Cortical Development Assessed by Ultrasound in Fetuses with Isolated Mild Fetal Ventriculomegaly: Asymmetric Cortical Growth, 'catch-up growth' Pattern and Postnatal Neurodevelopment Outcome

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Research Article

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Abstract

Background: Assessment of cortical development and identifying factors that may result in a poor prognosis for fetuses with isolated mild ventriculomegaly (IMVM) is a hot research topic. We aimed to perform a constant detailed assessment of cortical development in IMVM fetuses by ultrasound and determine whether asymmetric cortical development occurs in IMVM fetuses. Moreover, we aimed to estimate the prognosis of IMVM fetuses and compare the difference of prognosis of IMVM fetuses with symmetric and asymmetric cortical maturation.

Methods: IMVM was diagnosed by regular ultrasound, neurosonography, fetal MRI, and genetic and TORCH examinations. Ultrasound examinations were carried out with an interval of 2-3 weeks to record sulcus development in IMVM fetuses using a scoring system. The neonatal behavioral neurological assessment (NBNA), the Ages and Stages Questionnaire, Third Edition (ASQ-3) and the Bayley Scales of Infant Development (BSID-I) were used after birth.

Results: Forty IMVM fetuses were included, twenty showed asymmetric cortical maturation, and twenty showed symmetric cortical maturation. The mean gestational age (GA) at the first diagnosis of relatively delayed development was 24.23weeks for the parieto-occipital sulcus, 24.71weeks for the calcarine sulcus, and 26.43weeks for the cingulate sulcus. The mean GA that two sides developed to the same grade was 29.40weeks for the parieto-occipital sulcus, 29.30weeks for the calcarine sulcus and 31.27weeks for the cingulate sulcus. The NBNA, ASQ-3 and BSID-I scores of all patients were in the normal range.

Conclusion: IMVM fetuses may show mild asymmetric cortical maturation in the second trimester, but the relatively delayed sulci would undergo 'catch-up growth'. The neurodevelopment of IMVM fetuses with asymmetric cortical maturation and 'catch-up growth' is not statistically significantly different from that of IMVM fetuses with symmetric cortical maturation.

Background

Isolated mild ventriculomegaly (IMVM) is defined as mild ventriculomegaly (ventricular atrial width of 10–15 mm, regardless of gestational age) in the absence of additional structural abnormalities or chromosomal aberrance[1–4]. According to a recent meta-analysis, the incidence of abnormal or delayed neurodevelopment in IMVM infancy is approximately 7.9%[5]. However, there is no widely approved method to predict abnormal or delayed postnatal neurodevelopment. The uncertain prognosis of IMVM fetuses leads to difficulties in prenatal consultation, and identifying factors that may result in a poor prognosis for IMVM in fetuses is now a hot research topic.

The development of sulci and gyri is one of the most important markers of cortical maturation and is used as an indicator of cortical development[6]. Abnormal fetal cortical development is a major cause of dyskinesia, dysgnosia and behavioral disorders. With recent advanced imaging techniques, cortical malformations may be diagnosed in utero by ultrasonography and fetal magnetic resonance imaging (MRI)[7]. To describe prenatal cortical folding, an ultrasonographic subjective scoring system assessing fetal cortical development was developed by L. R. Pistorius. It ranges from Grade 0 (no development) to Grade 5 (maximum development)

based on the shape of the sulci and gyri[8], and several studies have evaluated the cortical development of IMVM fetuses and reported underdeveloped cortical structures based on this method[9, 10]. However, in these studies, only 2–3 ultrasound scans were performed, with no consistent systematic assessment. Moreover, these studies did not evaluate the prognosis of IMVM fetuses. In our clinical work, we have found that underdeveloped cortical structures and asymmetric cortical maturation in IMVM fetuses are not rare. If these features are an indicator of poor prognosis and abnormal neurodevelopment, this is contradictory to the incidence of abnormal or delayed neurodevelopment in IMVM infancy, which is approximately 7.9%, as we mentioned previously. To address this issue, a prospective cohort study was designed in which we performed sequential detailed assessment of cortical development in IMVM fetuses by ultrasound and examined whether asymmetrical cortical development occurs in IMVM fetuses. Moreover, we aimed to predict the prognosis of IMVM fetuses and the correlation between cortical development and infant outcomes.

Methods

Subjects

The present study was a prospective observational study involving 154 singleton pregnant women who attended Peking University First Hospital from January 2016 to December 2019. The study was conducted in accordance with the Declaration of Helsinki. Our study was approved by the Peking University First Hospital Human Research Ethics Committee, informed consent was obtained from all of the participants. The inclusion and exclusion criteria are shown in Fig. 1. We included fetuses between 21 weeks and 28 weeks of gestational age for two reasons. First, pregnant women underwent a second trimester ultrasound scan between 21 weeks and 23 weeks in our hospital; therefore, a fetus could be first diagnosed with mild ventriculomegaly at 21 weeks. Second, based on a previous study[8] and our experience, some sulci and gyri, such as the calcarine sulcus, could develop to grade 4 or 5 (maximum development) after 28 weeks, as it is of little value to assess the cortical development process of IMVM fetuses who are diagnosed after 28 weeks. In total, we included 40 singleton pregnant women. The clinical information of each participant, including name, age, reproductive history and family history of nervous system disease, was recorded after inclusion. The gestational (postmenstrual) age was determined as the time from the first day of the last menstruation and was confirmed by a crown–rump length (CRL) measurement in the first trimester.

Ultrasound

Ultrasound examinations were carried out at an interval of 2–3 weeks using GE Voluson E8 and E10 (GE Healthcare) through transabdominal and transvaginal ultrasonography after the initial detection of ventriculomegaly. Regular ultrasound including biometry measurements was carried out, followed by neurosonography. Transabdominal neurosonography was performed with 3–5-MHz probes. Transvaginal neurosonography was performed with 5–9-MHz probes.

As a general neurosonographic assessment, the distal lateral ventricle atrial width was obtained in the transventricular plane, and the proximal lateral ventricle was assessed using coronal planes[11–13]. Progression of ventriculomegaly was defined as ventricular enlargement of greater than 2 mm compared with the initial

measurement. Stable ventriculomegaly was defined as an enlargement of less than 2 mm, and regressive ventriculomegaly was defined as a decrease of 2 mm or more or as a ventricular diameter of less than 10 mm[9, 14].

