of FHW, 444 scans (222 pregnancies) of TOD, 446 scans (223 pregnancies) of width of the 3rd ventricle, 462 scans (231 pregnancies) of CSP, 442 scans (221 pregnancies) of the length of 4th ventricle and 448 scans (224 pregnancies) of the width of 4th ventricle were successfully achieved. For cohort study, a total of 424 scans (212 pregnancies) of OHW, 398 scans (199 pregnancies) of FHW, 382 scans (191 pregnancies) of TOD, 362 scans (181 pregnancies) of width of the 3rd ventricle, 408 scans (204 pregnancies) of CSP, 370 scans (185 pregnancies) of the length and the width of 4th ventricle were available for final analysis.

The morphological changes of the lateral ventricles with GA. In cross section study, both of OHW and FHW showed decreasing tendencies as GA increased (Figs. 6A-1, C-1). However, according to the negative r (coefficient of correlation) values of OHW, FHW against GA, OHW showed a weak decreasing trend (L: -0.116, R: -0.094), but the decreasing trend of FHW was comparatively moderate to fair (L: -0.437, R: -0.371). The values of OHW were generally stable throughout the pregnancy (Figs. 6 A-1). In cohort study, OHW and FHW showed similar decreasing tendencies (Figs. 6 B-1, D-1); however according to the r values (L: -0.171 and R: -0.398 of OHW, L: -0.639 and R: -0.597 of FHW, dimensional size against GA), the tendency of OHW and FHW were more significant compared to the relative data in cross section study (Table I).

The percentiles for OHW and FHW showed median, 5th, and 95th percentiles for both of the two research groups (Fig. 6 B-1, 2 and Fig. 6 D-1, 2). In cross section study, the values of OHW remained relatively stable or decreased

Table I. Correlation coefficient and asymmetry of the ventricular dimensions in both of cross section study and cohort study.

	Pearson r value				Wilcoxon test p value	
CSP	**0.584**		**0.650**			
3rd	**0.661**		**0.726**		**N/A**	
WFV	**0.817**		**0.911**			
LVF	**0.605**		**0.693**			
	L		R			
OHW	**-0.116**	**-0.094**	**-0.094**	**-0.199**	**0.199**	**P<0.05**
FHW	**-0.437**	**-0.371**	**-0.371**	**P<0.05**	**P<0.05**	**P<0.05**
TOD	**0.158**	**0.203**	**0.203**	**P<0.05**	**P<0.05**	**P<0.05**

The values with a blue background indicate data from cross section study; the values with a green background indicate data from cohort study; Pearson r value represents correlation coefficient of two studies, Wilcoxon test p value indicates the asymmetry of the two hemispheres. 3rd: the third ventricle; CSP: cavity of septum pellucidum; 3rd: width third ventricle; WFV: width of 4th ventricle; LFV: length of 4th ventricle; OHW: width occipital horn; FHW: width frontal horn; TOD: thalamo-occipital distance.

slightly throughout the pregnancy; however, after 24-week GA, the distribution of the values of OHW became more dispersed (Fig. 6 B-1). The value of FHW decreased fairly from 16-week to 24-week GA, and stabilized after 24-week GA; and the overall values of FHW were evenly distributed throughout the pregnancy (Fig. 6 D-1). The similar trend could be observed in cohort study, except that the distribution of values of OHW and FHW was more concentrated, and yet a more dispersed distribution of OHW values could be observed after 24-week GA (Fig. 6 B-2, D-2).

