Development and Validation of a Semiquantitative Brain Maturation Score on Fetal MR Images: Initial Results[1]

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Purpose: To develop a valid, reliable, and simple-to-use semiquantitative visual scale of fetal brain maturation for use in clinical fetal MR imaging assessment and interpretation.

Materials and Methods: This is a retrospective assessment of data from a previous study that was prospective, institutional review board approved, and HIPAA compliant. Forty-eight normal pregnancies with a gestational age (GA) of 25 to 35 weeks were studied. A fetal total maturation score (fTMS) was developed by utilizing six subscores that evaluated cortical sulcation, myelination, and the germinal matrix and provided a single combined numerical value to be evaluated as a marker of brain maturity. The fTMS was correlated with GA and segmented brain volume. A regression model that associated GA based on the visual fTMS scoring was determined. The model was validated with a leave-one-out cross validation procedure.

Results: Mean GA was 29.3 weeks ± 2.9 (standard deviation) (range, 25.2–35.3 weeks) and mean fTMS was 8.6 ± 3.7 (range, 4–16). The intraclass correlation coefficient between the three readers (independent and blinded) was 0.948 ($P < .001$). The correlations were as follows: GA and brain volume, $r = 0.964$ ($P < .001$); fTMS and brain volume, $r = 0.970$ ($P < .001$); and GA and fTMS, $r = 0.975$ ($P < .001$). A regression model to calculate GA based on fTMS yielded the following equation: calculated GA (weeks) = 22.86 + 0.748 fTMS ($P < .001$; adjusted $R^2 = 0.946$). The standard error of the model for calculation of fetal GA from the visual fTMS scale was ±4.8 days.

Conclusion: If validated further, the fTMS scale might be used to assess morphologic brain maturity of fetuses between 25 and 35 weeks GA on a single-case basis in a clinical setting.

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Assessment of fetal brain maturation has the potential to provide important prognostic information and to facilitate the future study of human brain development in normal and high-risk fetuses. It can also provide a means to assess the effect of cardiovascular, placental, and systemic conditions on the developing fetal brain (1–8).

Authors of numerous publications (9–14) focus on evaluation of the normal in utero changes that occur during development of the brain by using fetal magnetic resonance (MR) imaging. Authors of excellent pictorial atlases (9,10,15) demonstrate the stages of normal fetal brain development, but the atlases may be somewhat difficult or time consuming to use when the numerous and varied features of the brain of an individual fetus are compared to it, especially when the different rates of maturation in various areas of the brain are considered. Similarly, authors of a number of publications (12,14,16–19) reported quantitative and biometric measurements of the fetal brain in various stages of development. These biometric indices are certainly useful, but many of the individual quantitative measurements that are proposed do not provide a comprehensive multidimensional framework for evaluation of brain maturity, and interpretation of the importance of each of these measurements in an individual fetal patient may be difficult or limited. Additionally, some of them use complex and sophisticated image analysis methods that cannot be readily applied in the clinical setting. Therefore, there is a paucity of easy-to-use and reliable methods of brain maturation assessment that could be routinely used in the clinic. The primary goal of this study was to develop a valid, reliable, and simple semiquantitative visual scale of fetal brain maturation for daily clinical fetal MR image assessment and interpretation.

Advances in Knowledge

- A clinically simple-to-use fetal total maturation score (fTMS) was developed that evaluated cortical sulcation, myelination, and germinal matrix, and provided a single combined numerical value as a surrogate measure of brain maturity.
- The fTMS showed high interrater reliability with an intraclass correlation coefficient of 0.948 (95% confidence interval: 0.887, 0.974; $P < .001$).
- The fTMS was highly correlated with segmented fetal brain volumes ($r = 0.970$; $P < .001$) and gestational age (GA) ($r = 0.975$, $P < .001$).
- Regression analysis to calculate GA based on the fTMS yielded the regression equation: GA (weeks) = 22.86 + 0.748 fTMS ($P < .001$; adjusted $R^2 = .946$); standard error of the model for calculation of GA by the visual fTMS scale was ±4.8 days.