We also assessed the maturation of the parieto-occipital, calcarine and cingulate sulcus of both hemispheres of the IMVM fetuses at the specific planes according to the scoring method described by L. R. Pistorius[8]. The sulci that we chose to examine were close to the midline, which would not be shaded by the fetal skull and enables their continuous assessment throughout the entire pregnancy through transabdominal and transvaginal neurosonography. The parieto-occipital sulcus was evaluated on the axial cephalic plane, the calcarine sulcus was evaluated on the coronal transcerebellar plane, and the cingulate sulcus was evaluated on the coronal transcaudate and transthalamic plane. A subjective score ranging from grade 0 to grade 5 was used to assess the cortical development, where 0 is no development and 5 is the highest grade of maturation. More specifically, the sulcus of grade 0 is not visible, the sulcus of grade 1 displays a shallow indentation or echogenic dot shape, the sulcus of grade 2 exhibits a Broad V (width ≥ depth) shape, the sulcus of grade 3 has a Y or narrow V (depth > width) shape, the sulcus of grade 4 has an I- or J-shape, and the sulcus of grade 5 shows branches on the basis of grade 4. Asymmetric sulcal maturation of two hemispheres was defined as a difference of at least one grade between any sulci of two hemispheres. Furthermore, the fetuses were divided into the symmetric maturation group and the asymmetric maturation group.

Magnetic resonance imaging (MRI)

Fetal MRI was performed using a 1.5-T MRI System (Philips Multiva) with a 32-channel cardiac-phased array surface placed over the gravid uterus for signal reception. The fetal head at the scanning center was scanned in the coronal, transverse, and sagittal planes by Half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences (repeat time of 1500 ms, echo time of 107–160 ms, slice thickness of 3 mm, slice gap of 0 mm, matrix of 280 × 205). Additionally, the fetal head was scanned in the transverse plane by T1 fast field echo (T1-FFE) sequences (repeat time of 15 ms, echo time of 7.5 ms, slice thickness of 3 mm, slice gap of 0 mm, matrix of 160 × 151) and diffusion weighted imaging (DWI) sequences (repeat time of 3249 ms, echo time of 90 ms, slice thickness of 3 mm, slice gap of 0 mm, matrix of 92 × 72). A 24 cm to 30 cm field of view (FOV) was used.

Genetic and TORCH examination

Genetic examinations were performed in all cases to exclude common genetic abnormalities, including karyotype analysis, comparative genome hybridization array analysis and single nucleotide polymorphism array analysis, referring to the Database of Genomic Variants, Decipher Database, Online Mendelian Inheritance in Man (OMIM) database, PubMed, and other databases. Additionally, TORCH (toxoplasmosis, other, rubella, cytomegalovirus and herpes simplex virus) examination was performed in all cases to exclude common infection.

Prognosis analysis

Data on pregnancy outcomes (gender, Apgar score and perinatal and neonatal morbidity and mortality) were recorded for all cases. Pediatricians from the Department of Pediatrics in our hospital, with professional training, evaluated the neonatal behavioral neurological assessment (NBNA) scores for each included infant, including the general condition, action behavior, muscular tension, and primitive reflex, within seven days of age. Each parameter was assigned 0–2 points, with a total score of 40 and a score of greater than 36 being normal. The peripheral environment was kept quiet, and the temperature was maintained at a suitable level. The room temperature was maintained at approximately 26 °C. All evaluation parameters were assessed in sleeping children at 1 h after being fed.

Cranial ultrasound examinations of infants were performed by an experienced sonographer on an ATL 5000 Unit (Philips, Best, The Netherlands) within 6 months of age. Abnormalities of the neonatal brain were recorded.

At 6, 12 and 18 months after birth, all the included infants were assessed using the Ages and Stages Questionnaire, Third Edition (ASQ-3). Parents answered 30 questions covering 5 domains of development, including communication, gross motor, fine motor, problem-solving, and adaptive skills. Parents were instructed to try activities with their child to facilitate an accurate assessment. A pass/fail score was assigned for each area of development. The presence of a problem in any domain screened, 2 SDs below the mean area score, was considered to indicate delayed development. Moreover, some of the included children were assessed with Bayley Scales of Infant Development (BSID-I) at 6, 12 and 18 months old. Experienced physicians in our hospital used the BSID-I to assess neurodevelopment, including the mental developmental index (MDI) and psychomotor developmental index (PDI). Scores of less than 79 on the MDI or PDI were considered to indicate a low level of development. Others were unable to undergo this assessment due to the COVID-19 outbreak or because they lived far from our hospital.

Statistical analysis

Data analyses were performed using SPSS version 21 for Mac (SPSS Inc., Chicago, IL). Categorical variables are expressed as percentages and continuous variables as means or median values. Student’s t-test for independent samples and Pearson chi-square tests were used to compare quantitative and qualitative data between the symmetric maturation and asymmetric maturation groups.

Results

Subjects

A total of 40 fetuses were included in this study; 20 (50.0%) of them showed symmetric cortical maturation; the other 20 (50.0%) exhibited asymmetric maturation. The demographic characteristics of the two groups are presented in Table 1. The mean maternal age of the symmetric maturation group was 32.20 years (range from 27–38 years), the mean gestational age at birth was 38.95 weeks (range from 37–41 weeks), and the mean birthweight was 3574.00 grams (range from 3005–4190 grams). The mean maternal age of the asymmetric maturation group was 31.10 years (range from 27–37 years), the mean gestational age at birth was 38.56 weeks (range from 37–40 weeks), and the mean birthweight was 3464.94 grams (range from 2950–3835

grams). Apgar scores at 1 and 5 min were 10 in all cases. The abovementioned data showed no statistically significant differences between the symmetric and asymmetric maturation groups.

Table 1
Demographic characteristics

	Symmetric maturation group(n = 20)	Asymmetric maturation group(n = 20)	P value
Maternal age	32.20 ± 3.46	31.10 ± 2.94	0.29
primipara	11(55.0%)	12(66.7%)	0.52
yes	9(45.0%)	8(33.8%)	
no			
Fetus gender	11(55.00%)	13(65.00%)	0.75
male	9(45.00%)	7(35.00%)	
female			
GA at delivery	38.95 ± 1.23	38.56 ± 1.04	0.30
Birth weight (g)	3574.00 ± 342.25	3464.94 ± 284.68	0.29
Apgar score	10 ± 0	10 ± 0	1.00
1 minute	10 ± 0	10 ± 0	1.00
5 minute			
Data are given as mean ± standard deviation or number(percentage). GA: gestational age (weeks)			

Neurodevelopment

The mean gestational age at the first diagnosis of mild ventriculomegaly was 23.50 weeks (range from 21–28 weeks) in the symmetric maturation group and 24.00 weeks (range from 22–27 weeks) in the asymmetric maturation group. In the symmetric maturation group, 15 (75.0%) cases were bilateral ventriculomegaly, and 5 (25.0%) cases were unilateral ventriculomegaly. In the asymmetric maturation group, 19 (95.0%) cases were unilateral ventriculomegaly, and 1 (5.0%) case was bilateral ventriculomegaly. The incidence of unilateral ventriculomegaly was significantly different between the symmetric and asymmetric maturation groups. The prenatal assessment of the lateral ventricle of IMVM fetuses is presented in Table 2. Note that all the developmental delays compared with the other side in unilateral ventriculomegaly occurred in the hemisphere with ventriculomegaly. Only one case in the asymmetric group was bilateral ventriculomegaly. In this case, the right side of the ventriculomegaly was regressive, and the lateral width was back to normal in 32 weeks. The lateral width of the left side was stable throughout the pregnancy. As expected, relatively delayed development occurred on the stable side. The sulcal development of the asymmetric maturation group is presented in Table 3. Eight (40.0%) fetuses showed asymmetric development with one sulcus, 10 (50.0%) fetuses showed asymmetric development with two sulci, 2 (10.0%) fetuses showed asymmetric development with three sulci, and a total of 34 sulci with relatively delayed development compared with those in the other hemisphere were

