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ABSTRACT

BACKGROUND AND PURPOSE: Most ultrasound markers for monitoring brain growth can only be used in either the prenatal or the postnatal period. We investigated whether corpus callosum length and corpus callosum–fastigium length could be used as markers for both prenatal and postnatal brain growth.

MATERIALS AND METHODS: A 3D ultrasound study embedded in the prospective Rotterdam Periconception Cohort was performed at 22, 26 and 32 weeks' gestational age in fetuses with fetal growth restriction, congenital heart defects, and controls. Postnatally, cranial ultrasound was performed at 42 weeks' postmenstrual age. First, reliability was evaluated. Second, associations between prenatal and postnatal corpus callosum and corpus callosum–fastigium length were investigated. Third, we created reference curves and compared corpus callosum and corpus callosum–fastigium length growth trajectories of controls with growth trajectories of fetuses with fetal growth retardation and congenital heart defects.

RESULTS: We included 199 fetuses; 22 with fetal growth retardation, 20 with congenital heart defects, and 157 controls. Reliability of both measurements was excellent (intraclass correlation coefficient ≥ 0.97). Corpus callosum growth trajectories were significantly decreased in fetuses with fetal growth restriction and congenital heart defects ($\beta = -2.295$; 95% CI, −3.320–1.270; $P < .01$; $\beta = -1.267$; 95% CI, −0.972–0.562; $P < .01$, respectively) compared with growth trajectories of controls. Corpus callosum–fastigium growth trajectories were decreased in fetuses with fetal growth restriction ($\beta = -1.295$; 95% CI, −2.595–0.003; $P = .05$).

CONCLUSIONS: Corpus callosum and corpus callosum–fastigium length may serve as reliable markers for monitoring brain growth from the prenatal into the postnatal period. The clinical applicability of these markers was established by the significantly different corpus callosum and corpus callosum–fastigium growth trajectories in fetuses at risk for abnormal brain growth compared with those of controls.

ABBREVIATIONS: CC = corpus callosum; CCF = corpus callosum–fastigium; CHD = congenital heart defect; FGR = fetal growth restriction; GA = gestational age; US = ultrasound

In preterm infants and those small-for-gestational age, brain growth is an important predictor of neurodevelopmental outcome.[1-4] Although prenatal growth often predicts postnatal growth, there is a traditional division between fetal and neonatal growth charts.[5] This is mainly due to the lack of consistent measures of brain growth that can be used in both the prenatal and postnatal periods.

Markers of brain growth that can theoretically be used in both the prenatal and postnatal periods include head circumference and a few ultrasound (US) and MR imaging measures. Head circumference measured postnatally, however, lacks precision and does not correspond well with neurodevelopmental outcome.[6,7] Prenatal and postnatal US markers are largely based on individual brain structures, only reflecting growth of a specific part of the brain.[8-12] Moreover, these brain structures are not measured consistently during the prenatal and postnatal periods due to the absence of corresponding standard US planes. Although MR imaging provides more precise measures of brain growth, volume, and development, this technique is expensive and therefore not suitable for serial measurements.

Recently, we demonstrated that corpus callosum–fastigium

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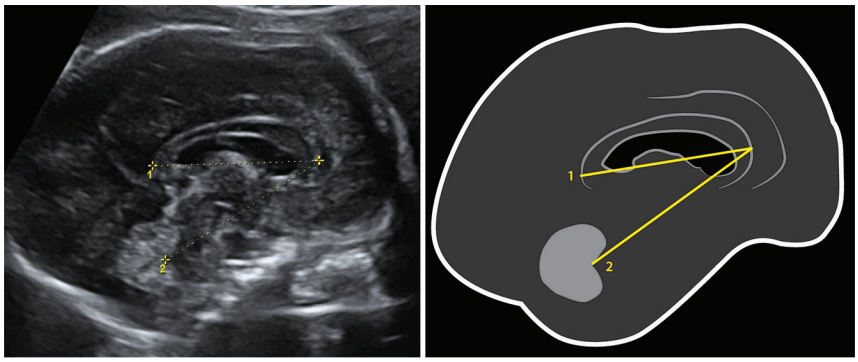

FIG 1. Prenatal measurement of CC and CCF lengths. 1, Corpus callosum length, outer-outer border. 2, Corpus callosum–fastigium length, from the genu of the corpus callosum to the fastigium (roof of the fourth ventricle).