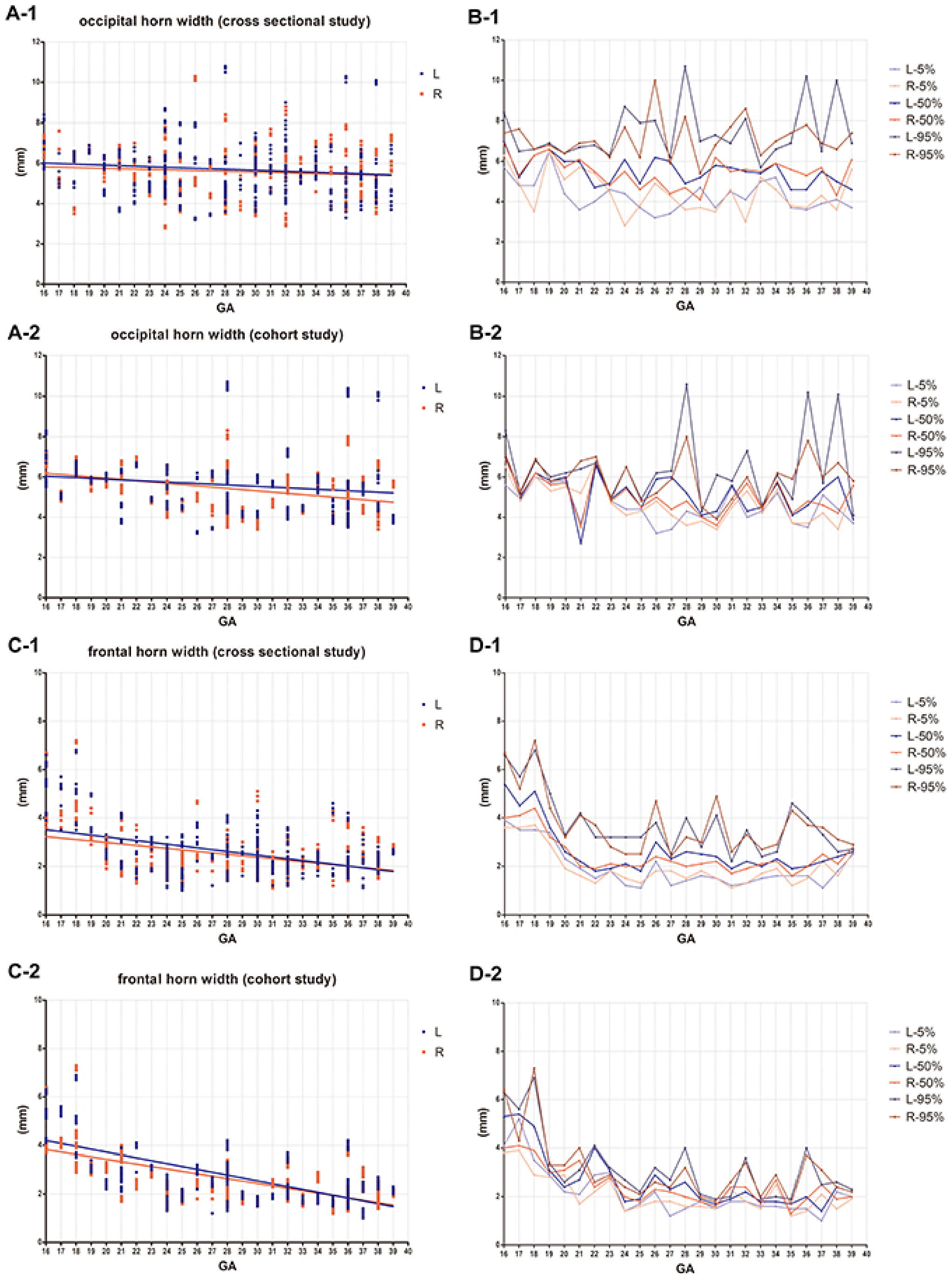

Fig. 6. Developmental regularities of OHW and FHW against GA. A-1. The scatter plot and correlation coefficient of OHW in cross section study; B-1. the percentiles for OHW in cross section study; A-2. the scatter plot and correlation coefficient of OHW in cohort study; B-2. the percentiles for OHW in cohort study; C-1. The scatter plot and correlation coefficient of FHW in cross section study; D-1. the percentiles for FHW in cross section study; C-2. the scatter plot and correlation coefficient of FHW in cohort study; D-2. the percentiles for FHW in cohort study; OHW: width occipital horn; FHW: width frontal horn.

The morphological changes of TOD with GA increased. In both research groups, TOD showed increasing tendency as GA increased (Fig. 7 A-1, A-2). However, the increasing tendency of TOD was fair in cohort study (L: 0.520, R: 0.467), while the increasing tendency of TOD was weak (L: 0.158, R: 0.203) in cross section study according to the r values (Table I).

The percentiles for TOD showed median, 5th, and 95th percentiles for both of two research groups (Fig. 7 B-1, 2). In cross section study, the values of TOD remained relatively stable or increased slightly throughout the pregnancy; whereas between 24-week to 32-week GA, the distribution of the values of TOD became more dispersed (Fig. 7 B-1). The similar trend could be observed in cohort study, except that the distribution of values of TOD was comparatively more concentrated (Fig. 7 B-2).

The morphological changes of the 3rd and 4th ventricles with GA. In both of cross section and cohort studies, dimensions of 3rd ventricle, CSP, as well as 4th ventricle all showed a clear increment as GA increased (CSP: fair, width of 3rd: good, WFV: very good, LFV: good, according to Table I). Moreover, these indicators showed highest increasing trend at the early GA and then went down in late gestational age, especially after 24-weekGA (Figs. 8 and 9).

In cohort study, the tendencies of the same indicators (dimensions of 3rd, 4th ventricle, and CSP), was more significant compared to the relative data in cross section study according to the r values (Table I).

The percentiles showed median, 5th, and 95th percentiles for both of the two research groups. In cross section study, the distribution of the values of dimensions of 3rd ventricle, CSP, width and length of 4th ventricle became more dispersed compared in cohort study (Fig. 8, Fig. 9).

The FHW and TOD showed significant asymmetry during the pregnancy. In the resent study, the Wilcoxon test was used to check the asymmetry of paired hemispheres. The Wilcoxon p values of FHW in both of cross section study and cohort study, as well as the p value of OHW in cohort study showed statistical significance, which indicated that the developmental asymmetry of the two cerebral hemispheres during the whole pregnancy. However, the p value of OHW was not statistically significant in cross section study, indicating the developmental symmetry of the two hemispheres during the GA (Table I).