observed. The mean gestational age at first diagnosis of relatively delayed development was 24.23 weeks (range from 22–27 weeks) for the parieto-occipital sulcus, 24.71 weeks (range from 22–28 weeks) for the calcarine sulcus, and 26.43 weeks (range from 25–29 weeks) for the cingulate sulcus. According to our assessment, all the sulci with delayed development underwent 'catch-up growth' and developed to the same grade as the sulci of the other hemisphere. The mean gestational week at which the two sides developed to the same grade was 29.40 weeks (range from 24–32 weeks) for the parieto-occipital sulcus, 29.30 weeks (range from 24–31 weeks) for the calcarine sulcus and 31.27 weeks (range from 27–34 weeks) for the cingulate sulcus. Figures 2–4 show the 'catch-up growth' of the parieto-occipital sulcus, calcarine sulcus and calcarine sulcus, respectively. The relatively delayed sulci showed one or two grades of delay compared with the other side, but none of them showed three or more grades of delay. The width change of the lateral ventricle and development of the included sulci are shown in Figs. 5–7, with a two-week interval during pregnancy. For statistical analysis, we used the width of the more dilated side in cases of bilateral ventriculomegaly. As Figs. 5–7 show, the parieto-occipital, calcarine and cingulate sulci of all the IMVM fetuses in our study, with symmetric or asymmetric cortical maturation, developed to grade 5 before birth. Figures 5–7 and Table 2 also show that only some of the IMVM fetuses had regression of ventriculomegaly, while others stayed stable or even had progression during the course of cortical maturation. The median value of the lateral ventricle stayed stable in both the asymmetric and symmetric groups.

Table 2
Prenatal assessment of lateral ventricle of IMVM fetuses

	Symmetric maturation group (N = 20)	Asymmetric maturation group(N = 20)	P value
GA of IMVM first diagnosed	23.50 ± 2.07	24.00 ± 2.16	0.47
Lateral ventriculomegaly	5(25.0%)	19(95.0%)	0.00
unilateral	15(75.0%)	1(5.0%)	
bilateral			
Width change between first diagnosed US and last US before born*:	N = 35	N = 21	0.51
progressive:	10(28.6%)	3(14.3%)	
stable:	11(31.4%)	8(38.1%)	
regressive:	14(40.0%)	9(42.9%)	

Data are given as mean ± standard deviation or number(percentage). GA: gestational age (weeks). US: ultrasonography. *: In lateral ventricle with ventriculomegaly.

Table 3
Prenatal cortical maturation of asymmetric maturation group

Number of relatively retarded sulci in a fetus	**N = 20**
1	**8(40.0%)**
2	**10(50.0%)**
3	**2(10.0%)**
Category of relatively retarded sulci	12(60.0%)
parieto-occipital sulcus	16(80.0%)
calcarine sulcus	6(30.0%)
cingulate sulcus	
GA of first diagnosed with relatively retardation	24.23 ± 1.40
parieto-occipital sulcus	24.71 ± 1.60
calcarine sulcus	26.43 ± 0.89
cingulate sulcus	
GA of bilateral sulci grew into symmetry	29.40 ± 1.71
parieto-occipital sulcus	29.30 ± 2.29
calcarine sulcus	31.27 ± 1.64
cingulate sulcus	
Data are given as mean ± standard deviation or number(percentage). GA: gestational age (weeks).	

Prognoses

The NBNA score of all the included cases was greater than 36 within the seventh day after birth. The cranial ultrasound of all infants showed no abnormalities other than mild ventriculomegaly.

The follow-up results are shown in Table 4. Up to the end of our study, the included children were of different ages. In the symmetric group, 6 children were between 6 and 12 months old, 3 children were between 12 and 18 months old, and 11 children were over 18 months old. In the asymmetric group, 7 children were between 6 and 12 months old, 7 children were between 12 and 18 months old, and 6 children were over 18 months old. We assessed the neurodevelopment of all the included children at 6, 12 and 18 months of age using the ASQ-3. Some of the included children were also assessed by BSID-I at 6, 12 and 18 months of age. All the included cases, including those who underwent the ASQ-3 assessment and who underwent both the ASQ-3 and BSID-I assessments, obtained scores in the normal range. None of the included children were defined as having delayed development according to the results of the assessments at 6, 12 or 18 months of age, and there were no statistically significant differences in the results between the children in the two groups. Furthermore, up to

the end of our study, none of the included children showed neurological disease other than mild fetal ventriculomegaly.

Table 4
Prognosis of IMVM fetuses after birth

	Cases underwent ASQ-3	Cases underwent ASQ-3 with normal result	P value	Cases underwent BSID-I	Result of Bayley-I			
					PDI(mean ± SD)	P Value	MDI(mean ± SD)	P Value
6months SMG	20	20	1.00	15	107.27 ± 12.44	0.57	107.87 ± 16.99	0.79
AMG	20	20		10	110.50 ± 13.49		109.70 ± 14.98	
12months SMG	14	14	1.00	7	106.86 ± 12.21	0.56	106.62 ± 12.52	0.64
AMG	13	13		3	113.00 ± 15.12		103.67 ± 9.03	
18months SMG	11	11	1.00	2	93.00 ± 7.00	/	102.50 ± 2.50	/
AMG	6	6		0	/		/	
SMG: IMVM fetuses in symmetric maturation group, AMG: IMVM fetuses in asymmetric maturation group								

Discussion

In this study, we observed the process of maturation of selected sulci after 21 weeks of gestation and the prognosis of 40 IMVM infants. All the cases of relatively delayed development in one hemisphere compared with the other hemisphere occurred in the hemisphere with ventriculomegaly or with continuously stable ventriculomegaly and not in the hemisphere with a normal lateral ventricle or with regressive ventriculomegaly. Therefore, we infer that asymmetric cortical maturation is not random and tends to occur in IMVM infants with unilateral ventriculomegaly or asymmetric bilateral ventriculomegaly.

Several studies have reported cortical development in IMVM fetuses using the same grade scoring method as that used in the present study[9, 10]. One of these studies evaluated the cortical development of IMVM fetuses at 26 and 30 weeks of gestation by ultrasound. This study reported underdeveloped calcarine and parieto-occipital sulci in IMVM fetuses[9]. Another study assessed the cortical development of IMVM fetuses at 23–25, 27–28 and 31–32 weeks of gestation. Cortical grading of the parieto-occipital sulcus, calcarine sulcus and sylvian fissure in this study showed no significant difference from that of normal fetuses at any gestational age[10]. To our knowledge, this is the first study to report the 'catch-up growth' pattern in IMVM fetuses with asymmetric cortical maturation. In our study, the relative delay of calcarine and parieto-occipital sulci occurred

at approximately 24 weeks and that of the cingulate sulcus occurred at approximately 26 weeks. The relatively delayed sulci underwent a process of 'catch-up growth' in which the sulci of the two hemispheres ultimately grew symmetrically and developed to the maximum grade before birth.