Materials and Methods

Patients

All patients were recruited for a previously published study (2) with institutional review board approval, Health Insurance Portability and Accountability Act compliance, and written informed consent. Study participants were prospectively enrolled into a longitudinal case-control study that compared brain development in fetuses that had congenital heart disease with healthy controls. The present report includes data from healthy controls that were recruited in the study. The patients included healthy pregnant volunteers with a normal fetal echocardiogram obtained for a family history of congenital heart disease or who were suspected of having congenital heart disease in their current pregnancy. Estimated gestational age (GA) was based on maternal dates and first-trimester ultrasonographic measurements, if available, by the pregnant mother's referring obstetrician. The working GA as determined by the referring obstetrician at the time of MR imaging was used. All pregnancies and prenatal ultrasonography examinations were normal. Exclusion criteria included GA older than 36 completed weeks, multiple-gestation pregnancy, gestational diabetes, maternal contraindication to MR imaging, inadequate MR imaging data quality, prenatally documented chromosomal abnormalities, congenital infection, fetal ultrasonographic findings of dysmorphic features, dysgenic brain lesions, or anomalies of other organ systems. Detection of structural fetal brain anomalies identified on fetal or neonatal MR imaging also excluded patients from the study. There were no predetermined minimum GA exclusion criteria. The patients were born with a median GA of 39 weeks (range, 37–41 weeks). All patients included in the study had normal postnatal brain MR examinations that were performed between 39 and 44 weeks GA. The Vineland Adaptive Behavior Scale (20) was used to assess functional performance in communication, daily living, socialization, and motor skills in the cohort between 18 and

Implication for Patient Care

- If further validated, fTMS has potential for use in evaluation of the effect of various systemic fetal, maternal, or placental disease states on brain maturation in utero.

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Abbreviations:
CI = confidence interval
fTMS = fetal total maturation score
GA = gestational age

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Conflicts of interest are listed at the end of this article.

24 months. Developmental scores on the Vineland Adaptive Behavior Scale were age appropriate for all patients.

Fetal MR Imaging Examinations

All images were acquired with a 1.5-T imager (Achieva; Philips Medical Systems, Best, the Netherlands) with a five-channel phased-array cardiac coil. Multiplanar single-shot turbo spin-echo imaging was performed (repetition time/effective echo time = 12500/120 msec; signal acquired, 0.625; field of view, 330 mm; matrix, 256 × 204; section thickness, 2 mm; no gap). No contrast material or maternal sedation was used.

Development of the Semiquantitative Brain Maturation Score

The semiquantitative brain maturation score was developed by major modifications and additions to previously used postnatal brain maturation scores (5,21), and based on the authors' clinical experience with fetal brain MR imaging and previously published fetal brain atlases (9,10,16). Six simple morphologic scoring criteria were used to construct a fetal total maturation score (fTMS) by assigning a numerical subscore to each of the six criteria (Table). These six subscores included degree of frontal and occipital sulcation, degree of insular sulcation, extent of visualization of the germinal matrix, extent of myelination, presence and depth of the superior temporal sulcus, and presence and depth of the inferior temporal sulcus (Fig 1, Figs E1–E4 [online]). Images of the right and left sides of the brain were scored separately and averaged, since there may be small differences between the right and left hemispheres. A cumulative fTMS of the brain was calculated by adding the results from those six individual subscores. A pediatric neuroradiologist (A.V.) and a pediatric neurologist (D.J.L.), each with 8 years of experience with fetal MR imaging, were blinded to GA and brain volume and independently scored brain MR images for each of the patients. For further assessment of interrater reliability, a third rater who was not involved with development of the fTMS scale (P.J.S.) and is a student with no fetal MR imaging experience but with 1 year of pediatric brain MR imaging analysis research experience, also scored the fetal MR images after blinded training on five randomly selected patient cases.