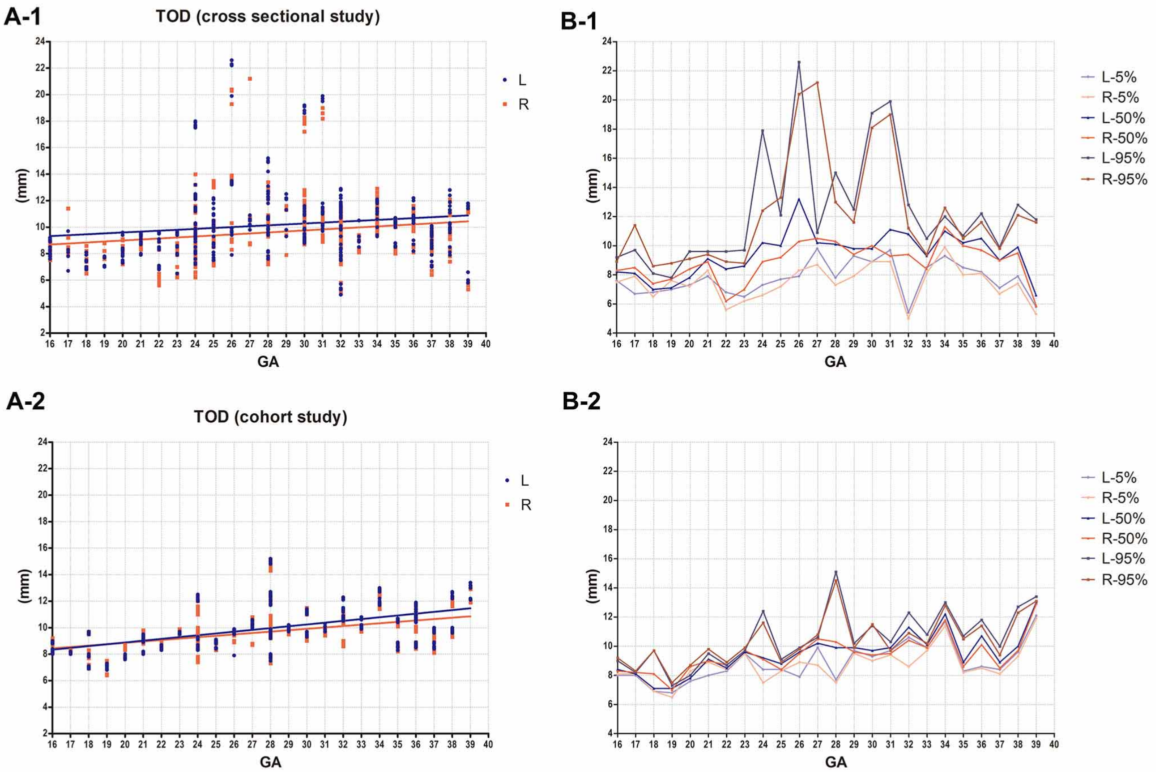

Fig. 7. Developmental regularities of TOD against GA. A-1. The scatter plot and correlation coefficient of TOD in cross section study; B-1. the percentiles for TOD in cross section study; A-2. the scatter plot and correlation coefficient of TOD in cohort study; B-2. the percentiles for TOD in cohort study; TOD: thalamo-occipital distance.

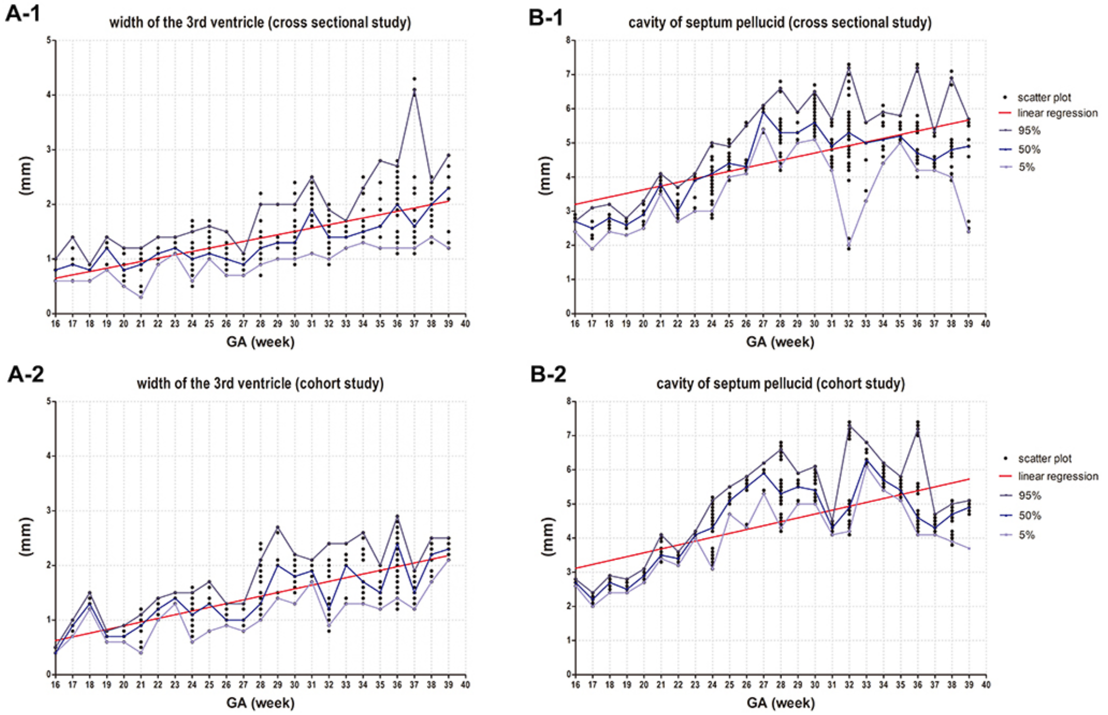

Fig. 8. Developmental regularities of 3rd ventricle and CSP against GA. A-1. The scatter plot and correlation coefficient of the width of 3rd ventricle in cross section study; A-2. the scatter plot and correlation coefficient of the width of 3rd ventricle in cohort study; B-1. the scatter plot and correlation coefficient of CSP ventricle in cross section study; B-2. the scatter plot and correlation coefficient of CSP in cohort study; CSP: cavity of septum pellucidum.