Several studies have reported asymmetrical cortical development in 'normal fetuses'. Hering-Hanit[15] and Kivilevitch[16] reported left-right hemisphere asymmetry by measuring the diameter of both hemispheres. Pistorius[8] evaluated fetal cortical development by ultrasound and reported that in 20 of the 28 fetuses, asymmetry was seen in at least one examination. Notably, these studies did not follow the fetuses to exclude those who were diagnosed with genetic or structural abnormalities after birth. As a result, further investigation is needed to assess the cortical development symmetry of normal fetuses and compare the cortical growth pattern between normal and IMVM fetuses.

As previously mentioned, all the cases of relatively delayed development in one hemisphere compared with the other hemisphere occurred in the hemisphere with ventriculomegaly or with continuously stable ventriculomegaly. The relatively delayed sulci underwent a process of 'catch-up growth' and the sulci of the two hemispheres ultimately grew symmetrically. However, only 42.9% of the enlarged lateral ventricles in IMVM fetuses with asymmetric cortical maturation showed regressive ventriculomegaly before birth, and 57.1% of the enlarged lateral ventricles showed stable or progressive ventriculomegaly. Therefore, we infer that delayed cortical development is not the reason for ventriculomegaly, and the possible correlations between ventriculomegaly and cortical development are still unclear, and the relationship between the cortical maturation and width change of ventriculomegaly remain uncertain.

All the included cases underwent cranial ultrasound examination after birth, and none of them were diagnosed with abnormalities other than mild ventriculomegaly, which proves that no false-negative diagnoses were made by prenatal neurosonography. Regarding the prognostic estimation, all cases underwent the NBNA 7 days after birth and ASQ-3 at 6, 12 and 18 months of age. Additionally, some of the included infants underwent both the ASQ-3 and BSID-I. The Bayley scales has traditionally been considered a comprehensive developmental assessment. Many investigators consider the Bayley scales to be the gold standard for infant developmental assessment. However, its universal clinical applicability is limited due to its high cost, timing, and requirement for administration by trained professionals[17]. Some of our participants were unable to undergo BSID-I due to the COVID-19 outbreak or because they lived far from our hospital, but all of the participants underwent the ASQ-3. The ASQ has been validated in many countries in different languages and settings[17, 18]. Multiple studies support its easy administration, short completion time, ease of interpretation, and capacity to identify children who have suspected developmental delays[19–21]. A systematic review showed that, compared with those of the Bayley scales, the sensitivity and specificity of the ASQ-3 are reliable[22]. Therefore, the results of the neurodevelopment assessment by the ASQ-3 in our study are reliable.

Although our participants differed in age at the end of the study, none showed evidence of delayed or abnormal neurodevelopment. Indeed, the fetuses of the asymmetric maturation group showed no statistically significant difference in neurodevelopment within 18 months of age compared with the symmetric maturation group. Considering that there were only 6 children over 18 months of age in the asymmetric group until the end of the study, further analyses with more cases are needed to prove this conclusion. Close observation of cortical maturation and whether the sulci undergo 'catch-up growth' during pregnancy is essential for IMVM

fetuses with asymmetric cortical maturation. Such mild asymmetric cortical maturation may be a physiological phenomenon.

According to a recent meta-analysis, the rate of abnormal or delayed neurodevelopment in IMVM infancy is approximately 7.9%[5]. In our study, none of the participants showed abnormal or delayed neurodevelopment. One possible reason is that the fetuses in our study underwent thorough prenatal examinations, with the strict exclusion of participants by neurosonography. We ensured that all fetuses with other structural abnormalities were excluded and that no single false-negative prenatal diagnosis occurred in our study, which was proven by cranial ultrasonography after birth. Another possible reason is that we followed the participants up to 18 months; however, neurodevelopmental disorders reported in previous research, including autism spectrum disorder and epilepsy[23], may require a longer follow-up time for diagnosis. Moreover, the sample size of our study was too small to illustrate the incidence of neurodevelopmental disorders in IMVM fetuses with asymmetric cortical maturation, which is also a limitation of our study. Further research with larger sample sizes is needed to evaluate the long-term prognosis of IMVM fetuses with asymmetric cortical development.

Conclusion

IMVM fetuses may show mild asymmetric cortical maturation in the second trimester, but the relatively delayed sulci undergo 'catch-up growth'. Limited cases have shown that the neurodevelopment of IMVM fetuses with asymmetric cortical maturation and 'catch-up growth' is not statistically significantly different from that of IMVM fetuses with symmetric cortical maturation. Such 'catch-up growth' may be a physiological phenomenon.

Abbreviations

IMVM: isolated mild ventriculomegaly; NBNA: neonatal behavioral neurological assessment; ASQ-3: Ages and Stages Questionnaire (Third Edition); BSID-I: Bayley Scales of Infant Development

Declarations

Ethics approval and consent to participate:

Our study was approved by the Peking University First Hospital Human Research Ethics Committee, informed consent was obtained from all of the participants.

Consent for publication:

not applicable.

Availability of data and materials:

The datasets during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' Contributions:

Rong Zhu and JunYa Chen performed the research, analyzed and interpreted the data. Rong Zhu drafted the manuscript. XinLin Hou, LiLi Liu, GuoYu Sun and JunYa Chen helped sample collection, analysis and interpretation of the data. XinLin Hou offered professional discussions and instructions. JunYa Chen and XinLin Hou conceived and designed the study, revised the manuscript, and provided the final approval of the manuscript.

