Original Article

Development and validation of a predictive model for fetal cerebral maturation using ultrasound for fetuses with normal growth and fetal growth restriction

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Background: Investigation of fetal cerebral maturation (FCM) is necessary and important to provide crucial prognostic information for normal and high-risk fetuses. The study aimed to develop a valid and quantitative predictive model for assessing FCM using ultrasound and validate the model for fetuses with normal and restricted growth.

Methods: This was a multicenter prospective observational study. Fetuses with normal growth recruited from a university teaching hospital (Center 1) and a municipal maternal unit (Center 2) were included in the training set and external validation set 1, respectively. The 124 growth-restricted fetuses enrolled in Center 1 were included in validation set 2. FCM was used to describe the gestational age (GA) in this study. The model was developed based on the sum of fetal cranial parameters (total fetal cranial parameters), including head circumference (HC) and depths of the insula (INS) and sylvian fissure (SF), parieto-occipital fissure (POF), and calcarine fissure (CF). A regression model, constructed based on total fetal cranial parameters and predicted GA, was established using the training set and validated using external validation set 1 and validation set 2.

Results: The intra- and interobserver intraclass correlation coefficients for HC, and depths of the INS and SF, POF, and CF were >0.90. An exponential regression equation was used to predict FCM: predicted GA of FCM (weeks) =11.16 × exp (0.003 × total fetal cranial parameters) ($P<0.001$; adjusted $R^2=0.973$), standard error of estimate, 0.67 weeks. The standard error of the predicted GA of FCM from the model was ±4.7 days. In the validation set 1, the mean standard error of the developed prediction model for FCM was 0.97 weeks. The predictive model showed that FCM was significantly delayed in validation set 2 (2.10±1.31 weeks, $P<0.001$), considering the GA per the last menstrual period.

Conclusions: The predictive performance of the FCM model developed in this study was excellent, and the novel model may be a valuable investigative tool during clinical implementation.

Keywords: Prenatal ultrasound; gestational age (GA); training set; validation set; birth weight (BW)

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Introduction

Fetal brain structure develops rapidly, and cortical folding drastically changes the brain shape during the second and third trimesters, from a largely smooth surface to a complex convoluted one (1). Investigation of fetal cerebral maturation (FCM) is necessary and important to provide crucial prognostic information for normal and high-risk fetuses. Fetal brain maldevelopment has been reported in fetuses with congenital heart disease (2-4), fetal growth restriction (FGR) (5), fragile-X syndrome (6), Down syndrome (7), and agenesis of the corpus callosum (8). Long-term neurodevelopmental impairment is the most common complication in patients with congenital heart disease (9) and FGR (10,11). Therefore, evaluation of FCM is pertinent in peripheral or central nervous system anomalies.

Numerous publications have reported characteristics of fetal brain development at different stages and quantitative measurements of gyral formation and sulcation with ultrasound screening (12-15). However, it is difficult to interpret FCM in an individual fetus, particularly because the growth patterns differ by regions (16,17). Developing a complete and comprehensive approach that could be routinely used in clinics to assess FCM might solve this problem. The fetal total maturation score (fTMS) (18) and cumulative maturity score (19) have been used for clinical interpretation; these were developed using magnetic resonance imaging (MRI). However, MRI cannot always be performed during prenatal screening and fetal MRI always is for the evaluation of suspected or proven central nervous system anomalies (20). Establishing a model using ultrasound to predict FCM has important implications in pregnancy care. Semi-quantitative morphological grading of evaluation including cortical grading of the sulci, sylvian fissure (SF) and cortical gyration by ultrasound has been established.

The primary aim of our study was to develop a quantitative model to predict FCM considering sonographic measurements of fetal sulcation, and the secondary aim was to validate the predictive model for FCM in fetuses with normal growth and FGR. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-786/rc).

Methods

Study population and design

The data for this study were derived from prospective screening for routine pregnancy care in the second and third trimesters (from 19^{+6} to 40^{+2} gestational weeks) at The First Affiliated Hospital of Sun Yat-sen University (Center 1) and Dalian Municipal Women and Children's Medical Center (Center 2), between October 10th 2019 and November 10th 2022. Written informed consent was obtained from participants' parents or legal guardians before screening, and Ethics Committees of The First Affiliated Hospital of Sun Yat-sen University and Dalian Municipal Women and Children's Medical Center approved the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

A normal last menstrual period (LMP) was defined as the most recent menstrual period of a regular cycle without the use of oral contraceptives for 6 months. For the cases with regular menstrual period, gestational age (GA) was calculated considering the first day of the last normal menstrual period and confirmed on first-trimester sonography at $11–13^{+6}$ gestational weeks. GA estimations in the first trimester were based on measurements of crown-rump length (21). If there is uncertainty about the date of the LMP or irregular menstrual cycles, or if there was a discrepancy of more than 1 week between menstrual age and sonographic measurements, GA was determined based on sonographic age.

