Assessment of Corpus Callosum Biometric Measurements at 18 to 32 Weeks’ Gestation by 3-Dimensional Sonography

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Objectives—The purposes of this study were to construct reference limits for corpus callosum dimensions measured on images reconstructed from 3-dimensional (3D) sonography and to evaluate the reproducibility of these measurements.

Methods—Three-dimensional sonographic volumes were acquired transabdominally from an axial view of the head in 361 fetuses cross-sectionally studied at 18 to 32 weeks’ gestation. Offline analysis of the fetal brain midsagittal plane was used to evaluate the length and area of the corpus callosum and corpus callosum–cavum septi pellucidi complex. The agreement between 2-dimensional (2D) and 3D measurements as well as the interobserver variability in 3D measurements were assessed by interclass correlation coefficients (ICCs).

Results—Adequate visualization of the midsagittal plane was obtained in 98.1% of the fetuses. A clear distinction between the corpus callosum and cavum septi pellucidi was obtained in 35.7% of the fetuses, whereas in the remaining cases, the corpus callosum–cavum septi pellucidi complex was visualized as a single echogenic structure. The corpus callosum–cavum septi pellucidi complex length ($r = 0.806; P < .0001$), corpus callosum–cavum septi pellucidi complex area ($r = 0.920; P < .0001$), and corpus callosum area ($r = 0.713; P < .0001$) showed a significant linear growth with gestation. A good agreement was found between measurements from both 2D and 3D sonographic views (corpus callosum length ICC, 0.916) as well as between measurements obtained by different observers (corpus callosum–cavum septi pellucidi complex length ICC, 0.936; corpus callosum–cavum septi pellucidi complex area ICC, 0.931).

Conclusions—Measurements of the corpus callosum and cavum septi pellucidi can be obtained from the midsagittal plane of the fetal brain reconstructed from 3D volumes acquired transabdominally. The constructed nomograms may facilitate the diagnosis of corpus callosum abnormalities.

Key Words—corpus callosum; fetal brain; fetal neurosonography; 3-dimensional sonography

The corpus callosum is the major brain commissure between the cerebral hemispheres, extending anteriorly from the frontal lobe to above the quadrigeminal plates posteriorly. The fetal corpus callosum is considered a sensitive indicator of normal brain development and maturation. Indeed, fetuses with partial or complete agenesis of the corpus callosum, even in the presence of an isolated defect, are at increased risk of abnormal neurodevelopment. Furthermore, differences in the size and shape of the corpus callosum in neonates and adults have been associated with abnormalities in cognitive abilities.
Although prenatal detection of corpus callosum anomalies has been widely reported,7,8 there is a scarcity of information on corpus callosum biometric changes during gestation.9,10 This may be due to difficulties in adequately measuring the corpus callosum because these measurements can be achieved only through a perfectly aligned midsagittal view of the fetal brain, a view that may be difficult to obtain particularly with the transabdominal 2-dimensional (2D) sonographic approach.

Instead, 3-dimensional (3D) sonography, by acquiring a volume of the fetal brain in a transverse section, allows multiplanar navigation and reconstruction of sagittal planes of the fetal head.7,11–14 Several studies have reported how the corpus callosum and cavum septi pellucidi can be easily visualized by using this technique.15–18 However, to the best of our knowledge, no data are available on biometric changes occurring to the corpus callosum and cavum septi pellucidi in utero and on the reproducibility of their measurements obtained from reconstructed planes obtained with 3D sonography.

The aims of this study were to assess the reproducibility and the repeatability of corpus callosum and cavum septi pellucidi measurements obtained with 3D ultrasound and to construct their reference limits for gestation.

Materials and Methods

For this study we considered 388 consecutive pregnancies undergoing routine sonographic examinations at 18 to 32 weeks' gestation. All pregnancies were singleton and accurately dated by first-trimester sonography, and the fetuses were free of structural and chromosomal abnormalities. A further exclusion criterion was the presence of maternal complications (hypertension and diabetes). As in a cross-sectional study, each fetus was considered only once. The study was approved by our Institutional Review Board, and all women gave written informed consent to participate in the study.