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Figures

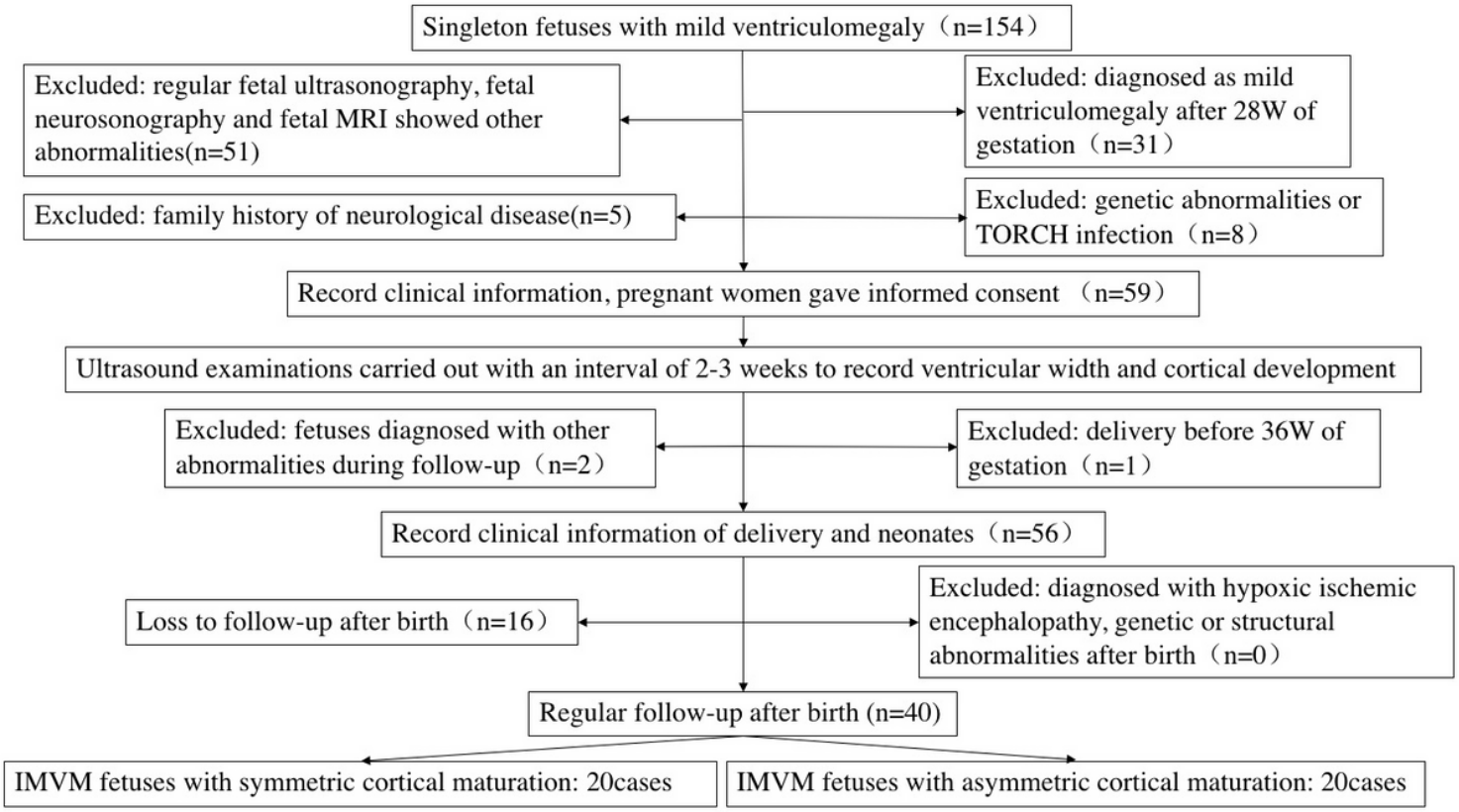

Figure 1

Participant flow chart.

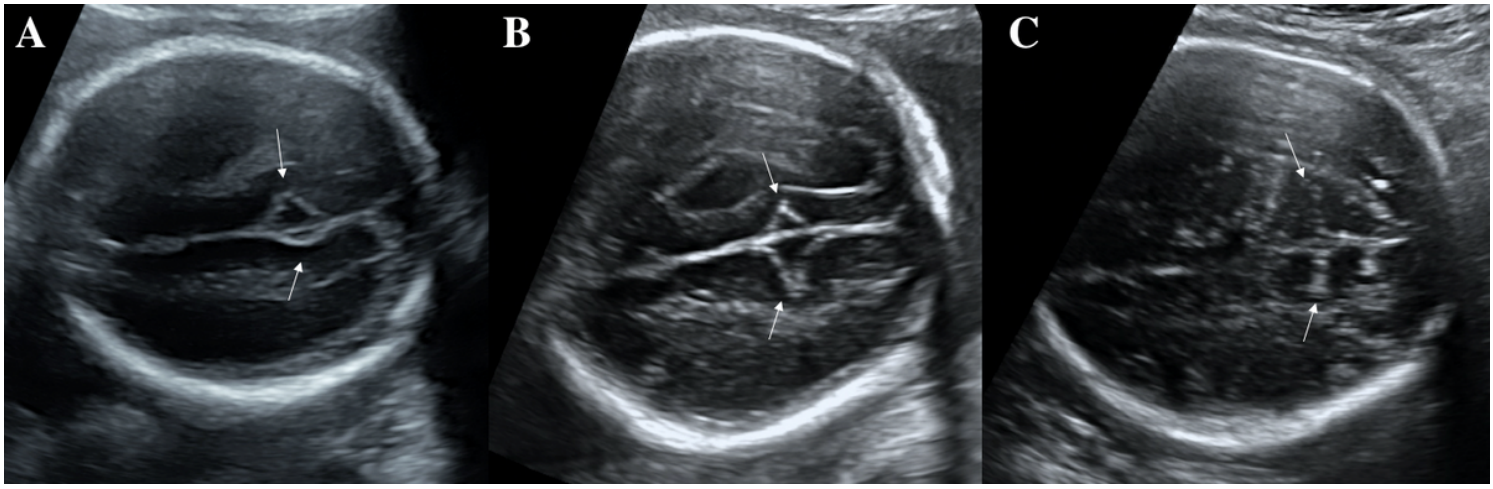

Figure 2

Asymmetry in the development and ‘catch-up growth’ of parieto-occipital sulcus in a IMVM fetus with unilateral ventriculomegaly. Ultrasound image of parieto-occipital sulcus on axial cephalic plane at 25weeks (A), 28weeks(B) and 31weeks (C) of gestation. A: the parieto-occipital sulcus was grade 1 on one side and was grade 2 on the other side. B: the parieto-occipital sulcus was grade 2 on one side and was grade 3 on the other side. C: the parieto-occipital sulcus was grade 4 on both sides.