(CCF) length is a reliable bedside-available US marker that can be used to monitor brain growth in preterm infants during neonatal intensive care unit stays.[13] CCF length is considered a composite marker of diencephalon and mesencephalon size and thereby adds information to the more widely used corpus callosum (CC) length.[13] We hypothesized that these 2 cranial ultrasound measures are feasible for use during prenatal US examinations. Thereby, these markers would provide a continuum for monitoring brain growth, bridging the period before and after birth.

Our main aim was to investigate whether CC and CCF lengths can be used as reliable US markers for monitoring fetal and neonatal brain growth. First, we assessed the reliability of the measurements. Second, we created reference curves from 22 to 42 weeks' gestational age (GA) by combining fetal and neonatal measurements. Finally, as a first step to evaluate the clinical applicability of these US markers, we investigated CC and CCF growth trajectories in fetuses at risk of abnormal brain growth and compared them with those of control fetuses.

MATERIALS AND METHODS

Study Design

This 3D-US study was embedded in the Rotterdam Periconceptional Cohort (Predict Study), an ongoing prospective cohort study at the Department of Obstetrics and Gynecology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.[14] At enrollment, all participating women and their partners gave written informed consent on behalf of themselves and their unborn child. This study was approved by the regional medical ethical committee and institutional review board of the Erasmus MC, University Medical Center in Rotterdam (MEC 2004-227; date of approval, January 25, 2013).

Pregnant women were enrolled between November 2013 and July 2015. They were either enrolled before 12 weeks' GA or between 22 and 32 weeks' GA. Controls were enrolled before 12 weeks' GA and were defined as fetuses without fetal growth restriction (FGR) before 32 weeks' GA, born after 37 weeks' GA, and without congenital anomalies. Cases included those pregnancies referred to our outpatient clinic with FGR or an isolated fetal congenital heart defect (CHD) between 22 and 32 weeks' GA. The diagnosis was confirmed by an extended structural US examination at our hospital. FGR was defined as abdominal circumference or estimated fetal weight percentile of <5 according to Hadlock et al.[15]

For this analysis, we excluded pregnancies ending in intrauterine fetal death, termination of pregnancy, or only preterm birth (without FGR or CHD). We also excluded fetuses with congenital anomalies other than CHD, with trisomy 21, and without US images.

Study Parameters

According to Dutch clinical practice, GA in spontaneously conceived pregnancies was calculated on the basis of the first trimester crown-rump length measurements before 13 weeks' GA.[16] In pregnancies conceived through in vitro fertilization, with or without intracytoplasmic sperm injection procedures, GA was calculated from the date of oocyte retrieval plus 14 days or from the day of embryo transfer plus 17 or 18 days after cryopreserved embryo transfer, depending on the number of days between oocyte retrieval and cryopreservation.

Data were collected on maternal characteristics, medical and obstetric history, pregnancy course, and neonatal outcome from self-administered questionnaires in the first trimester, second trimester, and around delivery. Follow-up data on pregnancy outcomes were validated on the basis of a US report of the routine second trimester anomaly scan and on obstetric medical records.