Morphologic Visual Criteria to Calculate fTMS in Assessment of Fetal Brain Maturation on MR Images

Morphologic Criteria Subscore Description	Score
Frontal and occipital cortex (axial images)	
FOC1: frontal and occipital cortex is completely smooth	1
FOC2: frontal cortex is rather smooth, some sulci evident in occipital cortex	2
FOC3: frontal and occipital cortex demonstrate similar number of sulci	3
FOC4: frontal and occipital cortex rich in sulci, and with deep sulcation along the interhemispheric fissure	4
Insular cortex (axial images)	
IC1: insula is completely smooth	1
IC2: insula has shallow sulci	2
IC3: insula has deep or multiple sulci	3
Germinal matrix (axial images)	
G1: matrix seen along posterior horn, CTN, and anterior horn of lateral ventricles	1
G2: matrix seen along CTN and anterior horn of lateral ventricles	2
G3: matrix seen along CTN	3
Myelination (axial images)	
M1: brainstem, cerebellar peduncle, inferior colliculus	1
M2: M1 and ventrolateral thalamus	2
M3: M2 and caudal portion of the posterior limb of internal capsule	3
Superior temporal sulcus (coronal and sagittal images)	
TS0: absent	0
TS1: shallow	1
TS2: deep	2
Inferior temporal sulcus (coronal and sagittal images)	
TI0: absent	0
TI1: shallow	1
TI2: deep	2

Note.—FTMS is the sum of the six subscores; minimum = 4, maximum = 17. The left- and right-sided scores are averaged.
CTN = caudothalamic notch.

Quantitative Brain Volumetric MR Imaging Analysis

The method for the quantitative brain volumetric MR imaging analysis has been previously reported (2). Briefly, the MR images of the fetal intracranial cavity were masked manually to extract the fetal brain from the intrauterine tissue, brain coverings, and cerebrospinal fluid. Images were corrected for intensity inhomogeneity by using the nonparametric nonuniformity intensity normalization method (22). To minimize the effects of image degradation secondary to fetal motion, an iterative section-by-section registration was used, which normalized the intensity of each section (23). The middle brain section, defined as the section at the midpoint of the brain, was used as a reference, and the global median intensity of each subsequent section was normalized to the reference with the use of single-scale intensity normalization with a nonlinear registration approach. A Gauss-Seidel iterative schema was then applied to register the sections to a weighted average of the considered section and the two neighboring sections. The rigid-body registration of the sections reached a steady point when it was identical to the previous registration. After correction for fetal motion, coronal sections were segmented manually by using image processing