Measurements of fetal biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length were performed to calculate the estimated fetal weight (EFW) using the Hadlock formula (22). Birth weight (BW) and HC at birth were calculated as Z-scores, considering reference ranges of the local population (23). The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)-FGR definition was used in this study, which follows the Delphi consensus criteria and includes either EFW or AC <3rd percentile, or EFW or AC <10th percentile combined with abnormal Doppler findings, or a decrease in growth centiles (24). Only singleton pregnancies were included in this study. Exclusion criteria for normal-growth fetuses included congenital infection, maternal complications (gestational diabetes, chronic

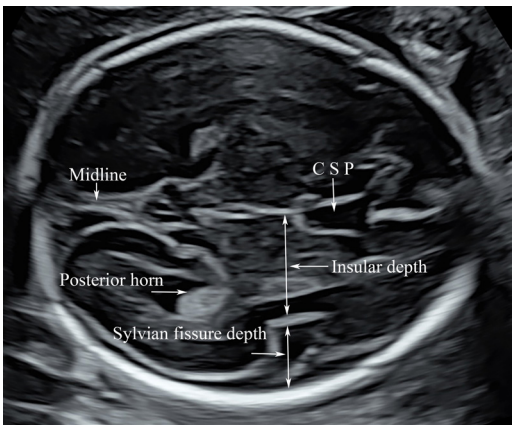

Figure 1 Ultrasound imaging for fetal brain measurements: measurements of the depth of insula (double-headed arrow) and sylvian fissure (double-headed arrow) in the trans-ventricular view at 25 gestational weeks. CSP, cavum septi pellucidum.

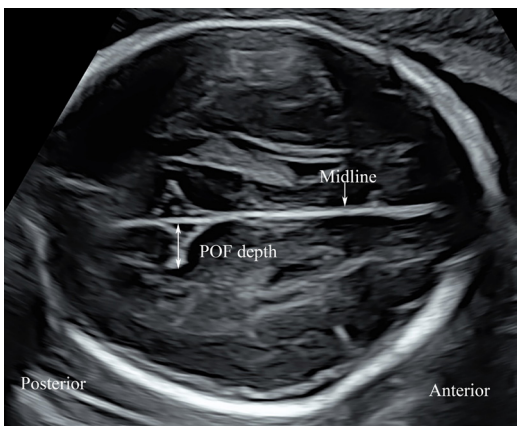

Figure 2 Ultrasound imaging for fetal brain measurements: measurements of the depth of parieto-occipital fissure in the view above and parallel to the trans-ventricular view at 28 gestational weeks. POF, parieto-occipital fissure.

hypertension, preeclampsia, or autoimmune diseases), ambiguous ultrasonographic images for analysis, delivery before 37 gestational weeks, and BW Z-scores <–1.29. Exclusion criteria for fetuses with FGR included structural malformations, recorded genetic anomalies (chromosomal anomalies, pathogenic copy number variations, or single gene disease), pregnancy termination, and loss to follow-up. FGR cases were classified, based on GA at the time of diagnosis, into early-onset FGR (<32 weeks) and late-onset FGR (≥32 weeks) (25). All normal-growth fetuses included in the study were confirmed via postnatal ultrasonography or MRI to have normal brain structures and normal prenatal development. Delayed development of sulci and gyri were confirmed in FGR fetuses via postnatal ultrasonography or MRI.

Sonographic measurements

Ultrasonography was performed using a Voluson E8 and E10 ultrasonography machine (GE Healthcare, Zipf, Austria) with a RAB2-5 (2–5 MHz) convex probe and RIC5-9-D (4–8 MHz) probe. Evaluation of structures and biological measurements in the second and third trimesters were performed by experienced operators, following the guidelines published by ISUOG (26). Both of the left and right hemisphere of the brain were evaluated and the average value was recorded for final analysis.