Prenatal Sonography

Prenatal 3D-US examinations were performed on the Voluson E8 system (GE Healthcare, Milwaukee, Wisconsin) by using a 1 to 7 MHz transabdominal transducer or a 6 to 12 MHz transvaginal transducer. Primarily, we used an abdominal approach, but a transvaginal approach was considered when the fetus was in a head-down presentation. Serial prenatal 3D-US examinations and measurements were performed at 22, 26, and 32 weeks of gestation by 1 certified sonographer (I.V.K.). Standard biometry was measured, including biparietal diameter, head circumference, abdominal circumference, and femur length. An estimation of fetal weight was calculated with the Hadlock equation.[15] Biometry was followed by detailed 3D neurosonography. Standard planes were obtained according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines.[17] CC and CCF length measurements were performed off-line in an exact midsagittal plane (Fig 1). CC length is measured from the genu to the splenium, outer-outer border. CCF length represents the length between the genu of the CC and the fastigium (roof of the fourth ventricle).[13] CCF length was only measured in images in which CC measurement was performed successfully. Manipulation of the 3D-US volume to ensure an exact midsagittal plane for the measurements was performed in 4D View, Version 5.0 (GE Healthcare).

Postnatal Assessments

After birth, cranial ultrasound was planned between 42 + 0 and 42 + 6 weeks' postmenstrual age, independent of GA at birth.

Table 1: Baseline characteristics[a]

Characteristics	Controls (n = 157)	FGR (n = 22)	CHD (n = 20)	Missing
Maternal				
Age at enrollment (yr)	32.3 (21–44)	29.7 (21–41)	33.0 (22–48)	7
Nulliparous	69 (44)	13 (68)	11 (58)	6
Mode of conception (IVF/ICSI)	48 (31)	2 (10)	2 (11)	3
Geographic background				6
Western	126 (81)	15 (79)	18 (90)	
Non-Western	29 (19)	4 (21)	2 (10)	
Educational level				8
Low	20 (13)	4 (20)	0	
Intermediate	56 (36)	12 (60)	7 (39)	
High	79 (51)	4 (20)	11 (61)	
Prepregnancy BMI (kg/m^2)	22.9 (15.2–39.7)	22.9 (17.6–43.4)	23.4 (18.0–35.8)	19
Periconception folic acid initiation (yes)	149 (96)	15 (79)	18 (95)	6
Periconception smoking (yes)	25 (16)	3 (16)	3 (16)	8
Periconception alcohol consumption (yes)	44 (29)	4 (21)	10 (53)	9
Neonatal				
Birth weight (g)	3345 (2035–4380)	1400 (400–2900)	3420 (1650–4140)	2
Gestational age at birth (wk)	39^{+1} (37^{+0}–41^{+5})	34^{+2} (26^{+3}–39^{+3})	38^{+6} (28^{+4}–41^{+5})	2
Males	82 (52)	11 (50)	13 (65)	0

Note:—BMI indicates body mass index; IVF/ICSI, in vitro fertilization with or without intracytoplasmic sperm injection; ICSI, intracytoplasmic sperm injection.
[a] Data are presented as median and range or number and percentage. Missing data were due to incomplete questionnaires.

Cranial ultrasound was performed by an experienced team of researchers with MyLab 70 (Esaote, Genoa, Italy) with a convex neonatal probe (7.5 MHz). CC and CCF length measurements were performed off-line by 1 researcher (J.A.R.) according to the method described above, with MyLab software.

To enhance precision, we repeated all prenatal and postnatal measurements 3 times. The mean values were used in the statistical analyses.

Statistical Analysis

For data analyses, we used SPSS (Release 21 for Windows; IBM, Armonk, New York) and R statistical and computing software, Version 3.1.3 (http://www.r-project.org). Results with P values $<$ .05 were considered statistically significant.

Previously, we demonstrated that postnatal measurements of CC and CCF length had good intra- and interobserver agreement.[13] To evaluate the reliability and reproducibility of prenatal measurements, we randomly selected 30 US examinations of 30 different fetuses, equally divided across the 3 prenatal time points from the whole study population. CC and CCF length measurements were then performed in 3-fold by 2 independent observers (I.V.K. [1] and J.A.R. [2]). We performed analyses for intra- and interobserver reliability, calculating the mean differences with 95% CIs and intraclass correlation coefficients. Moreover, the extent of agreement was examined with the Bland-Altman method.