Transabdominal 3D volume acquisitions were obtained by a single examiner (G.R.) using a Voluson E8 ultrasonic system (GE Healthcare, Milwaukee, WI) with a 4- to 8-MHz transabdominal probe. A standardized 2D imaging setting was used with harmonics on (low level), compound imaging at 1, speckle reduction at 3, and dynamic contrast at 7. Brain volumes were acquired starting with a transverse view of the fetal head at the level of the transserebellar axial plane by keeping the angle of insonation between the incident ultrasound beam and the cerebral midline at approximately 45° to minimize acoustic shading of the skull base on the brain structures of reconstructed planes. The sweep acquisition angle was set between 45° and 60° according to gestational age to include the entire fetal brain within the volume. Volumes were acquired during fetal rest and maternal apnea in a “maximum” quality mode. An example of an acquisition is shown in Video 1.

In 32 fetuses, a midsagittal view of the fetal head was also obtained by 2D sonography to allow comparisons with measurements obtained from 3D reconstructed planes (Figure 1).

Offline analysis was performed by 4D View version 9.1 software (GE Healthcare, Kretztechnik, Zipf, Austria) with the following technique. The reference point was placed in the middle of the cavum septum pellucidum, and the skull was rotated around the z-axis until the midline of reference image A became horizontal. If necessary, adjustments of plane B around the x-axis were performed to obtain the same axial alignment. In this way, the midsagittal view of the brain was obtained in reference plane C, which was then magnified. Volume contrast imaging with the slice thickness set at 2.5 mm was used to optimize the visualization. Either the corpus callosum and cavum septi pellucidi appeared as a single comma-shaped structure including both elements (the corpus callosum–cavum septi pellucidi complex), or the corpus callosum was visualized as a thin anechoic structure with well-defined echogenic contours overlying the cavum septi pellucidi (Figure 2).

The maximum length of either the corpus callosum or corpus callosum–cavum septi pellucidi complex was obtained in this sagittal view. Moreover, from this view, the area of either the corpus callosum–cavum septi pellucidi complex or, when possible, the isolated corpus callosum was acquired by planimetrering its contours. All measurements were performed by 1 author (M.E.P.), who was unaware of the measurements obtained with 2D sonography. To test interobserver variability in a series of 50 randomly selected volumes, a different author (G.R.) performed the corpus callosum–cavum septi pellucidi complex measurements blinded to the results of the other observer.

Regression analysis was used to determine the significance of the association between the variables measured and gestational age. The best fit to the means of these parameters was assessed using separate linear, quadratic, and cubic regression equations. The construction of normal ranges was done as described by Royston and Wright.19 Briefly, the appropriate regression curve for the relationship between the variables measured and gestational age was calculated. The distribution of the scaled absolute residuals was examined, and the SDs were obtained.
The 5th and 95th percentiles were calculated as mean ± 1.645 SD. To validate the model for each parameter, the values of the volumes were expressed as $z$ scores \([(\text{actual value} - \text{estimated mean for gestational age})/\text{estimated SD for gestational age}])$. The Kolmogorov-Smirnov test was used to confirm the normal distribution of $z$ scores and therefore the goodness of fit of each model.

To assess the agreement between measurements obtained with 2D and 3D sonography, corpus callosum and corpus callosum–cavum septi pellucidi complex lengths were compared using interclass correlation coefficients (ICCs). A proportionate Bland-Altman plot (difference in length between the 2 methods divided by the mean of both measurements expressed as a percentage against the mean length of the 2 methods) was constructed. The proportionate limits of agreement and the underestimations and overestimations of 2D compared with 3D sonography were calculated. Similarly, to evaluate interobserver reliability, the ICCs were assessed, and Bland-Altman plots were constructed. $P < .05$ was considered statistically significant.