First, we obtained a standard trans-ventricular plane of the fetal head to perform measurements of BPD and HC per ISUOG guidelines, in which the atrium and posterior horns of the left and right lateral ventricles, the cavum septi pellucidum (CSP), and the choroid plexus could be clearly identified. The depth of the insula (INS) was measured in the trans-ventricular plane by drawing a perpendicular line from the midline towards the upper border of the insular cortex (*Figure 1*). The depth of the SF was also measured in the trans-ventricular plane by drawing a line in continuation with the insular line from the insular cortex to the inner border of the parietal bone (*Figure 1*).

A plane above the level of the trans-ventricular plane was used to measure the depth of the parieto-occipital fissure (POF). After visualizing the BPD plane, the probe was moved cranially to obtain a plane for measurement of the POF, which was parallel to the BPD and HC planes. We moved the probe up and down in parallel to confirm that the full fissure depth could be visualized. In this view, the POF appeared as a triangular shape in the second and early third trimesters, and the apex of the POF was lateral to the midline. We drew a perpendicular line from the midline to the apex of the POF, representing the depth of the POF (*Figure 2*). After visualizing the trans-cerebellar plane, the probe was rotated 90° to obtain the coronal view of the cisterna magna and cerebellum, in which plane the calcarine fissure (CF) was measured. In this plane, a perpendicular line was drawn from the CF apex to the tentorium cerebelli, the length of which was obtained as the CF depth (*Figure 3*). All measurements were performed by two operators (authors 1 and 3, with 13- and 15-year experience of prenatal ultrasonographic image analysis, respectively) who were

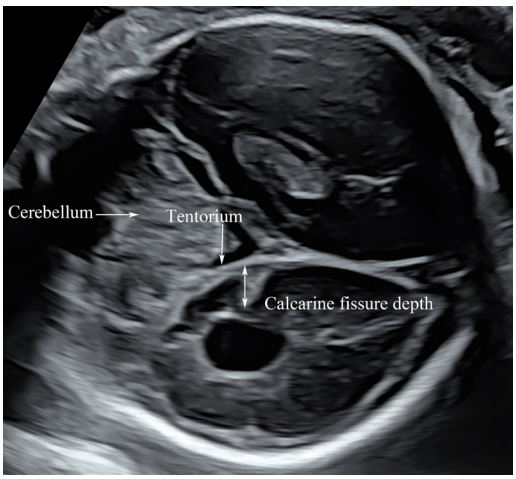

Figure 3 Imaging for fetal brain measurements (coronal view): measurements of the depth of calcarine fissure at the level of the posterior fossa at 28 gestational weeks.

blinded to the clinical data and outcomes. Each parameter was measured in triplicate from three separately obtained ultrasound images, and the mean of the three measurements was used for calculations.

Clinical data

Recorded variables for mothers included age at ultrasound examination, pre-pregnancy body mass index (BMI), delivery history, complications, smoking history, alcohol consumption, or drug abuse. Recorded variables for neonates included sex, BW, GA at birth, HC, Apgar score, transfer to the neonatal intensive care unit, length of hospitalization, and neonatal complications. Neonatal complications included respiratory distress syndrome, sepsis, intraventricular hemorrhage (grade III or IV), cystic periventricular leukomalacia, hypoglycemia (<2.2 mmol/L), and necrotizing enterocolitis.

Statistical analyses

In 30 cases, paired measurements were performed by one operator (author 1) to determine the intraobserver reproducibility and by a second operator (author 5) to determine the interobserver reproducibility. The between-observer 95% limits of agreement were depicted with Bland-Altman plots using MedCalc 9 Software (MedCalc Software, Mariakerke, Belgium). Furthermore, we calculated the intraclass correlation coefficient (ICC) to evaluate the interobserver and intraobserver reliabilities. Medium, good, and perfect agreement was defined as 0.4< ICC <0.6, 0.61< ICC <0.8, and 0.81< ICC <1.0, respectively.

Data from normal or non-normal continuous variables are expressed as mean ± standard deviation or median (interquartile range), respectively, and categorical data as n (%). Comparisons between the different datasets (fetuses with normal growth and FGR) were performed using the chi-square test for categorical variables and Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. The 95% confidence intervals (CIs) of the variables were reported, if necessary.