Generalized Additive Models for Location and Scale were used to create reference ranges of CC and CCF length measurements between 22 and 42 weeks' GA in controls.[18] To investigate whether cases showed deviations in CC and CCF growth, we created growth trajectories for each subject of the serial measurements of CC and CCF lengths between 22 and 42 weeks' GA. A maximum-likelihood approach was used to test whether polynomials of GA contributed to the best model fit. In the same manner, we tested the contribution of random and fixed effects of the intercept and slopes for all included polynomials. A quadratic model of GA with random intercept and slopes was designated as the best model. We placed the origin of the GA scale at 140 days' GA. In this model, the variable indicating whether a fetus was FGR, CHD, or control was used as the covariate of interest (model 1). Last, the final model (model 2) was adjusted for serial measurements of fetal weight and sex.

RESULTS

Study Population

In total, 227 pregnant women were enrolled prenatally. After excluding pregnancies ending in intrauterine fetal death (n = 1), termination of pregnancy (n = 1), preterm birth (n = 14), and those with congenital anomalies other than CHD (n = 4), trisomy 21(n = 2), and withdrawals (n = 6), the study population consisted of 199 pregnancies. Of these 199 fetuses, 22 had FGR, 20 had CHD, and 157 were controls. The general characteristics of the study populations are listed in Table 1.

Success Rates and Reliability Analyses

Of 542 prenatal 3D-US scans, 377 contained a high-quality midsagittal plane eligible for CC and CCF length measurements. Means and success rates of CC and CCF length measurements per gestational age are listed in Table 2. Success rates ranged between 61% and 75% for prenatal CC length measurements and between 59% and 72% for prenatal CCF length measurements. Postnatally, CC and CCF length measurements were successful in 97%. In 83% of the subjects, CC length was measured at least at 2 time points during the whole study period, and CCF length, in 65%.

The intra- and interobserver reliability and agreement are shown in Table 3. CC lengths measured by observer 1 were slightly smaller (mean difference, −1.109 mm; mean percentage difference, −3.4%) than those measured by observer 2. Ninety-five percent limits of agreement for all measurements represented excellent agreement when the CC and CCF length measurements were repeated by the same observer and good agreement when repeated by a second observer. Intraclass correlation coefficient

values of both intra- and interobserver were ≥0.97, which represents excellent reliability.

Linear Mixed-Model Analyses

In Fig 2*A*, *-B*, the reference curves and individual growth trajectories of CC and CCF lengths are shown. The results of the linear mixed-models estimating differences in the mean growth trajectories of CC and CCF lengths among controls and fetuses with FGR and CHD are shown in Table 4. Growth trajectories of CC length were significantly decreased in fetuses with FGR and CHD compared with growth trajectories of controls. CCF growth trajectories were only significantly decreased in fetuses with FGR compared with those of controls. In Fig 2*C*, these trajectories are graphically displayed.

DISCUSSION

Here, we demonstrate that CCF and CC length may serve as reliable markers for monitoring prenatal and postnatal brain growth. Fetuses with FGR showed decreased growth of both CC and CCF length, while in fetuses with CHD, only CC growth was decreased between 22 and 42 weeks' GA.

Our findings suggest that we are able to bridge the traditional division between fetal and neonatal US growth charts. To date, studies that combine fetal and neonatal US markers of brain growth in a single cohort are scarce. One explanation is that standard prenatal US planes containing easily recognizable landmarks of the brain do not correspond well with the standardized planes accessible by cranial ultrasound. This lack of correspondence results in differences in prenatal and postnatal measures and measuring methods. For example, head circumference assessed prenatally, calculated from the biparietal diameter and occipital frontal diameter, correlates poorly with direct postnatal measurements with a tape measure.[7,19] Furthermore, changes in head shape can be induced by delivery (eg, skull molding, edematous swelling, and hematomas).