Figure 1. Sonograms showing the corpus callosum (CC) and cavum septi pellucidi (CSP) obtained from the same fetus by 2-dimensional sonography (A) and 3-dimensional sonography (B). The rostrum (1), genu (2), body (3), and splenium (4) are indicated.

Figure 2. Three-dimensional sonograms showing a clear distinction between the thin anechoic structure representing the corpus callosum (CC) overlying the cavum septi pellucidi (CSP, A) and a single comma-shaped echogenic structure representing the corpus callosum–cavum septi pellucidi complex (B).
Results

In this study, we used 361 of the 388 pregnancies considered. Ten pregnancies were excluded because of the presence of maternal or fetal complications; 11 were lost to follow-up; and in 6, 3D volumes were not obtained because of an unfavorable fetal position, excessive fetal movements, or maternal obesity. The median gestational age was 24.7 weeks (range, 18.1–31.8 weeks). The median number of fetuses analyzed for each week of gestation was 24 (range, 20–38).

In 62.4% of the volumes analyzed (225 of 361), the corpus callosum–cavum septi pellucidi complex was visualized as a single comma-shaped echogenic structure; in 35.7% (129 of 361), both the corpus callosum and cavum septi pellucidi were visualized; and in the remaining 1.9% (7 of 361), it was impossible to reconstruct a distinct image of the fetal brain midsagittal view.

The corpus callosum–cavum septi pellucidi complex length (constant, 3.113; slope, 1.111; \(r = 0.806; P < .0001\)), corpus callosum–cavum septi pellucidi complex area (constant, –19.416; slope, 1.691; \(r = 0.920; P < .0001\)) and corpus callosum area (constant, –7.241; slope, 0.881; \(r = 0.713; P < .0001\)) increased linearly with gestational age. The scaled absolute residuals for the measurements considered did not change significantly with gestational age; therefore, the 95% CIs were 0.936 (0.890–0.963) for the corpus callosum–cavum septi pellucidi complex length and 0.931 (0.881–0.961) for the corpus callosum–cavum septi pellucidi complex area. In the Bland-Altman plots, the percentage of the mean difference and 95% limits of interobserver agreement were 1.89 (–9.75–13.52) for the corpus callosum–cavum septi pellucidi complex length and 1.95 (–16.79–20.69) for the corpus callosum–cavum septi pellucidi complex area (Figure 5).

Discussion

Our study shows how it is possible starting from the axial view of the fetal head, routinely obtained in screening sonographic examinations, to achieve a median view of the fetal brain that allows easy visualization of the corpus callosum and cavum septi pellucidi, thus confirming previous reports.\(^7,14,16,18\) In this study, we also show how fetal brain volumes may be acquired in most pregnancies and how diagnostic imaging of the corpus callosum and cavum septi pellucidi can be reconstructed in 95% of fetuses at 18 to 32 weeks’ gestation. A clear differentiation between the corpus callosum and cavum septi pellucidi is possible only in approximately one-third of fetuses, whereas in the remaining cases, the corpus callosum–cavum septi pellucidi complex is shown as an echogenic comma-shaped structure because of resolution limitations in 3D reconstructed planes.\(^21\) This echogenic structure is thought to represent the interface between the cingulate gyrus, cingulate sulcus, cerebrospinal fluid, and blood flow in the callosal arteries.\(^22\)

