Identification of the Fetal Hippocampus and Fornix and Role of 3-Dimensional Sonography

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Objectives—The purposes of this study were to identify the fetal hippocampus and fornix using 3-dimensional sonography, to measure their curved length during pregnancy, and to describe a systematic method for volume data set analysis of the fetal hippocampus and fornix.

Methods—Three-dimensional volumes of the fetal brain were acquired prospectively in 34 patients between 14 and 37 weeks’ gestation. Volumes were acquired with transabdominal and transvaginal transducers. All volumes were analyzed offline by 2 examiners separately. The feasibility of identifying the fetal hippocampus and fornix was analyzed. The curved length of the hippocampus-fornix structure was measured on the right and left hemispheres.

Results—The fetal hippocampus and fornix were identified bilaterally in 32 of 34 fetuses (94%) at gestational ages of 14 weeks 5 days to 37 weeks 1 day (mean, 23 weeks 3 days). In 1 fetus (3%), only one side was shown, and in another fetus (3%), both sides were obscured by acoustic shadows. A systematic approach for identification of the fetal hippocampus is described. Linear growth of the fetal hippocampus and fornix was shown during pregnancy and was correlated with both the gestational week and the head circumference ($R = 0.71$ and $0.74$, respectively; $P = .01$). The length of the hippocampus and fornix did not differ between the left and the right hemispheres ($P = .598$).

Conclusions—The fetal hippocampus and fornix can be identified by a systematic analysis of 3-dimensional data set volumes. The normal hippocampus and fornix show linear growth throughout pregnancy.

Key Words—fetal brain; fetus; fornix; hippocampus; neurosonography; 3-dimensional sonography

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Abbreviations
MRI, magnetic resonance imaging; 3D, 3-dimensional

The hippocampus is a sea horse–shaped structure situated in the medial portion of the anterior temporal lobe. It bulges laterally into the temporal horn of the lateral ventricle. The hippocampus plays a major role in memory processing (dorsal hippocampus) and in biological responses to stress (ventral hippocampus). The fornix is a C-shaped structure emerging from the hippocampal structure that contains axons connecting the hippocampus to the mammillary bodies and septal nuclei. The spatial appearance of the hippocampus and fornix is a C-shaped structure. Because sonographic dissection of the hippocampus from the fornix is unachievable, and their function is in contiguity, we chose to try to show the entire C-shaped structure of the hippocampus and fornix.
Abnormal hippocampus-fornix formation is associated with congenital brain anomalies such as agenesis of the corpus callosum, lissencephaly, and holoprosencephaly. In addition, in fetal alcohol syndrome, the development of both the dentate gyrus and the hippocampus is affected, resulting in brain damage manifested as cognitive, learning, and behavioral deficits. In these cases, postnatal magnetic resonance imaging (MRI) shows a small, unfolded, and vertically oriented hippocampus. Hypotrophy of the hippocampus has been found in both adults and fetuses with Down syndrome.

Abnormal hippocampus-fornix function can be shown in both children and adults with schizophrenia (≈4% volume reduction), temporal lobe epilepsy, bipolar disorder, and Alzheimer disease. Several studies described an association between obstetric complications such as maternal toxemia and prematurity and smaller volumes of the hippocampus among patients with schizophrenia and their biological relatives in comparison with healthy control patients.

Examination of the fetal hippocampus and fornix is not part of the fetal brain scan. Moreover, the 2-dimensional sonographic depiction of the fetal hippocampus and fornix is very difficult because of their curved oblique C-shape structure, with the upper part being medial and the lower part lateral. Therefore, to our knowledge, there are no data regarding the prenatal sonographic appearance of the live fetal hippocampus and fornix. Knowledge of the normal hippocampus-fornix formation may play a role in the understanding and classification of hippocampus-fornix abnormalities.

With the development of new sonographic technologies, improved learning about the fetal brain is feasible. Our goals were to identify the normal fetal hippocampus and fornix using 3-dimensional (3D) sonography, to describe a systematic method for analysis of volume data sets, and to measure their normal length during pregnancy.

Materials and Methods

A prospective study of uncomplicated pregnancies was performed. The following inclusion criteria were used: singleton pregnancies, adequate-for-gestational-age fetuses, and normal anatomic scans. Patients with maternal illness or complications of pregnancy (ie, preeclampsia and diabetes) were excluded from the study. The gestational age was determined by the last menstrual period and confirmed by a first-trimester sonographic examination. The study was approved by the Institutional Review Board of the Chaim Sheba Medical center. All women signed informed consent before performance of sonography.

Three-dimensional volumes of the fetal brain were acquired at the time of routine sonographic examinations. Verification of the gestational age and a complete anatomic scan were performed before volume acquisition.