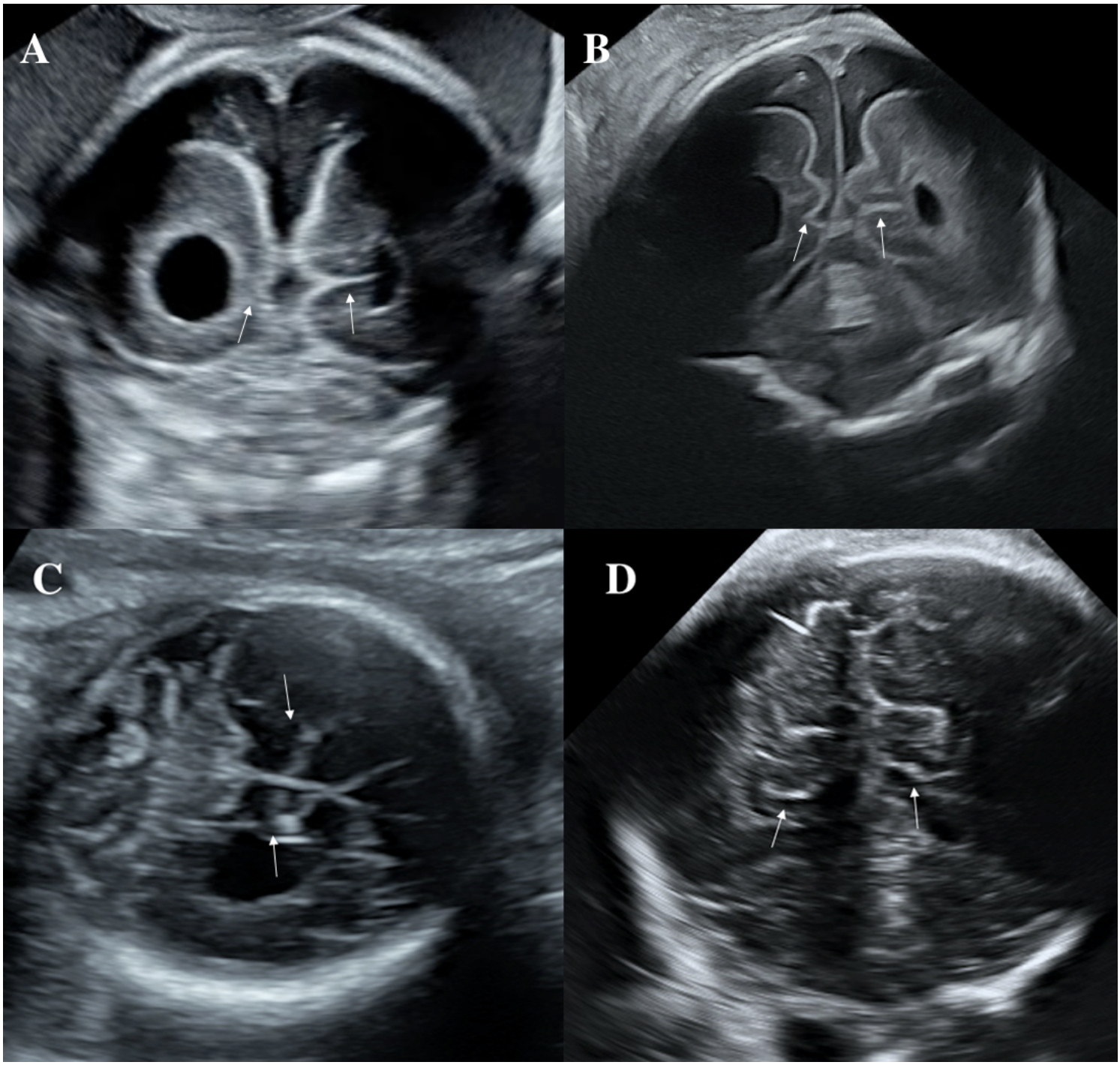

Figure 3

Asymmetry in the development and ‘catch-up growth’ of calcarine sulcus in a IMVM fetus with unilateral ventriculomegaly. Ultrasound image of calcarine sulcus on coronal transcerebellar plane at 25weeks (A), 27weeks (B), 30weeks (C) and 32weeks (D) of gestation. A: the calcarine sulcus was grade 1 on one side and was grade 2 on the other side. B: the calcarine sulcus was grade 2 on one side and was grade 4 on the other side. C: the calcarine sulcus was grade 4 on both sides. D: the calcarine sulcus was grade 5 on both sides.

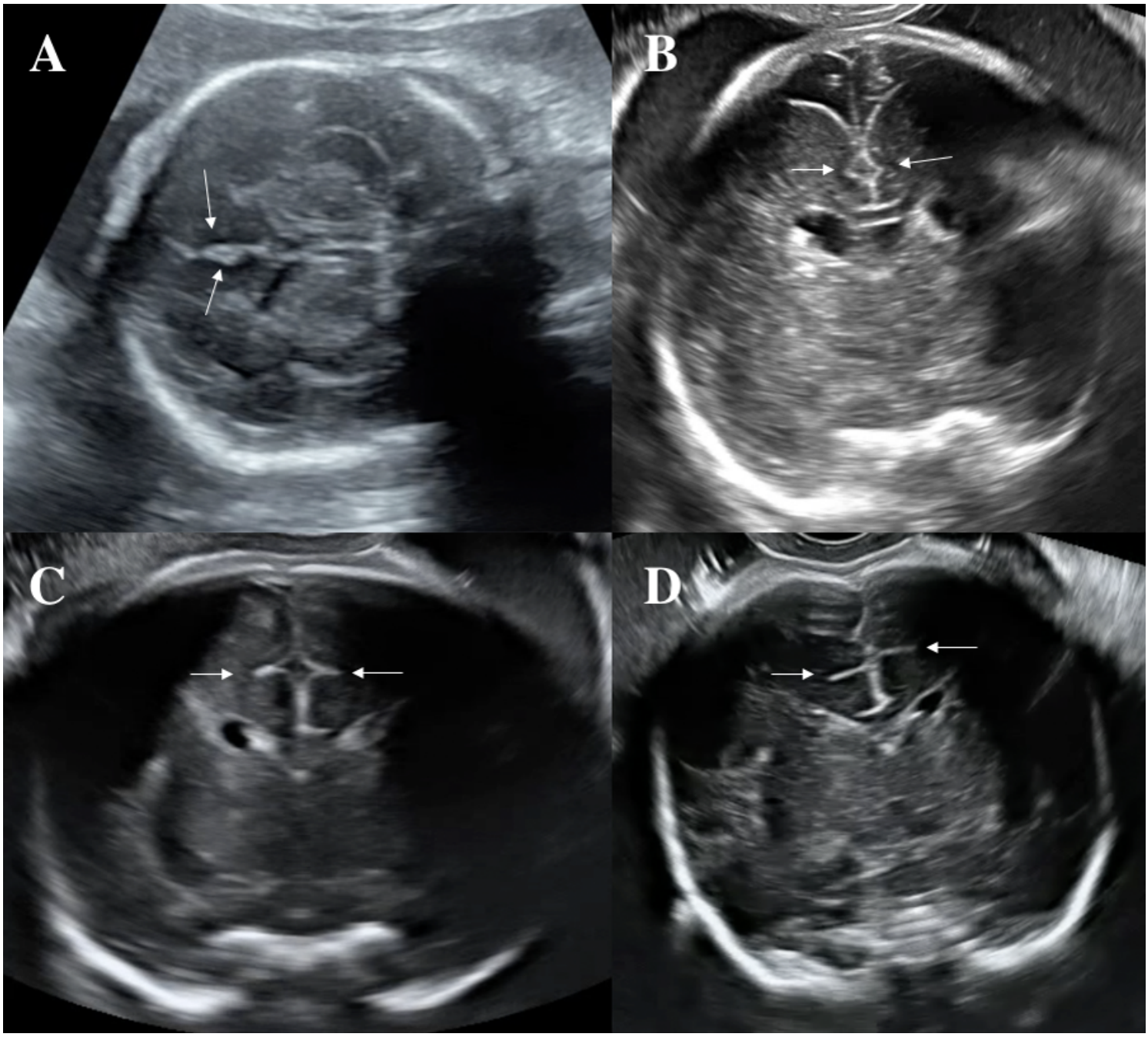

Figure 4

Asymmetry in the development and ‘catch-up growth’ of cingulate sulcus in a IMVM fetus with unilateral ventriculomegaly. Ultrasound image of cingulate sulcus on coronal transcaudate and transthalamic plane at 27weeks (A), 30weeks (B), 32weeks (C) and 34weeks (D) of gestation. A: the cingulate sulcus was grade 0 on one side and was grade 1 on the other side. B: the cingulate sulcus was grade 2 on one side and was grade 3 on the other side. C: the cingulate sulcus was grade 3 on both sides. D: the calcarine sulcus was grade 4 on both sides.