Partial or complete agenesis of the corpus callosum is a relatively frequent fetal brain anomaly and occurs in at least 0.1% of the general population.\(^23\) Its identification is of clinical interest because anomalies of the corpus callosum are frequently associated with other structural malformations and chromosomal or genetic diseases.\(^24\) Moreover, even an isolated corpus callosum anomaly can be associated with an increased risk of abnormal neurodevelopment.\(^5\) Therefore, imaging of the corpus callosum has been suggested as an integral part of fetal central nervous system studies.\(^24\) However, its visualization requires either a transvaginal approach when enabled by the fetal position or a transabdominal approach with a transfrontal view through the metopic suture. With both approaches, the success rate of obtaining a correct midline view is greatly dependent on operator expertise and the fetal position, and the procedure may be time-consuming. As a consequence, corpus callosum visualization has been limited up to now to referral cases in specialized centers where dedicated “neurosonography” is performed.\(^25\)
The advantage of the 3D approach when compared with 2D imaging for visualizing the corpus callosum must be pointed out. Three-dimensional sonography offers the potential of acquiring a volume of the fetal head from the axial view and then, by reconstructing the image using the multiplanar technique, of obtaining the appropriate view of the corpus callosum, greatly reducing the difficulties present with the 2D approach. Therefore, by enabling rapid and easy visualization of the corpus callosum, 3D sonography has been suggested as a potential tool worth including in routine examinations of the corpus callosum. However, before applying 3D sonography to the clinical study of the corpus callosum, it is crucial to construct reference limits for gestation to allow comparison with fetuses considered at risk of corpus callosum abnormalities.

This study shows that growth of the corpus callosum–cavum septi pellucidi complex length is linear between 18 and 32 weeks, and the values obtained correlated well with

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**Figure 3.** Reference limits for gestation (5th, 50th, and 95th percentiles) of corpus callosum (CC) length (A), corpus callosum–cavum septi pellucidi (CSP) complex area (B), and corpus callosum area (C).
previously reported reference limits constructed by using 2D sonography.\textsuperscript{9,10} We also generated reference limits for the corpus callosum area and corpus callosum–cavum septi pellucidi complex area that similarly showed linear growth during the gestational age period considered. Of interest is the agreement found between 2D and 3D measurements, which validates previous experiences\textsuperscript{7,16} and suggests that, although median views obtained by 2D sonography have superior quality, it is also possible to obtain reliable measurements of the corpus callosum with 3D sonography. To the best of our knowledge, the interobserver reproducibility and repeatability of corpus callosum measurements obtained from reconstructed 3D sonographic volumes have not been tested previously. The reliability of measurements taken between the 2 observers was good, as expressed by an ICC of greater than 0.90. This finding provides evidence supporting the hypothesis that corpus callosum and cavum septi pellucidi measurements are reproducible enough and have the potential to be applied in clinical practice.

Finally, caution is necessary in the interpretation of reconstructed 3D images of the corpus callosum because rare conditions such as callosal lipoma may be overlooked due to the similar hyperechogenicity of the corpus callosum in reconstructed 3D planes and lipoma,\textsuperscript{22} and imaging artifacts cannot be excluded.\textsuperscript{26} Therefore, we suggest that at the moment, critical decisions regarding the diagnosis of pathologic corpus callosum and cavum septi pellucidi anomalies should not be made on the basis of only 3D reconstructions. In such conditions, it is recommended that the 2D midsagittal plane be reevaluated, in serial recordings if possible, by an expert in neurosonography, and the diagnosis be complemented with fetal magnetic resonance imaging.

Figure 4. Bland-Altman plot of differences (percent) against the mean for measurement of the corpus callosum–cavum septi pellucidi (CC-CSP) complex length obtained by 2- and 3-dimensional sonography with the mean and 95% limits of agreement indicated.

Figure 5. Bland-Altman plots of the percentages of the mean differences and 95% limits of agreement between paired measurements obtained by 2 different operators of the corpus callosum–cavum septi pellucidi (CC-CSP) complex length (A) and area (B).
In conclusion, our study shows how the corpus callosum and cavum septi pellicudi can be visualized with 3D sonography and how it is possible to obtain accurate measurements and nomograms of these structures at 18 to 32 weeks' gestation. These newly constructed reference limits may facilitate identification of fetuses with suspected corpus callosum anomalies.

References