Normal-growth fetuses recruited from Centers 1 and 2 were included as a training set and an external validation set 1, respectively. Fetuses with FGR recruited from Center 1 underwent FCM assessment as validation set 2. The FGR fetuses recruited from Center 1 and included in the validation set were excluded from the training set. Normality tests for INS, SF, POF, and CF were performed using the Kolmogorov-Smirnov test. The predictive model for FCM using ultrasound images was developed considering five morphological variables: HC, INS, SF, POF, and CF. The fetal total cranial parameter (fTCP) was calculated by summing the measurements of HC, INS, SF, POF, and CF. A regression model for FCM was constructed considering fTCP. Linear, quadratic, cubic, logarithmic, and exponential models were compared and analyzed, and the optimal model was determined. When a more complex model could not significantly improve the goodness of fit, a simpler model was used. The prediction model developed from the training dataset was applied to the validation dataset to assess the predictive performance. P<0.05 indicated statistical significance. The Statistical Package for the Social Sciences (SPSS) 22.0 software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, 2013) was used for data analyses. We use complete-case analysis for handling missing data. The study size was acquired according to the formula that $n= [(Z_1-\alpha/2\times\sigma)/\delta]^2$, $\alpha=0.05$, $\delta=0.2$, $\sigma=1.0$.

Results

First, a total of 432 fetuses were examined, and their data were used to construct the predictive model after excluding 17 fetuses with BW Z-score <–1.29, 6 fetuses with delivery before 37 gestational weeks, and 21 fetuses with incomplete measurements of cranial parameters. A total of 214 normal-growth fetuses recruited from Center 2 were included in