In contrast to other prenatal US measurements, excellent reliability was shown for CC and CCF lengths, comparable with the reliability of the postnatal measurements.[13] On the basis of our data, we suggest that CCF length is the most reliable and relevant marker for monitoring brain growth. CCF length can be assumed to be a composite marker of multiple brain structures with different embryologic origins. Therefore, CCF length may be a better representative of global brain growth than previous sonographic markers based on individual brain structures.[8-12]

Growth trajectories of CC and CCF length were decreased in fetuses at risk for abnormal brain growth and impaired long-term neurodevelopmental outcome. While studies using CCF length have not been published in the literature before, CC length findings are in line with those in previous literature. The decreased CC growth trajectories in fetuses with FGR are in accordance with findings of a recent MR imaging study that showed significantly reduced CC length in fetuses with FGR compared with CC length of appropriate-for-gestational-age controls.[20] Results from our previous study in preterm infants demonstrated a similar association between CCF length and birth weight SD score.[13] There are, to the best of our knowledge, no publications on CC length in fetuses with CHD with which to compare our results, though previous studies did report anomalies of the CC and reduction of CC volume in children with CHD.[21,22] The decreased growth trajectory of CC length in fetuses with CHD is, however, supported by accumulating evidence reporting that fetuses with CHD are at risk for abnormal brain growth and development.[23-26]

Brain growth is an important predictor of neurodevelopmental outcome.[1,3,27] We hypothesize that the decreased CC and CCF growth trajectories observed in cases may have consequences for long-term outcome. In preterm infants, a shorter CC length is related to a higher risk of an adverse neurodevelopmental outcome at 2 years' corrected age.[4] Moreover, a significantly smaller corpus callosum was found in individuals with schizophrenia and autism.[28,29] CCF length represents the diencephalon and thus includes thalamus development, which is crucial for cognitive functioning. Derangements in thalamus development are associated with adverse neurodevelopmental outcome.[30] Yet, the clinical rele-

Table 2: Success rates and means of corpus callosum and corpus callosum–fastigium length per gestational age[a]

Length (mm)/ GA (wk)	US Scans (No.)	Measurements (No.)	Success Rate (%)	Mean (SD) (mm)
CC				
22	166	124	75	26.35 (1.22)
26	188	138	73	34.33 (1.86)
32	188	115	61	41.56 (2.19)
42	143	138	97	48.09 (3.15)
CCF				
22	124	89	72	33.09 (1.61)
26	138	82	59	39.39 (1.92)
32	115	81	70	45.86 (2.07)
42	143	138	97	52.26 (3.12)

[a] Presented are the success rates, means, and corresponding SD values of the CC and CCF measurements per full week of gestation. The success rates for CC length and postnatal CCF length were calculated by the number of successful measurements divided by the total number of US images. Success rates of prenatal CCF measurements were calculated by dividing the number of successful CCF measurements by the number of midsagittal images eligible for CC length.

Table 3: Intraobserver and interobserver reliability for prenatal measurements of corpus callosum and corpus callosum–fastigium length[a]

	Absolute Difference				Relative Difference		
	Mean Difference (mm)	95% CI Mean Difference (mm)	*P*	95% Limits of Agreement (mm)	Mean Difference (%)	95% Limits of Agreement (%)	ICC
Intraobserver							
CC	0.011	−0.228 to 0.250	.923	−1.373, 1.396	0.1	−4.1, 4.3	>0.99
CCF	0.180	−0.157 to 0.517	.284	−1.711, 2.071	0.4	−4.7, 5.4	>0.99
Interobserver							
CC	−1.109	−1.702 to −0.515	.001	−4.546, 2.329	−3.4	−14.9, 8.1	0.97
CCF	−0.125	−0.741 to 0.492	.684	−3.589, 3.340	−0.4	−9.5, 8.6	0.97

Note:—ICC indicates intraclass correlation coefficient.

[a] Intra- and interobserver reliability analyses for prenatal CC and CCF measurements in a random selection of 30 ultrasound scans.