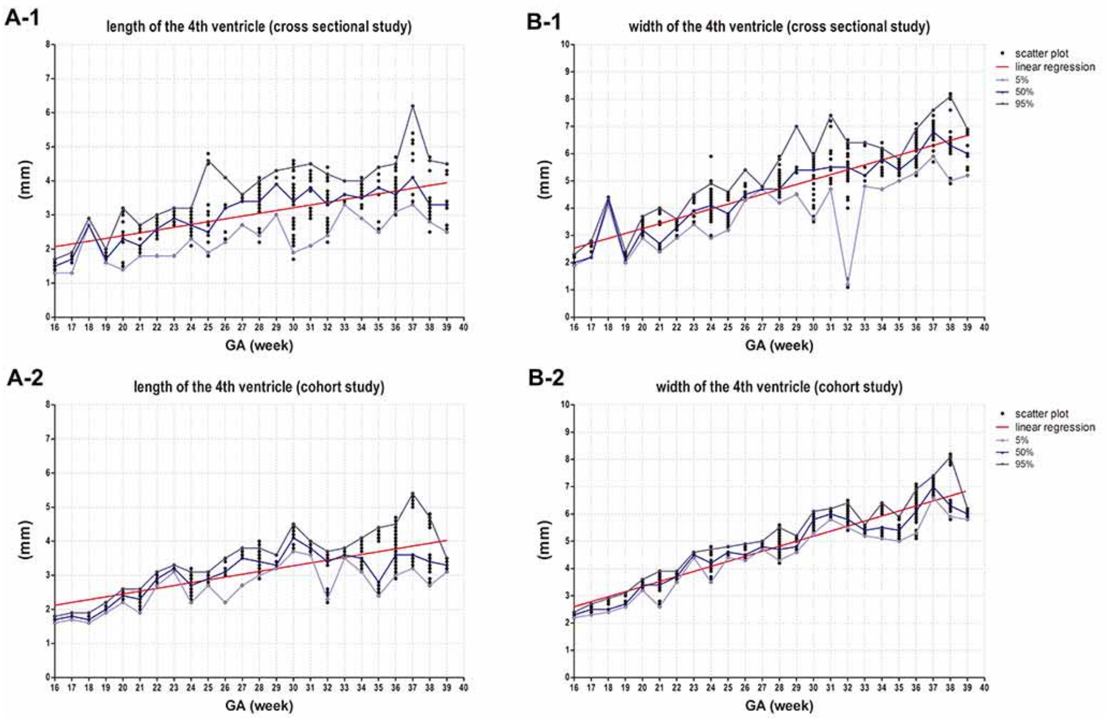

Fig. 9. Developmental regularities of 4th ventricle against GA. A-1. The scatter plot and correlation coefficient of the length of 4th ventricle in cross section study; A-2. The scatter plot and correlation coefficient of the length of 4th ventricle in cohort study; B-1. the scatterplot and correlation coefficient of the width of 4th ventricle in cross section study; B-2. the scatter plot and correlation coefficient of the width of 4th ventricle in cohort study.

Furthermore, the Wilcoxon p values of TOD in both of the two research groups showed statistical significance, indicated that the developmental asymmetry of the two cerebral hemispheres in the whole pregnancy.

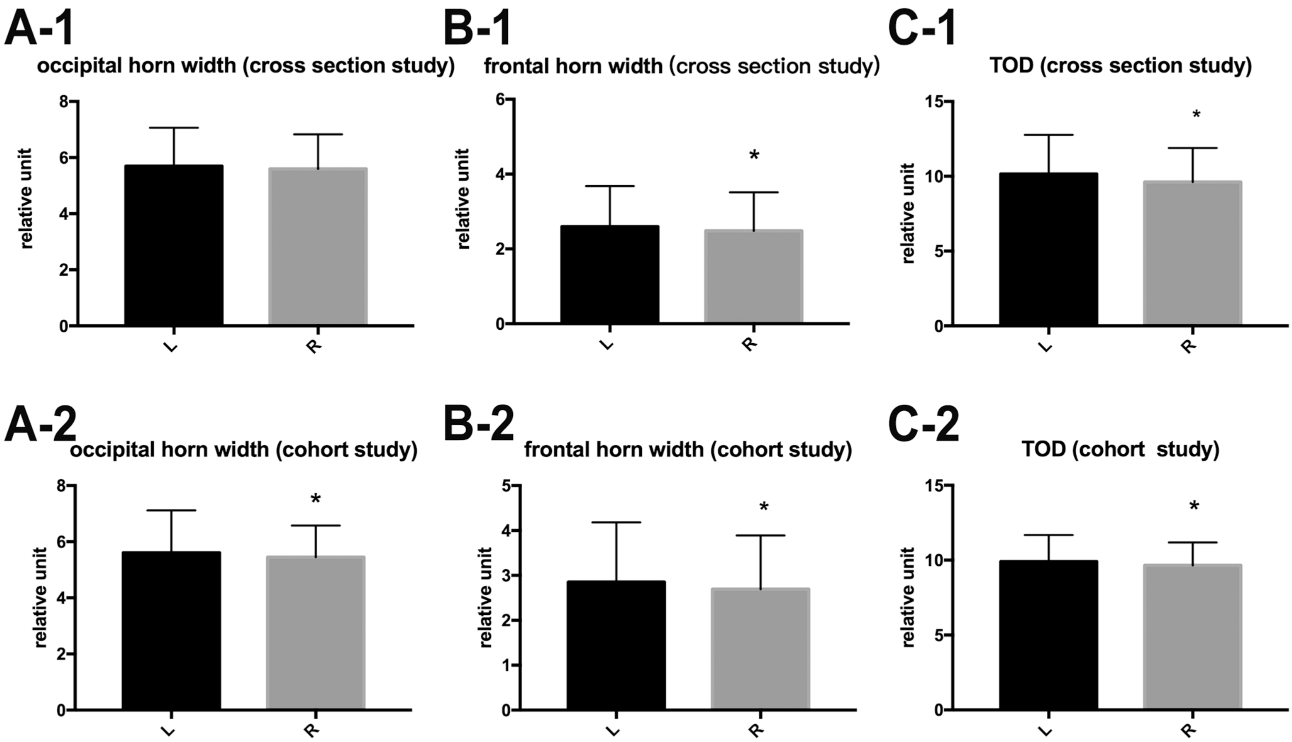

Fig. 10. Asymmetry of the ventricular dimensions. A-1. The asymmetry between the width of left and right occipital horn in cross section study. (n=470, p=0.508, Wilcoxon test); A-2. the asymmetry between the width of left and right occipital horn in cohort study (n=424); B-1. the asymmetry between the width of left and right frontal horn in cross section study (n=420); B-2. the asymmetry between the width of left and right frontal horn in cohort study (n=398); C-1. the asymmetry between TOD of left and right hemispheres in cross section study (n=444); C-2. the asymmetry between TOD of left and right hemispheres in cohort study (n=382); “*”: $p<0.05$, Wilcoxon test; TOD: thalamo-occipital distance.