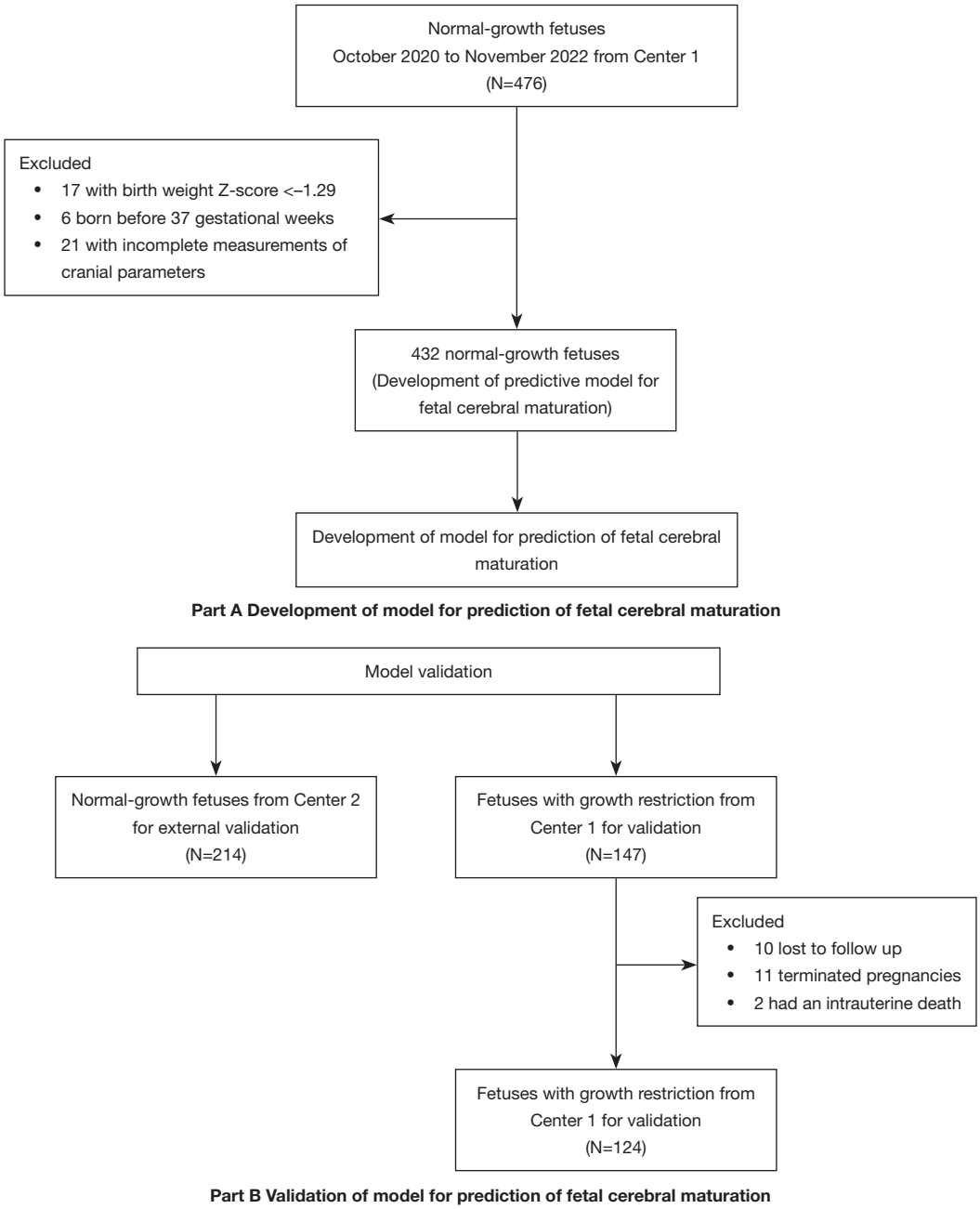

Figure 4 Flow diagram of fetuses with growth restriction and normal grown fetuses.

the external validation dataset. In addition, the developed predictive model was also applied to 124 fetuses with FGR from Center 1, after excluding 10 cases of lost to follow-up, 11 cases of terminated pregnancies and 2 cases of intrauterine death (*Figure 4*). Follow-up was performed with a median infant age of 15 months in all patients, ranging from 4 to 31 months. Fifty-eight (46.7%, 58/124) were identified as early-onset FGR and 66 (56.4%) were as late-onset FGR. The baseline maternal, obstetric, and neonatal characteristics in the training and validation datasets are summarized in *Table 1*.

The intra- and interobserver ICCs for the HC and depths of INS, SF, POF, and CF were >0.90, indicating good reliability. *Table 2* presents the interobserver agreement

Table 1 Baseline maternal, obstetric, and neonatal characteristics in the training and validation datasets

Characteristics	Training dataset (n=432)	Validation dataset (n=214)	FGR fetuses (n=124)	P
Maternal characteristics				
Age in years	31 [21–44]	31 [20–46]	31 [20–41]	0.853
Pre-pregnancy BMI, kg/cm^2	20.6 [15.2–34]	20.6 [14.2–31.7]	20.6 [15.6–30.8]	0.241
Cigarette smoking	2 (0.5)	1 (0.5)	1 (0.8)	0.889
Nulliparous	267 (61.8)	132 (61.7)	82 (66.1)	0.665
IVF-ET	21 (4.9)	12 (5.6)	8 (6.5)	0.893
Ultrasound examination				
Gestational age in weeks	29^{+6} [19^{+6}–40^{+2}]	28^{+5} [20^{+3}–40]	31^{+3} [22^{+4}–40^{+1}]	0.766
Cephalic presentation	371 (85.9)	181 (84.6)	102 (82.3)	0.601
Delivery and neonate				
Gestational age at birth, weeks	39^{+1} [37–41^{+3}]	39^{+2} [37–41^{+1}]	37^{+5} [27^{+3}–40^{+6}]	0.016
Cesarean delivery	209 (48.4)	89 (41.6)	63 (50.8)	0.168
Birth weight, g	3,150 [2,460–4,250]	3,180 [2,440–4,170]	2,310 [700–2,950]	<0.001
Birth weight Z-score	0.18 [–1.23 to 4.26]	0.15 [–1.22 to 4.24]	–2.19 [–5.16 to –1.33]	<0.001
Neonatal head circumference, cm	33 [31–37]	33.5 [31–37]	31 [23–34]	<0.001
Neonatal head circumference Z-score	0.33 [–1.96 to 4.21]	0.40 [–1.77 to 4.18]	–0.85 [–3.88 to 1.45]	<0.001
Male sex	250 (57.9)	108 (50.5)	59 (47.6)	0.061
5-min Apgar score ≤7	9 (2.1)	5 (2.3)	8 (6.5)	0.028
Lower umbilical artery PH (≤7.20)*	23 (7.3)*	11 (6.7)*	7 (8.5)*	0.868
Transferred to NICU	35 (8.1)	17 (7.9)	35 (28.2)	<0.001
Length of hospitalization in days	3 [2–15]	3 [2–28]	5 [2–91]	<0.001
Neonatal complications	30 (6.9)	13 (6.1)	20 (16.1)	<0.001

Data are presented as n (%) or median [range]. *, umbilical artery PH was obtained from 314 fetuses in the training dataset, 165 fetuses in the external validation dataset, and 82 fetuses with FGR. FGR, fetal growth restriction; BMI, body mass index; IVF-ET, in vitro fertilization and embryo transfer; PH, potential of hydrogen; NICU, neonatal intensive care unit.