Figure 1

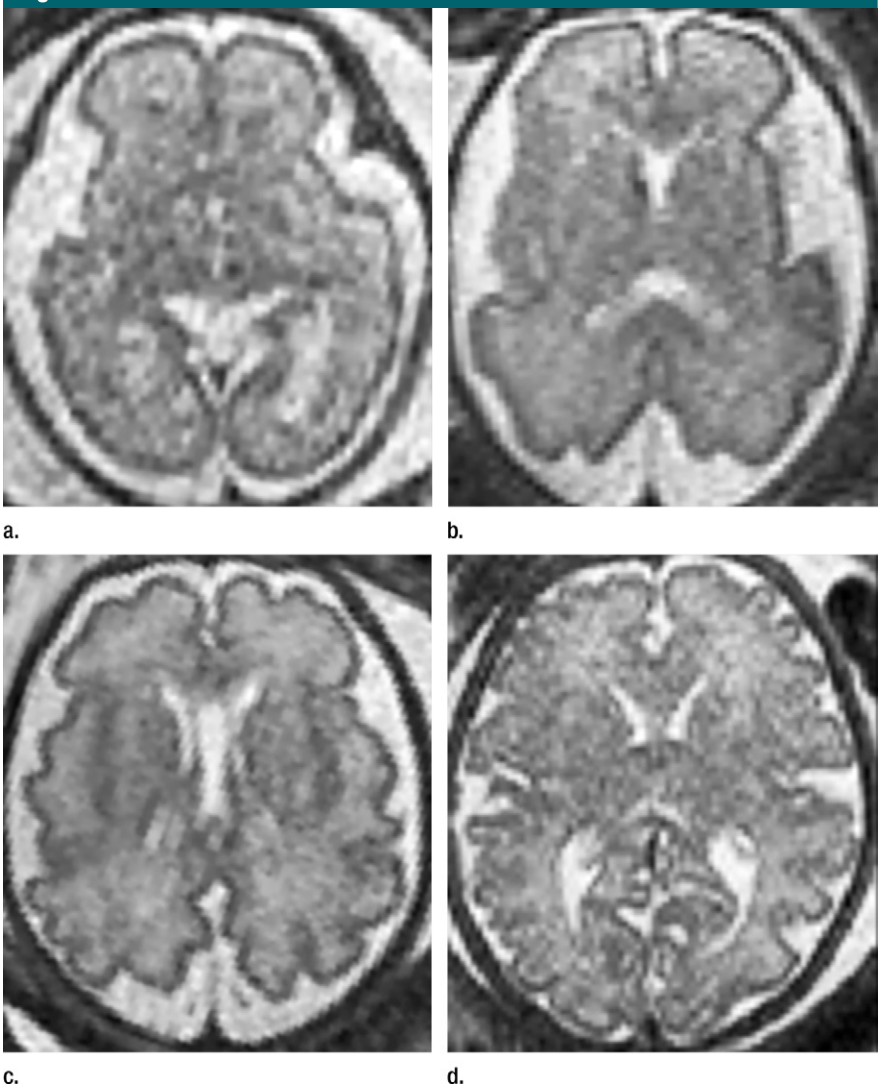

Figure 1: Demonstration of the frontal and occipital cortex sulcation subscore of the fTMS scale. Axial MR images at the level of the basal ganglia show increasing frontal and occipital sulcation. **(a)** Image from a 26-week GA fetus shows smooth frontal and occipital cortices; frontal and occipital cortex subscore of 1. **(b)** Image from a 28-week GA fetus shows relatively smooth frontal cortices, but with presence of sulci along the occipital cortices; frontal and occipital cortex subscore of 2. **(c)** Image from a 30-week GA fetus shows similar sulcation in the frontal and occipital cortices; frontal and occipital cortex subscore of 3. **(d)** Image from a 35-week GA fetus shows rich frontal and occipital cortical sulcation and relatively deep sulci along the interhemispheric fissures; frontal and occipital cortex subscore of 4.

software (MINC; McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, Quebec, Canada) to measure brain volume. Total brain volume was determined by the sum of brain parenchymal volumes measured on each coronal section. All measurements were made by a single operator (C.L., with 8 years of pediatric and fetal brain MR imaging analysis experience) who was blinded to clinical data. Each coronal area was traced twice, and the average of the two measurements was used for volume calculations. Brain volumes could not be calculated for three patients due to motion or image distortion, and they were therefore excluded from analyses that involved fetal brain volume.

Statistical Analysis

Interrater reliability between the three independent raters was assessed by using an intraclass correlation coefficient with a two-way random model for absolute agreement (24). Correlations between fTMS, GA, and total brain volume were estimated by using the Pearson product moment correlation coefficient corrected for multiple comparisons with a Bonferroni approach. Linear regression was used to assess the primary hypothesis that fTMS predicts GA on fetal MR imaging within the range of GA in the fetuses studied. To assess the validity of the model across various samples, cross validation was performed by a leave-one-out methodology in which the analysis is repeated $n-1$ times, each time with one patient left out of the analysis. Multivariable stepwise linear regression with assessment of colinearity was performed on the six morphologic subscores that composed the fTMS to assess whether other combinations of the subscores could provide an accurate calculation of GA.

Results

A total of 48 fetuses were studied. There were 27 (56%) males and 21 (44%) females. Brain volumes could not be calculated for three patients owing to motion or image distortion and they were therefore excluded from analyses involving fetal brain volume. The mean GA at the time of fetal MR imaging was 29.3 weeks ± 2.9 (standard deviation; range, 25.2–35.3 weeks). Mean calculated fetal brain volume was 179×10^3 mm^3 ± 63 (range, 102–321 $\times$ 10^3 mm^3). Average fTMS was 8.6 ± 3.7 (range, 4–16). There was no statistically significant difference between male and female fetuses regarding GA ($t = 0.45$; $P = .65$), brain volume ($t = 0.65$; $P = .51$), or fTMS ($t = 0.88$; $P = .38$).