DISCUSSION

The ventricular system consists of one pair of the lateral ventricles, the third and fourth ventricles; the interventricular foramina (Monro) connects the lateral ventricles to the third ventricle, the cerebral aqueduct (Sylvius) connects the third ventricle and the fourth ventricle, median aperture (Magendi) connects the fourth ventricle to subarachonoid space and cerebellomedullary cistern (CM) and the lateral apertures (Luschka) connect the fourth ventricle with the subarachnoid space and the cistern of the great cerebral vein. The CSF has been recognized as a natural cushion for the brain. Moreover, the CSF provides the circulation of metabolic products, hormones, and some of the neurotransmitters. In recent studies, the CSF was also considered to take part in maintaining the homeostatic balance of the central nervous system, protecting the brain against mechanical injuries, preventing direct contact of the brain with the extracellular region (Soytürk *et al*., 2021). Normal development of fetal ventricular system is conducive to the establishment and maintenance of CSF circulation, which is of great significance to the entire central nervous system.

The complexity of the fetal brain development in a variety of malformations that at times appear exactly challenging to diagnosis. However, the key to correctly diagnose these malformations lie in understanding the embryology, the certain structures appears in crucial gestational age and being very familiar with the morphological features of the brain in different scanning sonographic planes.

The CNS undergoes tremendous transformation in the first trimester, during the second and the third trimesters, the CNS slows its development pace. However, this period is characterized by an unparalleled growth of the brain volume (Monteagudo & Timor-Tritsch, 2009); Some of these changes can be imaged by CUS especially those that relate to the corpus callosum, CSP, ventricular system, cerebellum, vermis, and finally the development of gyri and sulci.

Dimensional changes regularity of lateral ventricles against GA. The lateral ventricles are in a parallel manner within the cerebral hemispheres and have three horns, including frontal, occipital and inferior horns, a body and a triangular atrium. Initially, the lateral ventricles appear larger due to the thin brain parenchyma and consist mostly of the frontal and inferior horns, it becomes slender as the pregnancy progresses. The occipital horn grow with the pregnancy progresses and at the 18-week GA the occipital horn can be clearly defined (Monteagudo & Timor-Tritsch, 2009).

As the lateral ventricles have the largest ventricular volume, they are currently considered to be the most important and reliable diagnostic indicators in fetal ventricular ultrasonography, morphological anomalies of the lateral ventricles can be a clue to several pathologies of the fetal nervous system.

Choroid plexuses in the ventricles, especially in the lateral ventricles are important landmark in the development of the CNS. During the first trimester the choroid plexuses fills the entire lateral ventricle; as the gestation progresses, their size decreases. Similarly, in the present study, our data showed that although both of OHW and FHW decreased weakly as GA increased, the values of OHW generally stayed at a stable level throughout the pregnancy (Fig. 6-A, C).

Increased ventricular dimensions and partial/complete absence of the choroid plexus were related to brain malformation. Progressive ventricular dilations determined by ultrasonography were signs of disturbed CSF dynamic. Amongst the developmental disorders, the ventriculomegaly (VM) is the most common fetal nervous system dysplasia. This disease refers to dilation of the cerebral ventricles and often has a poor prognosis and is associated with cerebral and/or extra-cerebral pathologies (D'Addario, 2004; Nagaraj *et al*., 2018).

Dilation of the lateral ventricles can be a clue to several pathologies of the fetal nervous system including VM. Based on previous publications, the established values of fetal cerebral lateral ventricles dimensions are: normal (<10mm), mild VM (10-12mm), moderate VM (13-15mm), and severe VM (>15mm) (D'Addario, 2015). Moreover, previous studies suggested that occipital horn enlarges at a greater rate than the anterior and middle regions of lateral ventricle in post-hemorrhagic ventricular dilatation (PHVD) (Brann 4th *et al*., 1991), implied the OHW has a greater diagnostic significance.

In the present study, our data showed that although the values of OHW remained relatively stable throughout the whole pregnancy, a more dispersed distribution of OHW values could be observed after 24-week GA (Fig. 6-B), which implied that after the basic formation of lateral ventricle, OHW will still undergo major changes after 24-week GA, and so that the third trimester of GA should be considered as the key observation period for ultrasound diagnosis of OHW.

However, on the other hand, in the present study, at the point of 28-week GA, we found that OHW values of some fetuses were>10.0mm, but <12mm, which indicated a mild dilation. These individuals were re-examined at 32-week and 36-week GA. In view of the downward tendency of this value and without any abnormality of other ventricular indicators, we just conducted a strict ultrasound follow-up and did not recommend termination of pregnancy. These fetuses are currently elder than 4-year old and healthy, no pathological abnormalities were found up to date. This indicated that mildly oversized OHW may not be sufficient to cause pathological changes in fetal neural system development.

According to previous study, FHW is the most prominent in the early second trimester, decreasing in the late second trimester, followed by a plateau in the third trimester (Perry *et al*., 1985). Our data revealed a similar developmental regularity. FHW showed a decreasing tendency in the whole pregnancy in both of cross section and cohort studies (Fig. 6-C); furthermore, it could be found that FHW decreased significantly between 16-week and 20-week GA, and then showed a relatively gentle decreasing trend until term (Fig. 6-D), this might be due to the increasing occupation of the choroid plexus within FHW. In general, FHW declined significantly between 16-week and 20-week GA, and any unrelated ultrasound measurements in this period could suggest abnormal lateral ventricle development.