Table 2 Interobserver agreement and intra/interobserver reliability for measuring the HC and the depths of the INS, SF, POF, and CF with ultrasonography

Parameters	Mean difference (95% CI) (mm)	95% LOA (mm)	Intraobserver ICC (95% CI)	Interobserver ICC (95% CI)
HC	–1.70 (–6.04–2.64)	–24.50–21.10	0.98 (0.97–0.99)	0.97 (0.94–0.98)
INS	0.29 (–0.16–0.74)	–2.08–2.66	0.96 (0.93–0.98)	0.95 (0.90–0.98)
SF	–0.43 (–0.70 to –0.15)	–2.34–0.54	0.98 (0.97–0.99)	0.97 (0.95–0.98)
POF	–0.05 (–0.36–0.26)	–1.45–1.42	0.98 (0.97–0.99)	0.97 (0.95–0.98)
CF	–0.30 (–0.70 to –0.10)	–2.40–1.80	0.97 (0.95–0.99)	0.96 (0.92–0.98)

HC, head circumference; INS, insula; SF, sylvian fissure; POF, parieto-occipital fissure; CF, calcarine fissure; CI, confidence interval; LOA, limits of agreement; ICC, intraclass correlation coefficient.

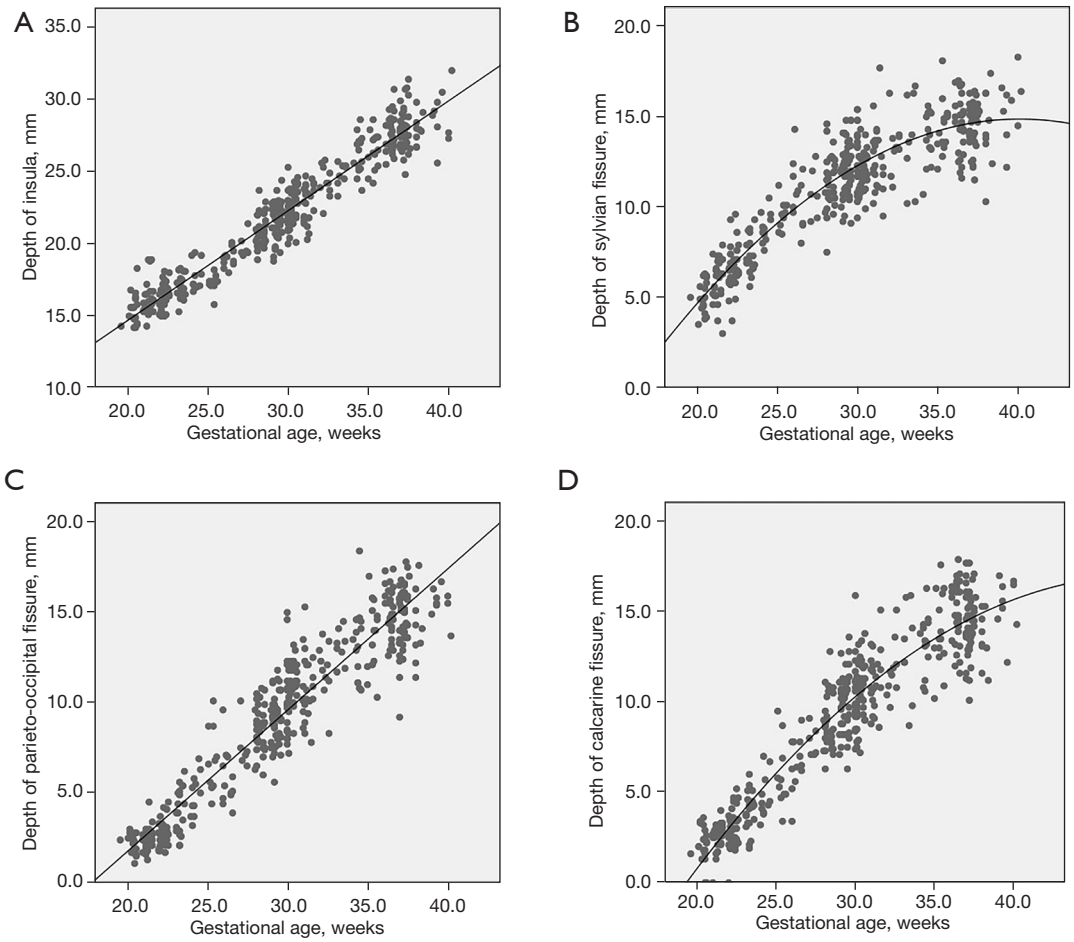

Figure 5 Relationship between fetal gestational age and fetal cerebral parameters. (A) Relationship between fetal gestational age and the depth of insula; (B) relationship between fetal gestational age and the depth of sylvian fissure; (C) relationship between fetal gestational age and the depth of parieto-occipital fissure; (D) relationship between fetal gestational age and the depth of calcarine fissure.

and intra/interobserver reliability for ultrasonographic measurements of HC and depths of INS, SF, POF, and CF.