The intraclass correlation coefficient between the three independent blinded readers who scored the MR

images for fTMS was 0.948 (95% confidence interval [CI]: 0.887, 0.974; $P < .001$). The correlation between GA and brain volume was $r = 0.964$ ($P < .001$), correlation between fTMS and brain volume was $r = 0.970$ ($P < .001$), and correlation between GA and fTMS was $r = 0.975$ ($P < .001$) (Fig 2).

Regression Analysis

Univariate regression analysis to predict GA based on the total fTMS yielded a regression equation in the form of: calculated GA (weeks) = 22.86 + 0.748 fTMS ($P < .001$; adjusted $R^2 = 0.946$); standard error of estimate, 0.69 week (Fig 3). The mean standard error of the model for calculation of GA from the total fTMS was ±4.8 days. This model indicated that for every 1-unit increase in fTMS, GA was predicted to increase by 0.748 weeks. Figure 3 shows the 95% CI across a range of fTMS. This CI is a reasonable bound on the value that GA would take in a new sample, and here it takes the form: calculated GA ± 1.41 × square root [0.00148 (fTMS)^2 − 0.0254 (fTMS) + 1.1299]. For example, for an fTMS of 10, the calculated GA is 30.3 weeks (95% CI: 28.9, 31.8 weeks). The results of the cross-validation leave-one-out procedure showed a standard error of 0.21 for the constant y (95% CI: 22.44, 23.29; $P < .001$) and a standard error of 0.02 for the slope x (95% CI: 0.703, 0.793; $P < .001$) in the model.

The relationship of the individual subscores to GA is shown in Figure 4. A model that utilized four of the six subscores was derived from the stepwise analysis, namely frontal-occipital sulcation, germinal matrix, superior temporal sulcation, and inferior temporal sulcation subscores, with a standard error of estimate of 0.74 and adjusted R^2 of 0.934.

Figure 2

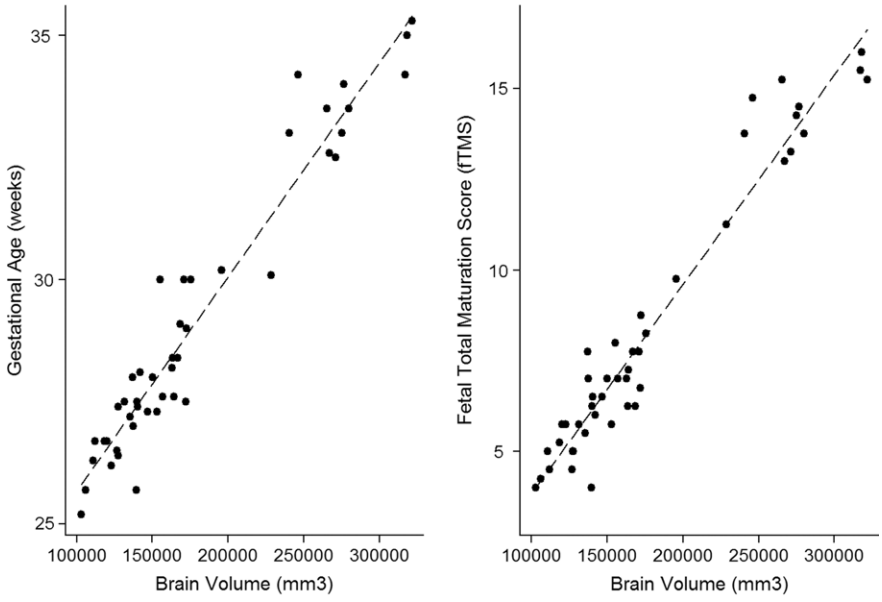

Figure 2: Relationship between calculated brain volumes with **(a)** fetal GA and **(b)** fTMS scores.