Dimensional changes regularity of CSP against GA. At fetal stage, CSP was separated, single and thin cavity between the two leaves of thalami. According to a publication at 1998, the fetal CSP width increased between 19-week and 27-week GA and plateaued between 28-week GA and term (Jou *et al*., 1998). In the present study, our data revealed that the CSP showed a fair increasing tendency as GA increased; in addition, our data demonstrated that the values of CSP still showed a dispersed distribution after 28-week GA (Fig. 8 B-1, 2). These results collectively implied that some obvious morphological changes may still occur in CSP within this period of GA, which is of significance for clinical CUS.

Furthermore, failure of CUS visualization of CSP was associated with neuropathology (Falco *et al*., 2000). In cross section study and cohort study, the visualization rate of CSP was 98.3 % (462/470) and 96.3 % (408/424). Some fetuses with GA of 16-week were undetectable due to improper examine position, indicated the importance of serial CUS in the second and third trimesters to determine the visibility of CSP, which is of clinical significance.

Dimensional changes regularity of 3rd and 4th ventricles in GA. The Combined dimensions of 3rd and 4th ventricle with the lateral ventricles contribute significantly to differentiate communicating and non-communicating VM. As a result, we also introduced the dimensions of 3rd and 4th ventricles in fetuses ultrasound measurements.

The 3rd ventricle is a thin rectangular structure that begins posterior to its inlet. 3rd ventricle could be detected by CUS at approximately 10-week GA (Hertzberg *et al*., 1997). In most fetuses at second and third trimesters, it can be clearly recognized on sonograms. Early in pregnancy choroid plexus are located in the frontal horn of the lateral ventricles; and then moves posteriorly; as a result, the CSF fills the cavity of 3rd ventricle mainly in third trimester. Thus with the development of the fetal CNS, 3rd ventricle increased with GA. In the present study, it was demonstrated that 3rd ventricle indeed showed an obvious upward tendency as GA increased. Moreover, the r value of 3rd ventricle implied a good correlation with GA (Fig. 8-A). At any stage of GA, if the width of 3rd ventricle was larger than 3.5mm, morphological abnormality should be suspected (Hertzberg *et al*., 1997). In the present study, dimensional values of the width of 3rd ventricle were found to be less than 3.5mm except in two fetuses with 37-week GA, we thus in parallel checked the other ventricular measurement values of these two fetuses. All of these values were within the normal range, and these two fetuses were later born healthy, this collectively indicated that whenever a certain indicator shows an abnormal tendency, it is clinically essential to comprehensively observe and consider the whole index of ventricular development. Additionally, three different shapes of 3rd ventricle has been found so far (D'Addario, 2015),which are single line type, parallel type and “V” type. According to previous study, within early second trimester, most of the fetuses showed single echogenic lines in CUS. As the brain and ventricular structures matured, a paralleled echogenic line becomes the prominent CUS appearance in the third trimester (Sari *et al*., 2016). Similarly, the parallel type was most commonly detected in the present study.

For 4th ventricle, the cerebellar peduncles form the lateral walls, while the roof is formed by the medullary velum, the cerebellar nodulus and part of the cerebellar peduncles, the floor is delineated by the surface of the pons and the medullar oblongata. At the end of the first trimester, 4th ventricle and the cisterna magna are visible in CUS (De Keersmaecker *et al*., 2011). According to our results, it was demonstrated that the dimensions of 4th ventricle showed good to very good increasing tendencies as GA increased (Fig. 9), which is similar to previous findings, and this may be due to the growth of the cerebellum, as the growth of cerebellum correlates with GA (da Graça *et al*., 2013). Furthermore, in the present study, compared to the lengths of 4th ventricle, the widths of 4th ventricle showed a more stronger increasing trend with GA (Fig. 9), which indicated that the development of the pons and medulla oblongata was faster than that of the cerebellar peduncles.

Importance of the TOD measurement. Since the occipital horn of the lateral ventricle is one of the most important indicators of fetal ventricular development (Davies *et al*., 2000). In the present study, we additionally quoted TOD in prediction of fetal dimensional changes of the occipital horn of the lateral ventricle. Currently, the dimension of TOD is used as the key value to predict ventricular volume of PHVD in preterm infants (Benavente-Fernandez *et al*., 2017). However in recent year, a study in 2020 introduced TOD in ultrasound diagnosis to predict the volume of the fetal lateral ventricle (Beijst *et al*., 2020). Moreover, a study in 2021 introduced TOD as a key indicator of fetal brain ventricle, which contributes to the prediagnosis of the intracranial hemorrhage (Is¸ık *et al*., 2021). Collectively, as a novel ultrasound indicator, TOD enables us to use the same measurement index before and after birth to facilitate the CUS observation of the ventricular development.

Recognized as a commonly used indicator of CNS development, however so far, clinically, TOD has been merely used in diagnose of neonates. In the present study, we for the first time introduced values of TOD to monitor the size of fetal lateral ventricle as one of main indicators for fetal brain development. For these reasons, no previous indicative data on TOD of the fetuses is available as a control.

According to the data of the present study, dimensional values of TOD showed a moderate increasing tendency as GA progressed (Fig. 6-A); on the other hand, especially in cross section study, the values of TOD displayed a more divergent distribution after 24-week GA, reflected the consistency with OWH's regularity during the whole pregnancy (Fig. 6-B). Along with the result of OHW, it was indicated that the lateral ventricle will still undergo major changes in the third trimester of GA, and thus the third trimesters of GA should be considered as the key observation period for CUS of both of OHW and TOD.