HC and depths of INS, SF, POF, and CF were normally distributed (P=0.118, P=0.200, P=0.073, P=0.166, and P=0.200, respectively). The relationship of depths of INS, SF, POF, and CF to GA is shown in *Figure 5*. The individual measurements of fetal cranial parameters for predicting FCM are shown in *Table 3*. An exponential regression equation was yielded to predict FCM: predicted gestational week of FCM (weeks) = 11.16× exp (0.003× fTCP) (P<0.001), standard error of estimate, 0.67 weeks (*Figure 6*). The mean model standard error for prediction of the GA of FCM was ±4.7 days. The correlation between FCM and fTCP was excellent (adjusted R^2=0.973). The fTCP increased with increasing GA.

The predictive model then underwent external validation testing to assess 214 normal-growth fetuses from Center 2. The model was found to well predict FCM (standard error of estimate, 0.97±0.81 weeks).

Among the 124 fetuses with FGR, the predictive model showed that FCM was significantly delayed (2.10±1.31 weeks, P<0.001), considering the GA calculated with first-trimester ultrasound. FCM, which was expressed as GA, was similar to sonographic age, with a difference of 0.75±0.79 weeks. The predictive model showed that FCM was delayed 1.38±1.06 weeks in early-onset FGR fetuses

Table 3 The individual measurements of fetal cranial parameters for predicting cerebral maturation

Parameters for predicting fetal cerebral maturation	Formula	R^2	Standard error (days)	P
HC	9.996*exp (0.004*HC)	0.968	7.84	<0.001
INS	$-4.332+1.884*INS-0.015*INS^2$	0.934	10.08	<0.001
SF	16.17*exp (0.052*SF)	0.815	18.41	<0.001
POF	20.09*exp (0.040*POF)	0.900	15.40	<0.001
CF	20.16*exp (0.039*CF)	0.877	15.26	<0.001

HC, head circumference; INS, insula; SF, sylvian fissure; POF, parieto-occipital fissure; CF, calcarine fissure.

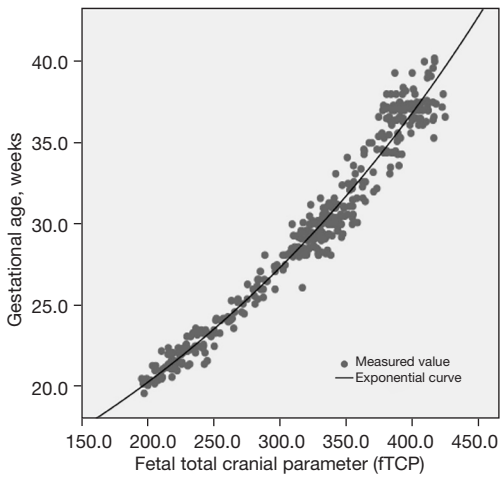

Figure 6 Scatterplots of fetal total cranial parameters in relation to gestational age, which represents fetal cerebral maturation.

and 2.58±1.47 weeks in late-onset FGR fetuses.

Discussion

Principal findings

The fetal brain maturation predictive model could help identify fetuses with abnormal or delayed brain development, thus enabling close monitoring and clinical intervention after birth. In this analysis, we confirmed that measuring fetal brain parameters to predict brain maturation was a valid approach, and the predictive models developed in this study were found to have a good predictive value and can be used in clinical settings to allow effective investigation of FCM.

Main results

Fetal brain development occurs during the entire pregnancy and mainly during the second half of pregnancy. Early in fetal life, the surface of the fetal brain is very smooth, and the cortical deep primary and more superficial secondary infoldings appear gradually, thus drastically changing the brain shape from a largely smooth to a complex convoluted one (1). Cortical folding of the neocortex is initiated at around 20 weeks and drastically changes the brain shape throughout the third trimester (1).