Figure 3

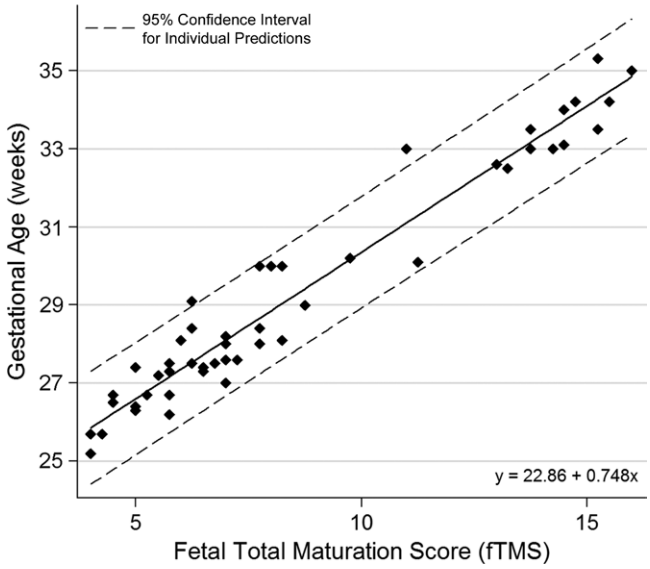

Figure 3: Relationship between the visual fTMS scores and fetal GA.

Discussion

A large part of brain development occurs in the second half of pregnancy, and includes neuronal migration and arborization, synaptogenesis, oligodendrocyte maturation, initiation of cerebral myelination, programmed cell death, reorganization, and increase of synaptic connections (5,13,25). The availability of quantitative clinical tools to assess brain changes during this critical time period by using noninvasive imaging methods is desirable for surrogate measures of brain maturity. As such, they can provide important clues to normal, abnormal, or delayed development of the brain.

Brain maturation progresses through a predictable series of morphologic changes of cortical and subcortical