According to the previous researches on neonates, there is no consensus about TOD changes with increasing GA. Part of previous researches suggested that TOD increased with GA because the maturity of infants ventricles as GA increases (Brouwer *et al*., 2012). Other research suggested that TOD in preterm neonates had a much lower value for r (coefficient of correlation, TOD values against GA), which means TOD was a more stable marker to determine the enlargement of the occipital horn of the lateral ventricles, and thus the post hemorrhagic ventricular dilatation of the fetuses can be measured in prenatal diagnosis of hydrocephalus with abnormal value of TOD (Davies *et al*., 2000). Moreover, as the TOD values in neonates without brain abnormality were less than 24 mm, a TOD value >24 mm suggested in-depth CUS observation should be performed additionally (Brouwer *et al*., 2012). In the present study, the values of TOD were all less than 24 mm, although TOD values were divergent after 24-week GA in the present study. Furthermore, in the general view, TOD values increased weakly during the whole pregnancy ($r=0.158$ for L, $r=0.203$ for R, $p<0.01$) in cross section study, but increased fairly with GA ($r=0.520$ for L, $r=0.467$ for R, $p<0.01$) in the 36 women of cohort study, these results suggested more in-depth observation of TOD may be necessary in future. Considering the continuity and contrast, in the present study, the dataset obtained from the cohort study may have more profound clinical significance.

Developmental asymmetry of ventricular hemispheres. According to previous publications, the left ventricular prominence was observed in most of the cases, the authors suggested it is not pathological but due to physiological individual differences or a larger choroid plexus, the birth weight, birth length, as well as the head position of the infants while being examined (Ichihashi *et al*., 2002). In the present study, all of the ventricular indicators except OHW in cross section study showed a similar asymmetry (Table I). According to our data, during the ventricular development, the left side appeared slightly larger compared to the right side (Fig. 10). We were not yet clear about the specific factors that contribute to the results of the outcome to the unbalanced development. However, we believe that these results must have more profound physiological implications for the development of the entire human central nervous system. As this result, we are continuing to carry out the related research of this topic, including continuing to measure and collect data on bilateral values of OHW, FHW and TOD during fetal ventricular development, and conduct more in-depth comparisons in order to dig out more significant findings.

In conclusion, the human brain primarily develops in fetal stages; CUS provides a convenient, safe and repeatable method to measure the ventricular dimensions in fetuses. The results of the resent study revealed the morphological change regularities during the GA. At the same time, the data of the present study could be taken as an improvement and expansion to the current diagnostic index. Additionally, according to the data of the present study, TOD could be considered as an important clinical indicator for evaluating lateral ventricle development.

ACKNOWLEDGMENTS. This study was supported by Liaoning provincial department of education (507058); Natural Science Foundation of China (NSFC31871213, NSFC32071184). This work was not associated with any commercial entity.

YUE, C.; DING, Q.; HENG, Y.; YU, S. B.; GONG, J.; WANG, Y. F.; LI, C. & SUI, H. J. Índice morfológico del desarrollo ventricular cerebral fetal: un estudio ecográfico diagnóstico. *Int. J. Morphol., 40(5)*:1308-1320, 2022.

RESUMEN: El objetivo del estudio fue establecer un índice de referencia indicativo diagnóstico no demostrable para el examen ecográfico de los ventrículos cerebrales fetales, basado en las características morfológicas a lo largo del desarrollo del sistema nervioso fetal. Indicadores morfológicos ultrasónicos clave del desarrollo ventricular fetal, que incluyen el ancho del cuerno frontal (FHW), el ancho del cuerno occipital (OHW), el ancho del tercer ventrículo, la cavidad del septo pelúcido (CSP), el ancho y el largo del cuarto ventrículo y la distancia tálamo-occipital (TOD) fueron medidos y analizados conjuntamente. Todos los datos de los indicadores se recopilaron en mujeres embarazadas de un solo feto entre 16 y 39 semanas de edad gestacional (EG), entre noviembre de 2017 y junio de 2021 en el Segundo Hospital de la Universidad Médica de Dalian. Un total de 235 mujeres embarazadas se inscribieron en el estudio transversal; otras 36 mujeres embarazadas se unieron voluntariamente a un estudio de seguimiento de línea de tiempo (estudio de cohorte) bajo los mismos criterios de examen. Se observó una disminución de FHW y OHW de los ventrículos laterales a medida que aumentaba la GA; mientras que los valores dimensionales de TOD, tercer ventrículo, CSP y cuarto ventrículo aumentaron con GA. La mayoría de estos indicadores mostraron una tendencia de variación mejorada dentro de un cierto período de GA. Además, los valores de FHW y TOD mostraron asimetría de los dos hemisferios dentro de toda la AG. Nuestros hallazgos revelaron la regularidad morfológica del desarrollo ventricular fetal, lo que mejoraría de manera instructiva el diagnóstico clínico de ultrasonido relativo; además, TOD también mostró cambios regulares a medida que aumentaba la GA, lo que sugiere que TOD debe considerarse como un indicador ultrasónico de rutina adicional para el desarrollo ventricular fetal.

PALABRAS CLAVE: Desarrollo ventricular fetal; índice de medición de ultrasonido craneal prenatal; Morfología cerebral.

REFERENCES

Beijst, C.; Dudink, J.; Wientjes, R.; Benavente-Fernandez, I.; Groenendaal, F.; Brouwer, M. J.; Isgum, I.; de Jong, H. W. A. M. & de Vries, L. S. Two-dimensional ultrasound measurements vs. magnetic resonance imaging-derived ventricular volume of preterm infants with germinal matrix intraventricular haemorrhage. *Pediatr. Radiol., 50(2)*:234-41, 2020.

Benavente-Fernandez, I.; Lubián-Gutierrez, M.; Jimenez-Gomez, G.; Lechuga-Sancho, A. M.; Lubián-López, S. P. & Neonatal Neurology Foundation (Fundación Nene). Ultrasound lineal measurements predict ventricular volume in posthaemorrhagic ventricular dilatation in preterm infants. *Acta Paediatr., 106(2)*:211-7, 2017.

