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Development of the human fetal corpus callosum: a high-resolution, cross-sectional sonographic study

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ABSTRACT

Objective *To establish reference ranges during human pregnancy for normal fetal corpus callosum dimensions.*

Design *In a prospective, cross-sectional study of 258 fetuses between 16 and 37 weeks of gestation, measurements of the length, width, and thickness at the level of the anterior midbody of the corpus callosum were performed, using high-resolution, transvaginal and transabdominal transducers.*

Results *The mean length of the corpus callosum was 27.2 (standard deviation, 1.2; 95% confidence interval, 26.02–28.37) mm. Width and thickness of the corpus callosum were 5.6 (standard deviation, 1.6; 95% confidence interval, 5.41–5.82) mm and 1.9 (standard deviation, 0.7; 95% confidence interval, 1.87–2.06) mm, respectively. The size of the corpus callosum as a function of gestational age was expressed by regression equations: length (mm) = −20.40 + 1.92 × gestational age; width (mm) = −0.052 + 0.225 × gestational age; thickness (mm) = −0.174 + 0.085 × gestational age. The dimension–gestational age correlation coefficients were:* r *= 0.779 for length,* r *= 0.676 for width and* r *= 0.494 for thickness; these were statistically significant (*P *< 0.01). The maximum increase in thickness and width of the corpus callosum occurred between 19 and 21 weeks' gestation, while its length followed a constant growth rate. The normal mean length, width and thickness of the corpus callosum per week, and the 95% confidence limits, were defined.*

Conclusions *The present study offers normative measurements of the fetal corpus callosum and may facilitate a more objective diagnosis of its congenital abnormalities.*

INTRODUCTION

The corpus callosum (CC) is an important brain commissure connecting the cerebral hemispheres and is essential for efficient cognitive function. This structure differentiates as a commissural plate within the lamina terminalis at 39 embryonic days[1]. The plate acts as a passive bed for axonal passage and provides a preformed glial pathway to guide decussating growth cones of commissural axons[2]. In the human embryo, the earliest callosal axons appear at 74 days, the genu and the splenium are recognized at 84 days, and adult morphology is achieved by 115 days[3]. During the 3 months after birth, the size decreases, as a large proportion of the huge population of callosal axons (over 109 billion), is eliminated[4]. This weeding out confines contacts between the hemispheres to certain cortical zones. Differences in the size and form of the CC in adults have been shown to relate to differences in hemispheric representation of cognitive abilities[5].

The fetal CC serves as a sensitive indicator for normal brain development and maturation. A comprehensive evaluation of CC development during normal human fetal gestation is essential to detect and understand the congenital abnormalities within the fetal brain. As the CC is part of the highest order, latest maturing mental network of the brain, its measurements are important to assess normal brain development and to locate structural changes that may disturb cognitive skill development. Although prenatal detection of CC abnormalities has been widely reported[6–9] its normal *in utero* growth and development are scarcely documented[10,11]. Until quite recently, direct *in utero* evaluation of the human fetal CC was not possible[12]. However, with the introduction of advanced, high-resolution ultrasound technology, imaging of the fetal brain from the early stages of gestation became possible[13]. Our aim was to measure prospectively the dimensions of the human fetal CC in apparently normal fetuses in a cross-sectional study. As it is still uncertain at what stage of gestation the fetal brain becomes adversely affected by callosal abnormalities, fetal CC size was measured over a wide range of gestational ages.

MATERIALS AND METHODS

A total of 270 pregnant women were recruited into the study. The inclusion criteria comprised a regular 28-day menstrual cycle, and a known date of the first day of the last menstrual

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period. Women with a history of congenital central nervous system (CNS) abnormalities or any other systemic disease, or those with fetuses suspected of being at risk for any CNS anomaly, were excluded. Similarly, fetuses with an abnormal karyotype or neonates with an abnormal facial appearance at delivery were excluded. All gestational ages, calculated according to the last menstrual day, were in agreement with the expected crown–rump lengths measured sonographically early in pregnancy. All fetuses were appropriate-for-gestational age (> 10th percentile growth curve) according to fetal biometry, and all fetuses had normal anatomical structures, including the CNS. On clinical examination in the nursery, all neonates were normal. The study was cross-sectional, and each patient was evaluated only once. All measurements were made between 16 and 37 weeks' gestation. A 6.5-MHz transvaginal transducer was used for fetuses in vertex presentation, and a 5-MHz transducer was used for those in breech presentation (Synergy, Diasonics, Haifa, Israel).