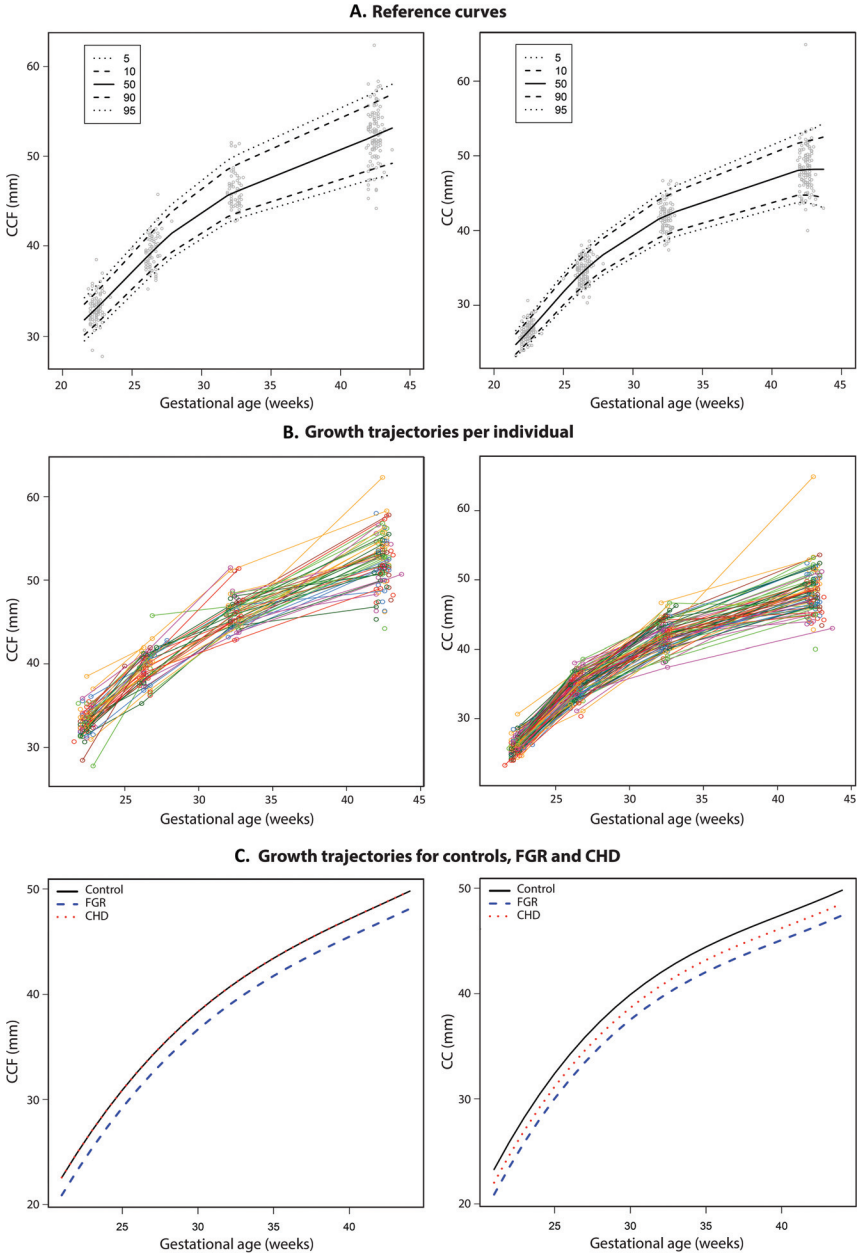

FIG 2. Growth curves. *A*, Reference curves between 22 and 42 weeks of gestation for CCF (*left*) and CC (*right*) length, with the 5th, 10th, 50th, 90th, and 95th percentiles. *B*, Individual growth trajectories of CCF (*left*) and CC (*right*) length between 22 and 42 weeks of gestation. *C*, Growth trajectories for controls (*black*) and fetuses with FGR (*striped blue*) and CHD (*dotted red*).