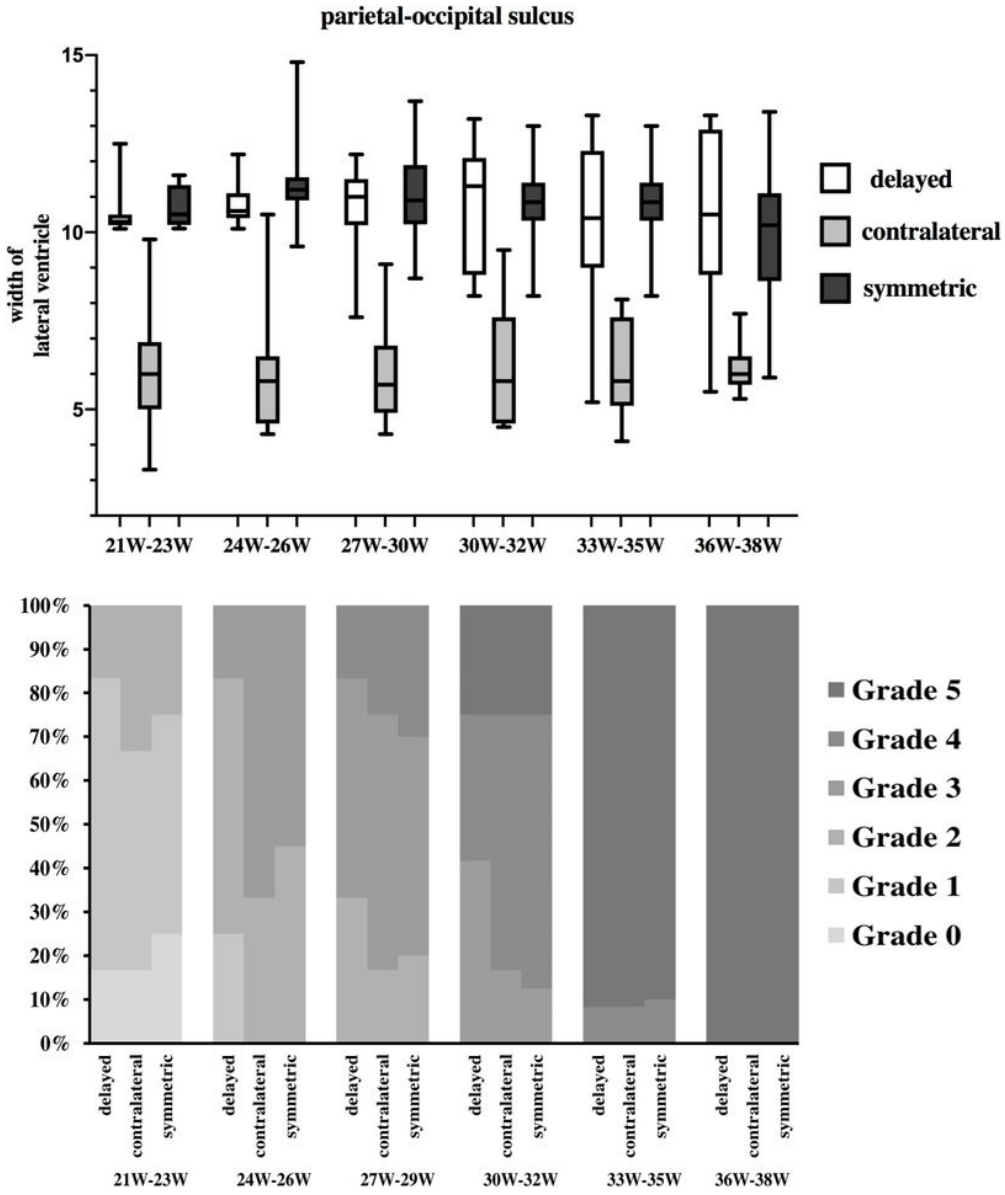

Figure 5

The width of lateral ventricle and cortical grading of IMVM fetuses with parietal-occipital sulcus asymmetry and IMVM fetuses with symmetric cortical development at different gestational ages. The upper part of this figure are box plots that describe the width change of lateral ventricle. The box plots show minimum, median and maximum values and the 1st and 3rd quartiles. The lower part of the figure are percentage bar charts that describe the distribution of cortical grading scores. Delayed: the relatively delayed side of IMVM fetuses with parietal-occipital sulcus asymmetry. Contralateral: the contralateral side of IMVM fetuses with parietal-occipital sulcus asymmetry. Symmetric: IMVM fetuses with symmetric cortical development.