Figure 4

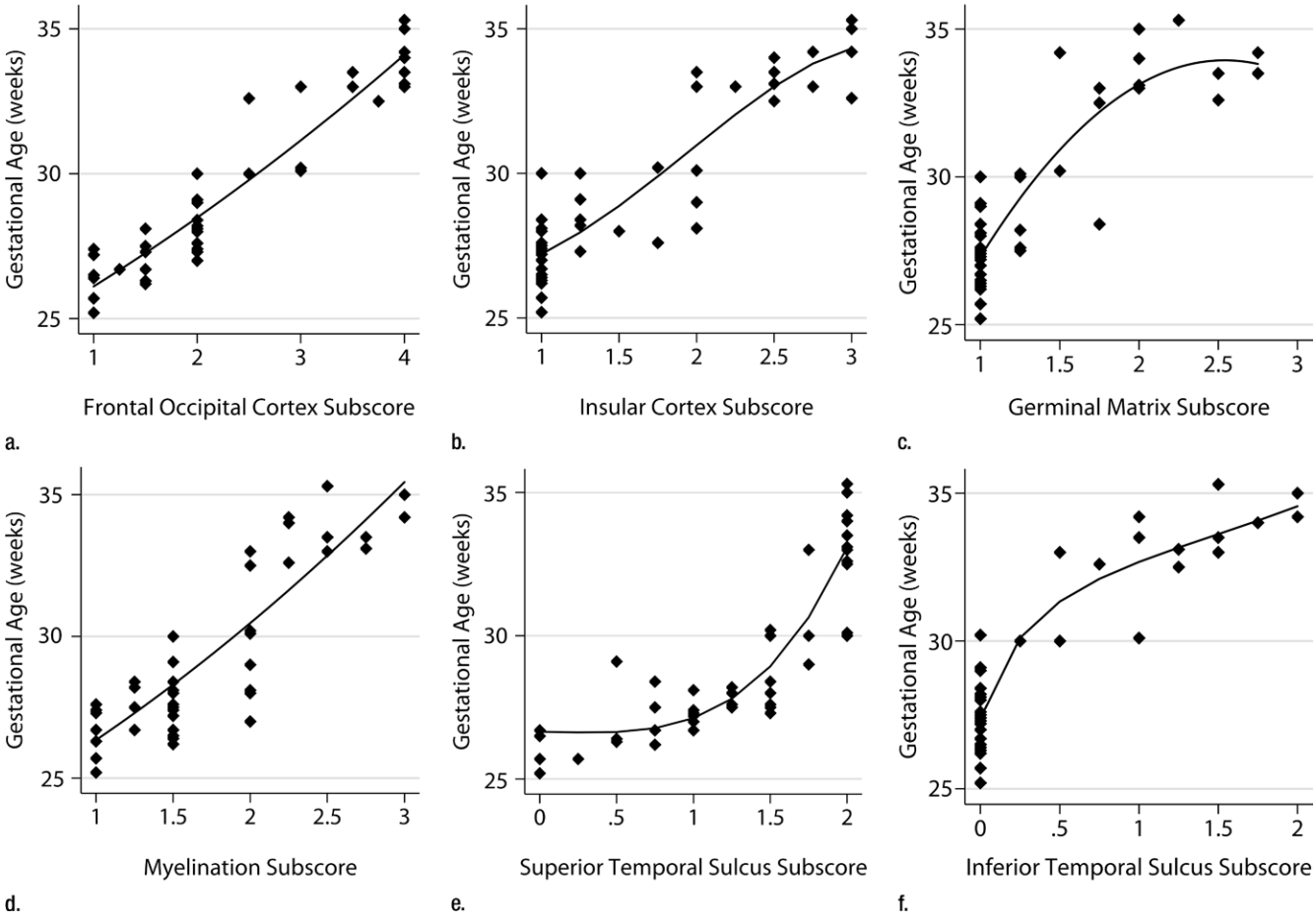

Figure 4: Relationship between fetal GA and the six components of the fTMS scoring system, including **(a)** the frontal and occipital cortex subscore, **(b)** the insular cortex subscore, **(c)** the germinal matrix subscore, **(d)** the myelination subscore, **(e)** the superior temporal sulcus subscore, and **(f)** the inferior temporal sulcus subscore.

structures. The fetal cortex undergoes a predetermined temporal sequence of sulcation and gyration in various lobes (9–11,13,16). Early in fetal life, the cortex begins as a smooth structure, and deep primary and more superficial secondary cortical infoldings gradually appear. The earliest signs of surface indentation and sulcation on MR images occurs at the sylvian fissure at 16 weeks and the parieto-occipital and anterior cingular sulci at 18 weeks GA (11,25). Toward the 35th week, all primary and most of the secondary sulci are present; the secondary sulci appears from the 24th week and the tertiary sulci appears after the 28th week (13,25). Some of these sulci can be used as landmarks for a certain GA, and enable the estimation of age-related brain cortical development (11,13,14,16,25). The germinal matrices or germinal zones are the sites of origin and migration of cortical neurons and glial cells, and they appear robust between 10 and 28 weeks GA. The blood supply to the germinal matrix gradually involutes as neuronal proliferation halts and glial multiplication (which forms migrating bands of glial cells) begins; this starts at 20 weeks GA (26). The myelination of the cerebral hemispheres is largely postnatal, but can be detected in certain locations as darker foci on routine T2-weighted fetal MR images. Myelination in the fetal brain undergoes a sequence of steps during fetal development (14,21,27). Early changes can be seen in the brainstem, cerebellar vermis, cerebellar peduncles, and inferior colliculi. Later, the ventrolateral thalamus and globus pallidus show myelination, and the posterior limbs of the internal capsule subsequently demonstrate myelination, which starts caudally and later involves the more cranial portions. The fTMS uses these detectable morphologic changes on visual inspection of fetal MR images.

Some research groups have focused on brain development beyond simple morphologic assessments. Measurements of diffusion imaging parameters, such as diffusivity or anisotropy in various areas of the brain, have been shown to provide valuable information

on fetal brain development and maturity (6,19,28–34). Nevertheless, routine clinical use of these measurements is hindered by various technical issues, practical factors, and limitations that affect quality and reproducibility of these measures. Additionally, while these indices are quite useful in performance of group studies of fetal brain development, it is almost impossible at this stage to interpret the importance of these measured individual values in a particular patient. MR spectroscopic assessment of known brain metabolites, such as *N*-acetylaspartate, choline, and lactate in the fetus, has also been investigated as a marker of brain development (6,33,35–37). Again, various technical complexities, lack of standards, limitations in availability, and difficulty of interpretation of individual values hamper the usefulness of MR spectroscopy in routine clinical assessment of brain development.