Freeze-frame ultrasound magnification and electronic on-screen calipers were used for fetal CC measurements. All women gave informed verbal consent for participation in the study. Measurements of CC dimensions included length, thickness and width. The fetal CC could be visualized from the 16th week of gestation as a hypoechoic structure bound by two echogenic lines. On the mid-sagittal plane it was delineated superiorly by the sulcus of the CC and the cingulate gyrus, and inferiorly by the hypoechoic pericallosal cisterns (cavum septi pellucidi and cavum vergae). In this plane the length was

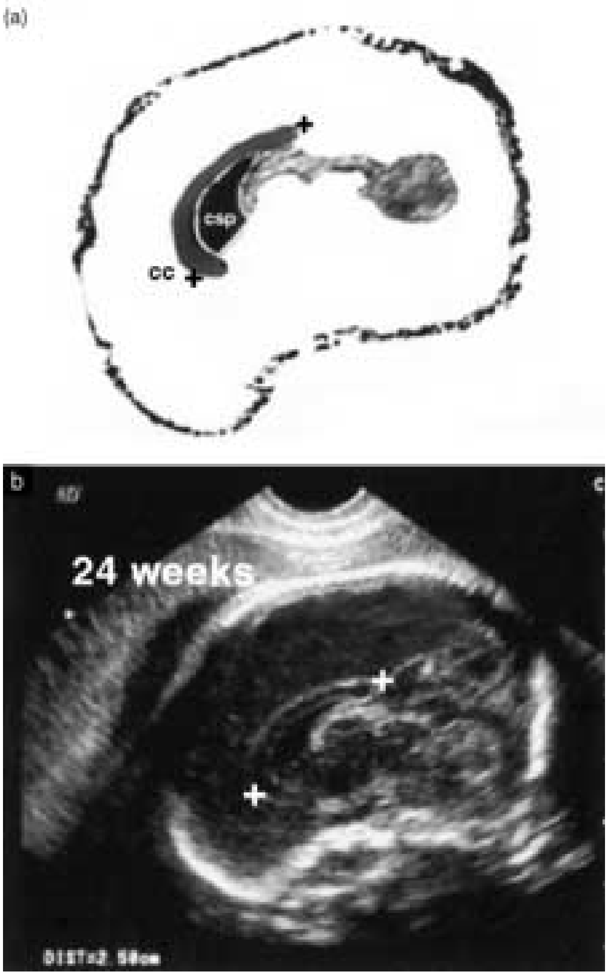

Figure 1 Mid-sagittal view of the development of the human fetal corpus callosum: schematic diagram illustrating the plane in which length of the corpus callosum was measured (a) and ultrasound image of a fetal corpus callosum at 24 weeks' gestation (length 2.58 cm). CC, corpus callosum; csp, cavum septum pellucidum.