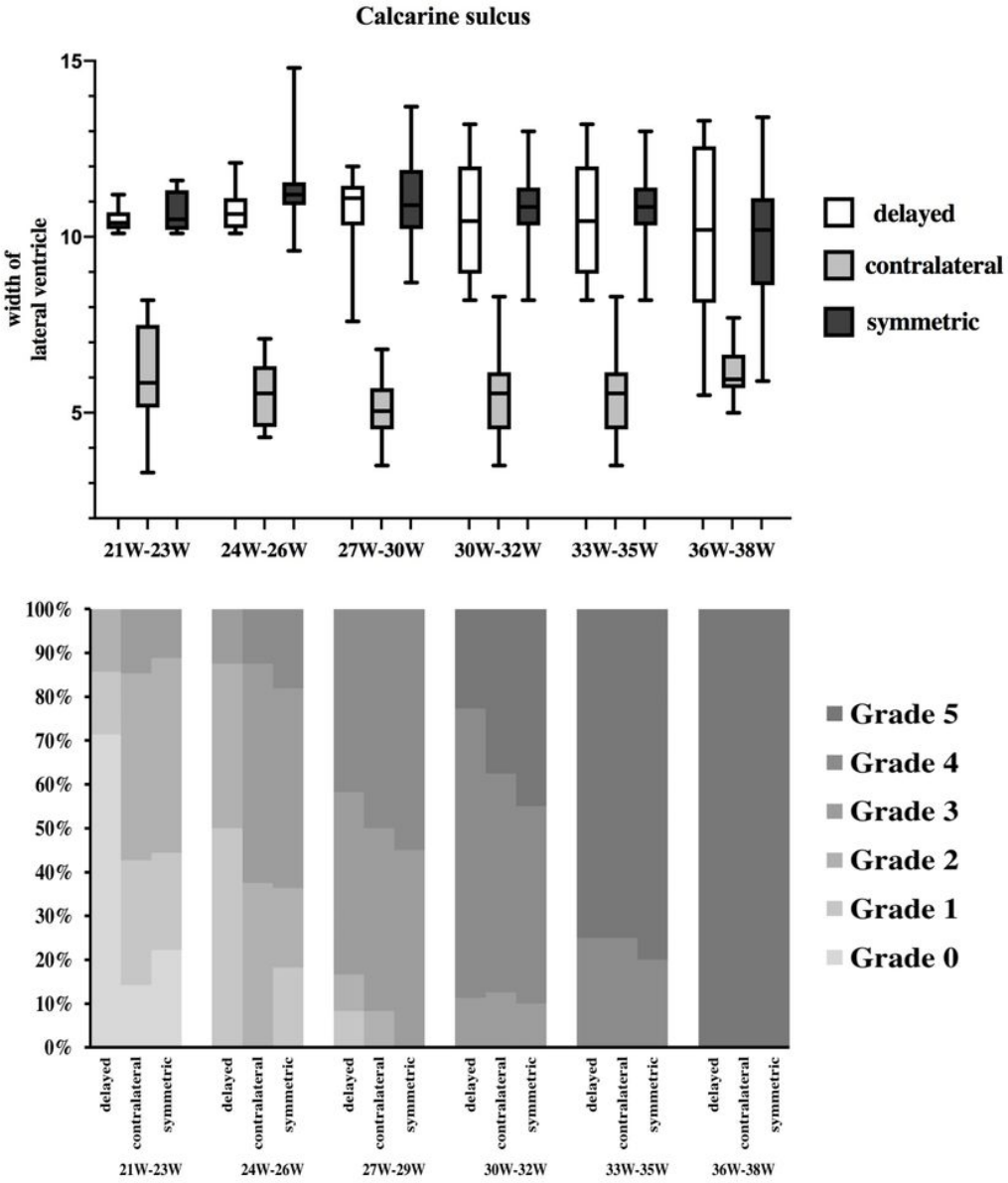

Figure 6

The width of lateral ventricle and cortical grading of IMVM fetuses with calcarine sulcus asymmetry and IMVM fetuses with symmetric cortical development at different gestational ages. The upper part of this figure are box plots that describe the width change of lateral ventricle. The box plots show minimum, median and maximum values and the 1st and 3rd quartiles. The lower part of the figure are percentage bar charts that describe the distribution of cortical grading scores. Delayed: the relatively delayed side of IMVM fetuses with calcarine sulcus asymmetry. Contralateral: the contralateral side of IMVM fetuses with calcarine sulcus asymmetry. Symmetric: IMVM fetuses with symmetric cortical development.

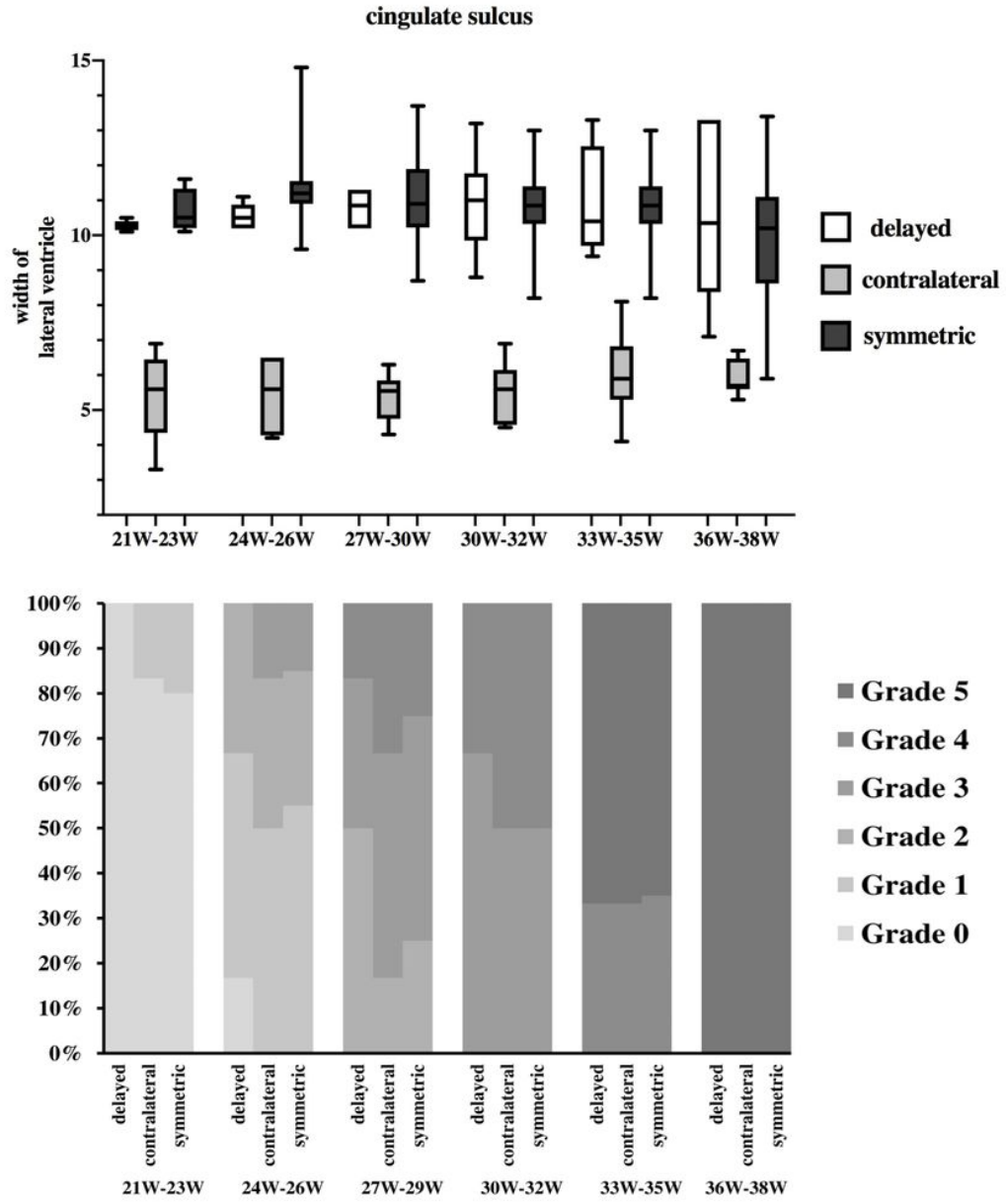

Figure 7

The width of lateral ventricle and cortical grading of IMVM fetuses with cingulate sulcus asymmetry and IMVM fetuses with symmetric cortical development at different gestational ages. The upper part of this figure are box plots that describe the width change of lateral ventricle. The box plots show minimum, median and maximum values and the 1st and 3rd quartiles. The lower part of the figure are percentage bar charts that describe the distribution of cortical grading scores. Delayed: the relatively delayed side of IMVM fetuses with cingulate sulcus asymmetry. Contralateral: the contralateral side of IMVM fetuses with cingulate sulcus asymmetry. Symmetric: IMVM fetuses with symmetric cortical development.