Brann 4th, B. S.; Qualls, C.; Wells, L. & Papile L. Asymmetric growth of the lateral cerebral ventricle in infants with posthemorrhagic ventricular dilation. *J. Pediatr., 118(1)*:108-12, 1991.

Brouwer, M. J.; de Vries, L. S.; Groenendaal, F.; Koopman, C.; Pistorius, L. R.; Mulder, E. J. H. & Benders, M. J. N. L. New reference values for the neonatal cerebral ventricles. *Radiology, 262(1)*:224-33, 2012.

Cagneaux, M.; Vasiljevic, A.; Massoud, M.; Allias, F.; Massardier, J.; Gaucherand, P. & Guibaud, L. Severe second-trimester obstructive ventriculomegaly related to disorders of diencephalic, mesencephalic and rhombencephalic differentiation. *Ultrasound Obstet. Gynecol., 42(5)*:596-602, 2013.

D'Addario, V. Fetal mild ventriculomegaly: still a challenging problem. *J. Perinat. Med., 43(1)*:5-9, 2015.

D'Addario, V. The role of ultrasonography in recognizing the cause of fetal cerebral ventriculomegaly. *J. Perinat. Med., 32(1)*:5-12, 2004.

da Graça, A. L. F. M.; Cardoso, K. R. V.; da Costa, J. M. F. P. & Cowan, F. M. Assessment of gestational age using cerebellar measurements at cranial ultrasound: what is the best approach? *Early Hum. Dev., 89(1)*:1-5, 2013.

Davies, M. W.; Swaminathan, M.; Chuang, S. L. & Betheras, F. R. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. *Arch. Dis. Child. Fetal Neonatal Ed., 82(3)*:F218-23, 2000.

De Keersmaecker, B.; Claus, F. & De Catte, L. Imaging the fetal central nervous system. *Facts Views Vis. Obgyn., 3(3)*:135-49, 2011.

Falco, P.; Gabrielli, S.; Visentin, A.; Perolo, A.; Pilu, G. & Bovicelli, L. Transabdominal sonography of the cavum septum pellucidum in normal fetuses in the second and third trimesters of pregnancy. *Ultrasound Obstet. Gynecol., 16(6)*:549-53, 2000.

Farrell, T. A.; Hertzberg, B. S.; Kliewer, M. A.; Harris, L. & Paine, S. S. Fetal lateral ventricles: reassessment of normal values for atrial diameter at US. *Radiology, 193(2)*:409-11, 1994.

Hertzberg, B. S.; Kliewer, M. A.; Freed, K. S.; McNally, P. J.; DeLong, D. M.; Bowie, J. D. & Kay, H. H. Third ventricle: size and appearance in normal fetuses through gestation. *Radiology, 203(3)*:641-4. 1997.

Ichihashi, K.; Iino, M.; Eguchi, Y.; Uchida, A.; Honma, Y. & Momoi, M. Difference between left and right lateral ventricular sizes in neonates. *Early Hum. Dev., 68(1)*:55-64, 2002.

Isık, S¸.; Büyüktiryaki, M.; Simsek, G. K.; Kutman, H. G. K. & Canpolat, F. E. Relationship between biparietal diameter/ventricular ratio and neurodevelopmental outcomes in non-handicapped very preterm infants. *Childs Nerv. Syst., 37(4)*:1121-6, 2021.

Jou, H. J.; Shyu, M. K.; Wu, S. C.; Chen, S. M.; Su, C. H. & Hsieh, F. J. Ultrasound measurement of the fetal cavum septi pellucidi. *Ultrasound Obstet. Gynecol., 12(6)*:419-21, 1998.

Malinger, G.; Paladini, D.; Haratz, K. K.; Monteagudo, A.; Pilu, G. L. & Timor-Tritsch, I. E. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 1: performance of screening examination and indications for targeted neurosonography. *Ultrasound Obstet. Gynecol., 56(3)*:476-84, 2020.

Monteagudo, A. & Timor-Tritsch, I. E. Normal sonographic development of the central nervous system from the second trimester onwards using 2D, 3D and transvaginal sonography. *Prenat. Diagn., 29(4)*:326-39, 2009.

Nagaraj, U. D.; Calvo-Garcia, M. A. & Kline-Fath, B. M. Abnormalities associated with the cavum septi pellucidi on fetal MRI: what radiologists need to know. *AJR Am. J. Roentgenol., 210(5)*:989-97, 2018.

Perry, R. N.; Bowman, E. D.; Murton, L. J.; Roy, R. N. & de Crespigny, L. C. Ventricular size in newborn infants. *J. Ultrasound Med., 4(9)*:475-7, 1985.

Sari, A.; Ahmetoglu, A.; Dinc, H.; Saglam, A.; Kurtoglu, U.; Kandemir, S. & Resit Gümele, H. Fetal biometry: size and configuration of the third ventricle. *Acta Radiol., 46(6)*:631-5, 2016.

Schulz, M.; Bührer, C.; Pohl-Schickinger, A.; Haberl, H. & Thomale, U. W. Neuroendoscopic lavage for the treatment of intraventricular hemorrhage and hydrocephalus in neonates. *J. Neurosurg. Pediatr., 13(6)*:626-35, 2014.

Soytürk, H.; Yılmaz, M.; Önal, C.; Suveren, E. & Kılıç, Ü. *Circulation of Cerebrospinal Fluid (CSF)*. In: Bektas¸og˘lu, P. K. & Gürer, B. (Eds.). Cerebrospinal Fluid. IntechOpen, 2021.

Wyldes, M. & Watkinson, M. Isolated mild fetal ventriculomegaly. *Arch. Dis. Child. Fetal Neonatal Ed., 89(1)*:F9-13, 2004

Corresponding author:
Hong-Jin Sui
Department of Anatomy
Dalian Medical University
116044
West-9 Lushun-nanlu
Dalian
CHINA

E-mail: suihj@hotmail.com
dllichan@163.com