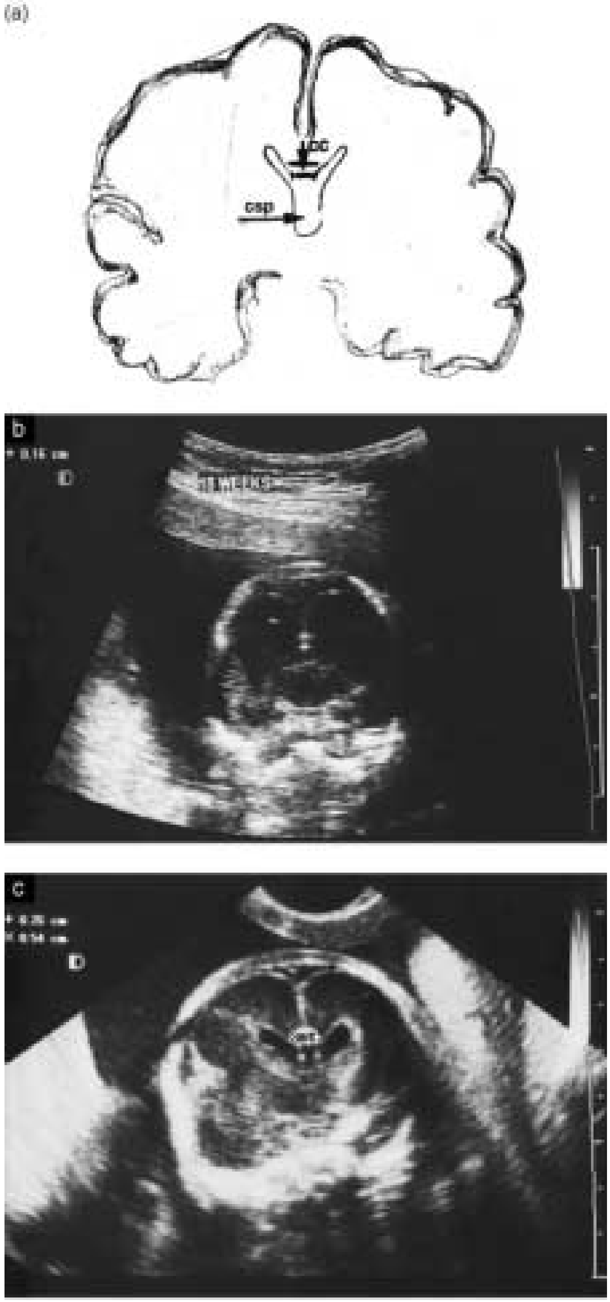

Figure 2 Mid-coronal view of the development of the human fetal corpus callosum: schematic diagram illustrating the plane in which width and thickness of the corpus callosum were measured (a) and the corresponding ultrasound images (b, c). Note the increase of thickness from 0.16 cm at 18 weeks' gestation (b) to 0.26 cm at 23 weeks' gestation (c). CC, corpus callosum; csp, cavum septum pellucidum.

measured from the most anterior aspect of the genu to the most posterior aspect of the splenium by using a straight rostrocaudal length, in a manner similar to that reported by Witelson[5] (Figure 1). The thickness and width of the CC were then measured at the mid-coronal plane. This was obtained by moving the transducer perpendicular to the previous longitudinal axis of the brain. Probe orientation was readjusted during continuous viewing until the anterior mid-body portion of the CC appeared as a hypoechogenic band between two echogenic lines, bordered superiorly by the interhemispheric echogenic midline, laterally by the frontal horns of the lateral ventricles, and inferiorly by the anechoic cavum septum pellucidum (Figure 2). The anterior mid-body portion of the CC was selected for these measurements since it was the most simple, consistent, reproducible and unequivocal measurement that could be obtained[5]. The coefficient of variation was calculated in order to show intraobserver variability. Interobserver variability was not calculated, since only one observer performed the study.

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC, USA). The 95% confidence limit was calculated in order to define the normal range of CC size.

RESULTS

Length, thickness and width measurements of the CC were adequately obtained in 258 of 270 fetuses. We were unable to measure 12 fetuses, eight due to extremely obese women, and four due to unfavorable fetal head position. The intraobserver variation of CC measurements, as determined by the coefficient of variance, was 13% (mean, 3%; standard deviation (SD), 0.39). The mean CC length was 27.2 (SD, 1.2; 95% confidence interval (CI), 26.02–28.37) mm and the mean width and thickness of the CC were 5.6 (SD, 1.6; 95% CI, 5.41–5.82) mm and 1.9 (SD, 0.7; 95% CI, 1.87–2.06) mm, respectively. The earliest stage in pregnancy in which clear unequivocal CC was identified was the 16th week of gestation. Figures 3, 4 and 5 show the apparently linear association between CC length, thickness and width, and gestational age. The regression equations for CC length, width and thickness as a function of gestational age were: length (mm) = –20.40 + 1.92 × gestational age; width (mm) = –0.052 + 0.225 × gestational age; thickness (mm) = –0.174 + 0.085 × gestational age. The statistically significant ($P < 0.01$) dimension–gestational age correlation coefficients were: $r = 0.779$ for length, $r = 0.676$ for width and $r = 0.494$ for thickness. The maximal growth of CC width and thickness was observed between 19 and 21 weeks' gestation, while the growth of its length seemed to be constant (Figure 6). The mean upper and lower limits of the 95% CI for CC length, width and thickness at gestational ages between 16 and 37 weeks' gestation are depicted in Tables 1, 2 and 3.