The earliest cerebral fissure observed using MRI is the SF, which appears at 16 gestational weeks, followed by the POF at 18 weeks (1). Some of these sulci can be used as landmarks for certain GAs. Previous study has suggested that the INS, SF, POF, and CF increase in depth with increasing gestation between 19 and 30 weeks (15); thus, we could establish a predictive model based on the intracranial structure. During ultrasound screening, we found that the CF could usually be visualized at 20 gestational weeks, presenting as a tiny dot that deepened gradually during the second and third trimesters. In the training dataset, the CF was identified with a detection rate of 96.5%.

The findings of our study indicate the feasibility and efficacy of developing a predictive model for assessing fetal brain maturation. The predictive model was established from measurements performed in standard ultrasound planes for biometric measurements, and landmarks for measurements were easy to identify; therefore, we can evaluate fetal maturation during routine scanning, with excellent predictive accuracy. The reported fTMS was developed using MRI for the evaluation of FCM, and the standard error of the model for the calculation of fetal GA

from the visual fTMS scale was 4.8 days (18). Previous study also showed that fetal cerebral cortical folding measures could be used to predict GA in the third trimester, with a mean absolute error of 0.43±0.45 weeks (27). Our results are consistent with these two studies; however, these two approaches were established using MRI, which is not routinely performed in daily prenatal care.

Clinical implications

The fTMS has also been confirmed to be sensitive to differences in brain maturation between fetuses with isolated congenital heart disease and healthy controls (2). The fTMS is an MRI model and included different criteria such as frontal and occipital cortex, insular cortex, germinal matrix, myelination, and temporal sulci. We developed the score using measurements of sulci and HC by ultrasound. The fTMS is highly reproducible and has high interrater reliability (18). The performance of these two models were similar. The predictive model established in this study used ultrasound images that are easily obtained in prenatal care and can be applied in routine clinical settings.

Prior studies support prenatal neurodevelopmental vulnerability in fetuses with FGR by showing decreased brain volumes (28,29), reduced frontal lobe growth (30), and abnormal metabolic ratios using MRI (5,31). FGR is associated with lower neurobehavioral test scores after birth (32,33), and gyrification development across cortical areas in the brain conveys prematurity effects on adult IQ critical for cognitive performance after premature birth (34). Therefore, we speculate that gyrification could contribute to impaired cognitive performance in fetuses with growth restriction and that intracranial parameters could be used to predict FCM. In our study, the fTCP was calculated as the sum of HC and depths of INS, SF, POF, and CF. Our data indicate that this quantitative predictive model is sensitive to delays in brain maturation that are present during the second and third trimesters in fetuses with FGR. The external validity of the main findings of this study was pretty well. The model is applicable to the Asian population studied.

Research implications

This quantitative predictive model is a valuable tool to assess FCM. However, the relationship between the predictive model and neurodevelopmental outcome is not performed in this study. Future studies can be performed to evaluate the association between predictive models and neurodevelopmental outcomes.

Strengths and limitations

Our study has several strengths. First, the predictive model can be applied directly and routinely in clinical settings. Second, for normal fetuses, MRI or postnatal ultrasonography was performed to evaluate for and confirm normal prenatal development. Third, the cranial parameters used were highly reproducible and had high interobserver reliability; thus, the reliability of the predictive model was excellent. Previous literature has also demonstrated that evaluation of cortical development and the corpus callosum could detect those small fetuses with brain reorganization (35) which may benefit from early intervention, including paying attention to maternal psychological health (36), supporting health care teams who care for the infants (37), and so on. The findings of this study support the use of neurosonography for assessing neurodevelopment in appropriate growth and FGR fetuses. The predictive model of this research can be applied directly and routinely in clinical settings and to identify the fetuses with delayed cerebral maturation. Pediatricians and care providers may provide specific developmental supports to FGR infants.

Previous MRI studies have demonstrated that cortical morphometry was significantly different in late-onset small GA fetuses and was associated with poorer neurobehavioral performance compared with controls (38). However, there is no follow up of neurodevelopmental outcome in FGR fetuses, which is a main limitation of our study. In addition, cases with no follow-up were left out of the study, which may have led to selection bias. A large sample study is needed to evaluate the association between predictive models and long-term neurodevelopmental outcomes.

Conclusions

The predictive performance of the model developed in this study for FCM was excellent. It may serve as a valuable tool to effectively investigate FCM during clinical implementation. This quantitative predictive model is sensitive to delays in cerebral maturation that occur during the second and third trimesters in fetuses with FGR.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-786/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-786/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethics Committees of The First Affiliated Hospital of Sun Yat-sen University and Dalian Municipal Women and Children's Medical Center approved this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from participants' parents or legal guardians before screening.

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