Table 4: Linear mixed models—growth trajectories of CC and CCF influenced by the presence of fetal growth restriction and congenital heart defects[a]

	Model 1			Model 2		
	β	95% CI	*P* Value	*β*	95% CI	*P* Value
CC						
FGR	−2.384	−3.26 to −1.505	<.01[b]	−2.295	−3.320 to −1.270	<.01[b]
CHD	−1.252	−1.954 to −0.549	<.01[b]	−1.267	−1.972 to −0.562	<.01[b]
CCF						
FGR	−1.413	−2.500 to −0.326	.01[b]	−1.295	−2.595 to 0.003	.05
CHD	0.012	−0.829 to 0.963	.98	0.000	−0.835 to 0.835	.99

[a] Data are presented in *β* values with corresponding 95% CI and *P* values, compared with controls. Model 1 represents the crude model with GA and its polynomials as predictor and type of case as covariate of interest. Model 2 is the fully adjusted model for the covariates in model 1 and for serial measurements of fetal weight and sex.
[b] Significant.

vance for neurodevelopmental outcome of differences in CC and CCF growth trajectories needs further investigation.

Clinical Applicability

The landmarks used for CC and CCF length measurements are relatively easy to distinguish on US images. Prenatally, the main challenge is obtaining an exact midsagittal plane. The prenatal success rates are predominantly influenced by acoustic shadowing and the position of the fetus. 3D-US can enhance precision by manipulating volumes to reconstruct the exact midsagittal plane.[31-33] When a midsagittal plane is obtained, both measurements take <1 minute in experienced hands. Postnatally, a standard midsagittal plane is easy to obtain through the anterior fontanelle; also, the off-line measurements of CC and CCF lengths take <1 minute. Newly developed software that enables the identification of the midline automatically could still improve the measurements for clinical practice.[34]

Strengths and Limitations

Some considerations should be taken into account. First, our study was conducted in a tertiary hospital population, with a relatively high maternal age, mainly of Western origin, and a high educational level. Therefore, replication of the data is warranted to validate our findings for the general population. Second, the small number of cases limits the conclusions of our study. We cannot exclude that absence of statistically significant findings may be due to lack of power. Third, the growth charts are based on measurements at 4 time points and may improve by including intermediate time points to further smooth the curves. Finally, the US scans and measurements were performed by experienced observers, which potentially enhanced the quality of the midsagittal images and thus success rates and reliability. Clinical applicability may be overestimated as a consequence. Success rates of the measurements were mostly influenced by fetal position, which we assume to be independent of the variables in this study. We consider the prospective and longitudinal study design as a strength of our study. Combining prenatal and postnatal measurements in

1 reference curve is an innovative method to facilitate monitoring of fetuses at risk of impaired brain growth.

Future Implications for Clinical Care and Research

Tight collaboration between obstetric and neonatal researchers and caregivers is needed for bridging the gap when monitoring fetal and neonatal brain growth. This is of great importance for optimizing neurodevelopmental care in fetuses and infants at risk of abnormal brain growth and neurodevelopmental impairment. Easily applicable US tools that can be used independent of the prenatal or postnatal period will have clinical implications. We consider our reference curves useful for age-equivalent preterm infants because they are largely comparable with the postnatal reference curves between 24 and 32 weeks in preterm infants from Roelants et al.[13] In addition, CC and CCF length measurements may be applicable from midgestation onward and may theoretically be prolonged until closure of the anterior fontanelle in the first year of life. Future research should correlate these measurements to commonly used MR imaging markers and explore the link between the growth measures and functional neurodevelopmental outcome.

CONCLUSIONS

In this prospective cohort, we demonstrated that CC and CCF length measurements are reliable markers for brain growth from the fetal into the early neonatal period. By combining prenatal and postnatal CC and CCF length measurements in 1 reference curve, we created a continuum for monitoring brain growth, irrespective of the intra- or extra-uterine environment. We demonstrated that fetuses at risk of abnormal brain growth (ie, those with CHD and FGR) showed significantly decreased CC and CCF growth between 22 and 42 weeks' GA. Whether these markers could serve as early predictors of neurodevelopmental outcome in later life warrants further research.

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