DISCUSSION

Human brain development is a sequential process that begins early in gestation[14]. Interest in anatomical evaluation of the CC is based upon the expectation that its function is influenced by its structure. The CC, which begins to develop at 12 weeks of gestation, is composed of collections of axons connecting corresponding neocortical areas of the cerebral hemispheres. The rostral part of the CC, the genu, forms first and then grows caudally, forming the body (corpus) and the splenium[15]. Although pathological studies have

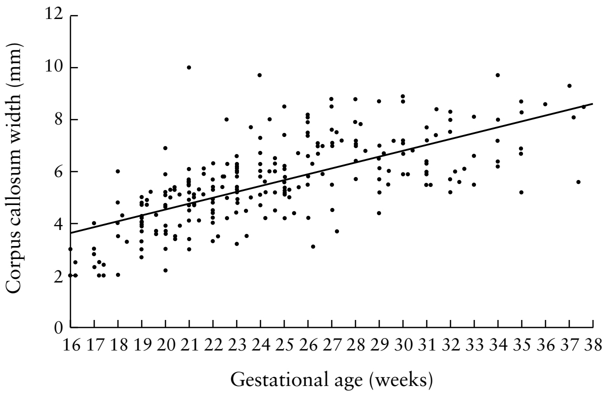

Figure 4 Individual scatter plot of width of the corpus callosum with gestational age of 258 normal fetuses showing a linear regression ($r = 0.676$).

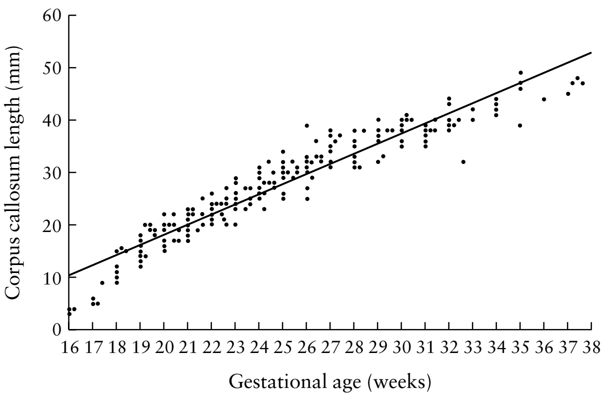

Figure 3 Individual scatter plot of length of the corpus callosum with gestational age of 258 normal fetuses showing a linear regression ($r = 0.779$).

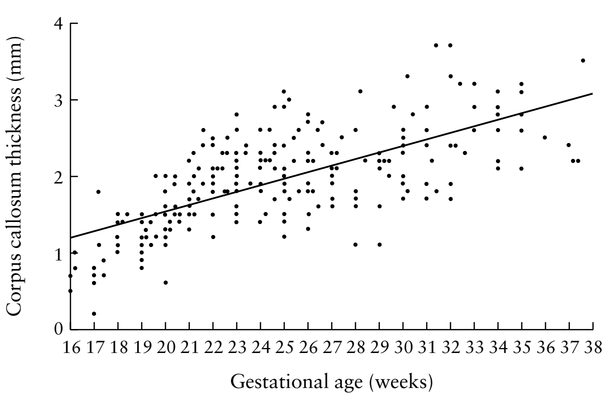

Figure 5 Individual scatter plot of thickness of the corpus callosum with gestational age of 258 normal fetuses showing a linear regression ($r = 0.494$).

established the size of the fetal CC, and neonatal development has also been assessed by magnetic resonance imaging[16], no comprehensive studies have described its normal *in utero* development. Malinger and Zakut[10] demonstrated that using a transvaginal transducer, it is feasible to identify and measure various sections of the fetal CC. However, their data are limited to a small number of fetuses in each gestational week, which cannot provide an accurate reference chart for normal development. Establishing norms for the development of the fetal CC is crucial, since it has been shown that the CC is an important indicator of normal development of the fetal brain[17,18].