Technique

Volume acquisition of the fetal head was taken in the median (midsagittal) plane, in which the corpus callosum and vermis were both visualized. Examinations were done with Voluson E8, 730 Expert, and Pro ultrasound machines (GE Healthcare, Kretz Ultrasound, Zipf, Austria) using volumetric abdominal RAB 4-8 and volumetric transvaginal RIC 5-9 transducers. The volumes were taken during conventional scanning while examining the fetal head.

In this study, acquisitions were performed during fetal rest and absence of fetal movement. The standard volume sweep angle was 55°, but it was manipulated to include the whole fetal brain, according to the gestational age and the distance of the fetal head from the transducer. Offline analysis and postprocessing were performed with 4D View software (GE Healthcare, Kretz Ultrasound).

All volumes were analyzed offline by 2 experienced examiners separately (L.G. and A.W.-B.). The feasibility of identifying the fetal hippocampus and fornix was analyzed. Interobserver and intraobserver variability rates were calculated. Measurements were calculated on sectional planes, but for clearer images, static volume contrast imaging may be used.

Statistical Analysis

Data were analyzed with SPSS version 11.5 software (SPSS Inc, Chicago, IL). Comparison of means was done by an independent t test. P < .05 was considered significant. Correlations were analyzed by 2-tailed Pearson correlation and presented as linear regression with a 95% prediction interval.

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Results

Thirty-four patients constituted the study population. Gestational ages ranged between 14 weeks 5 days to 37 weeks 1 day (mean, 23 weeks 3 days; median, 23 weeks 0 days).

Volumes were taken in the median plane showing both the corpus callosum and the vermis. The volume was acquired with the vertex or face up, according to the fetal position. Transvaginal examinations were done for early anatomic scans between 14 and 16 weeks and for later scans if the fetus was in a vertex position and the median plane was not obtained transabdominally.
The step-by-step method for obtaining optimal visualization of the fetal hippocampus and fornix is described in Table 1 and Video 1. The volumes were rotated into an anatomic orientation in the multiplanar mode: the coronal view in plane A, the median view in plane B, and the axial view with the back down in plane C. With this method, the left organs are on the left side of the screen, as if looking at the fetus from the posterior aspect of the body. The best angle of acquisition was median, and there was no difference in whether the vertex, brow, or face was toward the transducer.

In the coronal plane, the region of interest cursor was moved to the parasagittal area to get the hippocampus-fornix structure in plane B. Next, by looking at plane B, the dot of interest was moved to the hippocampus-fornix area, and the volume was rotated using the x-, y-, and z-axes to get the full hippocampus-fornix structure, which was positioned obliquely, with the cephalic part more medial than the caudal part (Figure 1).

The hippocampus-fornix structure is a curved echogenic line (like the letter C), more curved than the corpus callosum. The hippocampus and fornix are lateral to the corpus callosum, with the upper part being more medial and the lower part more lateral (an oblique plane; Figure 2 and Video 2). To get the full hippocampus-fornix structure, the plane should be sagittal with a small tilt laterally toward the axial position.

We measured the length of the hippocampus-fornix structure on both the right and left hemispheres (Figure 3) and compared it with the gestational age (Figure 4) and the head circumference (Figure 5). In 32 patients (94%), both the right and left hippocampus and fornix were meas-

**Table 1. Step-by-Step Instructions for Showing the Fetal Hippocampus and Fornix With 3-Dimensional Sectional Planes**

<table>
<thead>
<tr>
<th>Step</th>
<th>Instructions</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Manipulate the image setting to get a better image. Obtain the image at the median view, showing both the corpus callosum and vermis.</td>
</tr>
<tr>
<td>2</td>
<td>Rotate the volume in a way that plane A will be the coronal plane, plane B will be the sagittal plane, and plane C will be the axial plane.</td>
</tr>
<tr>
<td>3</td>
<td>Put the fetal back down on image C; image A is the coronal view, image B is the sagittal view with the face to the right; the left side of the fetus will be on the left.</td>
</tr>
<tr>
<td>4</td>
<td>Put the cursor dot on the corpus callosum. On image A, both lateral ventricles can be seen with the coronal view of the corpus callosum and the cavum septum pellucidum. Straighten the image according to the falx cerebri. On image B, the corpus callosum, cavum septum pellucidum, and vermis are clearly shown.</td>
</tr>
<tr>
<td>5</td>
<td>Magnify the image.</td>
</tr>
<tr>
<td>6</td>
<td>Put the cursor dot on image A lateral to the left ventricle, and look for the hippocampus and fornix on image B.</td>
</tr>
<tr>
<td>7</td>
<td>Fine tune the y-axis on image B to get the whole length of the hippocampus and fornix (or z-axis on image A). Remember that the upper ends of the hippocampus and fornix are more medial than the lower ends that are lateral.</td>
</tr>
<tr>
<td>8</td>
<td>For measurement, use image B only. A curved line should be placed in the middle of the echogenic area of the hippocampus and fornix.</td>
</tr>
<tr>
<td>9</td>
<td>Repeat steps 6–8 on the right side for the right hippocampus and fornix.</td>
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</table>