Many of these previous studies cannot be directly or routinely used in the clinical setting because of their complex or time-consuming nature. Others are limited in their reproducibility or the information they provide for a single-patient assessment. This study was undertaken to address some of these limitations. The fTMS scale was developed by major modifications and additions to a previously developed and validated postnatal total maturation score in healthy preterm infants to make it appropriate for fetal MR imaging assessment. The postnatal total maturation score scale is a semiquantitative scoring system that uses predictable anatomic maturational changes in the brain on early postnatal MR images (21). The postnatal total maturation score scale has been applied by a number of research groups and has demonstrated great usefulness with assessment of brain maturational changes in various disease states (1,5,7,8).

Our study results demonstrated the feasibility of developing a highly accurate, reproducible, and simple-to-use clinical scale of brain maturation that capitalizes on brain morphologic changes that can be easily detected with routine T2-weighted fetal MR imaging sequences. It simultaneously tapped into various aspects of brain development during the second half of pregnancy, including cortical sulcation in various parts of the brain, myelination, and changes in the germinal matrix, and provided a single combined numerical value as a surrogate marker of brain maturity. The fTMS scale demonstrated excellent correlations with segmented fetal brain volumes and GA. It was reproducible as shown by the very high correlations between three independent blinded readers. The regression model showed that the fTMS scale is highly accurate, with a standard error of 4.8 days in calculation of the GA of the fetus, all by just a short visual assessment of routine clinical fetal MR images. The cross-validation assessment demonstrated that it may be applied in a similar way across different patient samples. The total fTMS regression model may have appeared slightly more accurate for calculation of GA compared with the four subscore model from the stepwise regression. We note that fTMS was specified in advance whereas the stepwise model developed a new algorithm based on the data and thus overestimates the adjusted R^2 that would be obtained in a new sample. Thus, in a new sample the difference between fTMS and the simpler model is expected to be even larger than the difference described here.

An important advantage of this scoring system is that calculation of the fTMS is simple, and can be easily learned and applied to routine clinical fetal T2-weighted MR images without any specialized MR imaging sequences, additional imaging time, specialized software, quantitative measurement tools, or complex analyses. The evaluation can be done in a few minutes on standard clinical axial, coronal, and sagittal T2-weighted images by using clinical reading workstations. It has the potential to be easily implemented in routine clinical assessments, if needed.

This scoring system has great potential to detect gross delays in morphologic maturation of the brain during pregnancy. It can be further used to assess the fetal brain in various systemic fetal, maternal, or placental disease states that may affect brain maturation in utero. It is important to note that correct interpretation of this scoring system necessitates accurate determination of and comparison with GA of the pregnancy.

Our study had limitations. One limitation of this study was its small size. Further validation of this scoring system is desirable in larger population samples. Another limitation of the study was that the study population consisted of fetuses 25–35 weeks GA. Many clinical fetal MR examinations are performed before 25 weeks GA, and it would be helpful to have a simple scale to assess brain maturity at these ages. Another limitation was the use of the working GA, determined by the pregnant mother's referring obstetrician, at the time of MR imaging as an alternative to more strict pregnancy dating. It should also be noted that this scoring system has not been validated for nor is it currently meant to assess brain maturity in fetal brains with gross malformations, masses, frank hydrocephalus, infarcts, or other major insults. Finally, the clinical utility of the scale in assessment of abnormal growth or development will need to be addressed in future studies.

By providing superior anatomic detail, fetal brain MR imaging has an important role in evaluation of the structurally abnormal brain. Assessment of morphologic brain maturity and intersubject variability on fetal brain MR imaging is valuable in both research and clinical situations. The fTMS semiquantitative scale presented and validated in this study can be used to assess morphologic brain maturity of fetuses between 25 and 35 weeks GA on a single-case basis in a clinical setting. It also has potential for evaluation of the effect of various conditions on the developing fetal brain.

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