In the present study, we have shown for the first time that measurements of the three dimensions of the CC are feasible from 16 weeks of gestation. We found an approximately three-fold increase in the thickness and width of the CC during gestation. In contrast, Malinger and Zakut[10] observed only a two-fold increase in the thickness of the CC. This difference is explained by the fact that their measurements began at 18–19 weeks' gestation, while ours were at 16 weeks. Careful analysis of our data revealed that between 16 and 20 weeks,

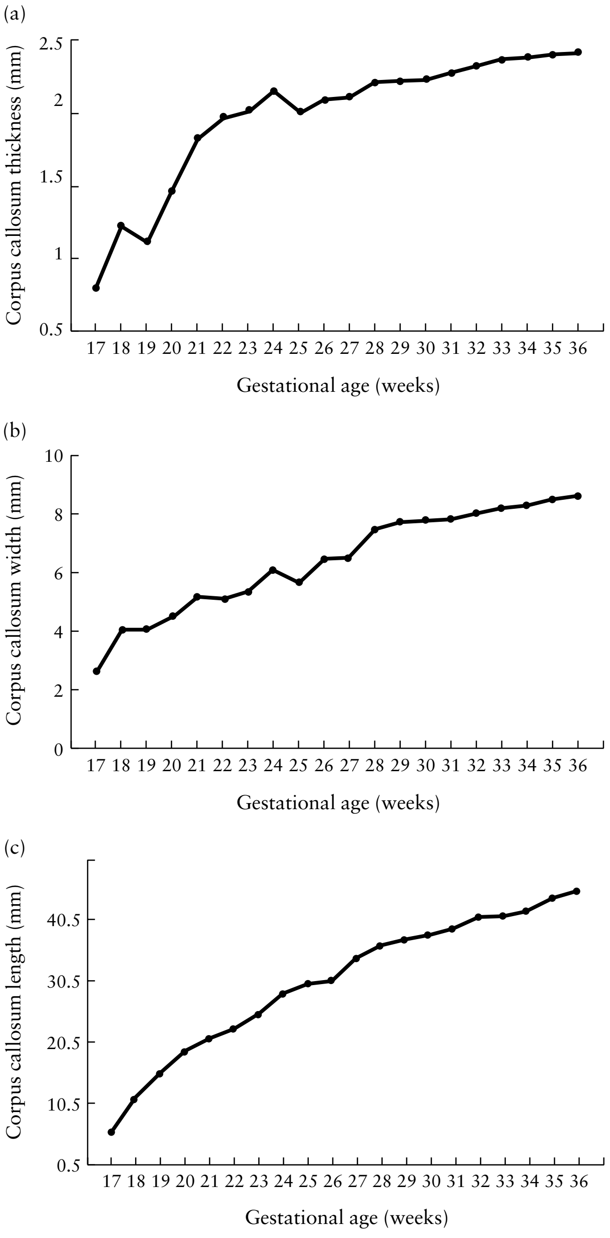

Figure 6 Maximum growth in thickness (a) and width (b) of the corpus callosum occurred between 19 and 21 weeks' gestation, while its length (c) followed a constant growth rate.

Table 1 Length of fetal corpus callosum by gestational age

Gestational age (weeks)	*Observations (n)*	*Lower 95% CI*	*Mean length (mm)*	*Upper 95% CI*
16	4	2.95	3.75	4.55
17	8	4.77	6.24	7.70
18	7	10.04	12.51	14.99
19	18	14.51	15.78	17.05
20	21	18.13	18.95	19.77
21	21	19.54	20.38	21.23
22	18	21.53	22.39	23.24
23	22	23.19	24.45	25.72
24	18	26.32	27.61	28.90
25	23	28.66	29.65	30.64
26	18	29.91	31.44	32.98
27	12	32.75	34.33	35.92
28	9	32.30	34.44	36.59
29	10	34.21	36.40	38.59
30	12	37.14	38.33	39.52
31	10	36.18	37.30	38.42
32	7	38.37	40.43	42.49
33	4	31.44	38.50	45.56
34	6	41.40	42.50	43.60
35	5	40.82	45.60	50.38
36	2	40.00	44.00	45.00
37	3	42.5	44.67	46.84

CI, confidence interval.

Table 2 Width of fetal corpus callosum by gestational age

Gestational age (weeks)	*Observations (n)*	*Lower 95% CI*	*Mean width (mm)*	*Upper 95% CI*
16	4	1.61	2.38	3.14
17	8	2.08	2.63	3.17
18	7	2.82	3.99	5.15
19	18	3.80	4.18	4.55
20	21	3.93	4.43	4.93
21	21	4.40	5.02	5.64
22	18	4.56	4.99	5.43
23	22	4.90	5.39	5.88
24	18	5.49	6.16	6.83
25	23	5.26	5.68	6.11
26	18	5.74	6.40	7.06
27	12	5.72	6.69	7.66
28	9	6.50	7.19	7.88
29	10	5.35	6.18	7.01
30	12	6.45	7.16	7.87
31	10	5.92	6.63	7.34
32	7	5.43	6.61	7.80
33	4	4.81	6.58	8.34
34	6	5.90	7.32	8.73
35	5	5.43	7.16	8.89
36	2	5.60	8.60	8.80
37	3	2.98	7.67	12.36

CI, confidence interval.

Table 3 Thickness of fetal corpus callosum by gestational age

Gestational age (weeks)	*Observations (n)*	*Lower 95% CI*	*Mean thickness (mm)*	*Upper 95% CI*
16	4	0.42	0.75	1.08
17	8	0.58	1.12	1.32
18	7	1.12	1.30	1.48
19	18	1.03	1.13	1.24
20	21	1.31	1.47	1.63
21	21	1.60	1.73	1.86
22	18	1.82	2.00	2.18
23	22	1.87	2.04	2.20
24	18	1.90	2.07	2.24
25	23	1.89	2.11	2.34
26	18	1.87	2.09	2.31
27	12	1.94	2.14	2.35
28	9	1.66	2.14	2.63
29	10	1.73	1.99	2.25
30	12	2.04	2.35	2.66
31	10	1.93	2.37	2.81
32	7	1.96	2.66	3.36
33	4	2.13	2.75	3.37
34	6	2.20	2.62	3.03
35	5	2.21	2.76	3.31
36	2	2.20	2.50	3.00
37	3	1.98	2.27	2.55

CI, confidence interval.

approximately 50% of the total thickness and width of the CC have been achieved. Further growth is accelerated until 21–22 weeks (Figure 6) and then remains stable throughout the rest of gestation. These findings correspond well with the classic pathological observations of Rakic and Yakovlev[15] that the CC completes its structural formation around the 21st week of gestation. Our data also showed a 10-fold increase in the length of the CC during gestation. Rapid growth of thickness was recorded during the period between 16 and 20 weeks' gestation. This pattern of growth of the CC was previously observed by Chasen *et al.*[11] and Birnholz[18]. These authors found that the length of the CC had a similar growth-spurt pattern around the 20th week of gestation. This rapid development of the fetal CC, not surprisingly, corresponds to the first phase of neuronal migration. These combined findings clearly support the assumption that cortical development and myelination have a rapid growth spurt around mid-gestation, over the period during which the CC develops gradually, mainly along its longitudinal axis. Accordingly, a recent study has shown that between 15 and 22 weeks' gestation, mRNA and protein expression of myelin genes are increased by more than 80-fold[19].

In summary, the present study elucidates the development of the CC during fetal life. Furthermore, our normative data establish reference ranges of fetal CC dimensions for gestational age. These data can be used for the assessment of normal brain development, as well as that for fetuses suspected of having congenital malformations of the brain and for patients at risk for CC anomalies.

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