**Figure 1.** Hippocampus and fornix of a healthy fetus at 23 gestational weeks. A lateral sagittal plane is shown, with minor rotation to optimize the whole length of the hippocampus-fornix structure. The hippocampus and fornix are encircled with a white line, forming a C shape. Ant indicates anterior; CP, choroid plexus; LV, lateral ventricle; and Post, posterior.
ured. Only 1 side was shown in 1 patient (3%). In another patient (3%), we were not able to show both the hippocampus and fornix at a gestational age of 32 weeks 1 day because of acoustic shadows. We found linear growth of the fetal hippocampus and fornix throughout pregnancy according to the gestational week and head circumference \((R = 0.71\) and \(0.74,\) respectively; \(P = .01)\). There was no significant difference between the right and left hippocampus and fornix \((P = .598)\). The interobserver variability was 7.1% for the left hippocampus and fornix and 7.5% for the right hippocampus and fornix. Follow-up revealed that all fetuses had no abnormalities at birth.

Discussion

Our study shows that the fetal hippocampus and fornix can be visualized when a systematic analysis is performed using 3D data set volumes. Three-dimensional imaging is needed because the spatial hippocampus-fornix structure is oblique and has a C shape, with the upper part being medial and the lower part lateral. Two-dimensional sonography cannot show this complex shape in a single sagittal oblique image. The structure of the hippocampus and fornix is located inside the medial temporal lobe (Figure 2), extends to the floor of the inferior horn of the lateral ventricle, and becomes contiguous with the fornix below the splenium of the corpus callosum.

Evaluation of the fetal hippocampus and fornix was described on postmortem MRI at 13 to 24 weeks’ gestation\(^5\) using coronal sections and looking at the hippocampus-fornix shape at the level of the red nucleus. To our knowledge, no in vivo MRI or sonographic studies to date examined the fetal hippocampus and fornix. From 13 to 14 weeks’ gestation, the hippocampus is unfolded. The folding process begins at 15 to 16 weeks, but the cornu ammonis are arranged linearly. By 18 to 20 weeks, the hippocampus and fornix begin to resemble the adult structures. Hippocampus-fornix development includes progressive infolding of the dentate gyrus, cornu ammonis, and parahippocampal gyrus around the smaller hippocampal sulcus (hippocampal fissure) between 10 and 18 weeks’ gestation.\(^5,23,24\) The final hippocampal structure resembles a sea horse. The fornix is a bundle of axons continuing this structure to form a C-shaped structure. To our knowledge, a description of a live sagittal view of the fetal hippocampus and fornix has not been reported previously. Using 3D sonog-
raphy, we also looked at the axial plane and moved the dot of interest to the point described by the coronal plane in examination of postmortem fetal brains. On sonography, the coronal plane supplies very little information because of insufficient resolution, but navigation of the volume allows localization in 3 planes at the same time. We obtained the same image obtained in the postmortem examinations, supporting the anatomic position and shape that are unique to the hippocampus and fornix.

We have shown that the length of the hippocampus and fornix increases linearly during pregnancy, as can be expected from our knowledge of other fetal organs. To our knowledge, measurements of the fetal hippocampus and fornix have not been reported previously. We found that the right and left hippocampus and fornix are symmetric in their length and spatial arrangement. In a minority of cases, acoustic shadows prevented measurement of both sides, but with attention during volume acquisition, this limitation can be overcome. In such cases, the volume acquisition may be repeated from another direction. In a study on MRI measurements of the hippocampus performed in children aged 4 to 18 years, asymmetry was shown between the right and left hippocampus. We found no such differences, probably because of the small size of the organ in the fetus. Another reason may be that asymmetry may develop later in life.

The limitations of this study were the small sample size and the absence of knowledge of what an abnormal fetal hippocampus and fornix look like on sonography. We could not compare our results with the literature because MRI measurements of the hippocampus and fornix in children use the coronal view, which does not show the whole hippocampus-fornix structure. We found a better sonographic depiction of the hippocampus and fornix when the volume acquisition was taken in the sagittal plane; therefore, no comparison with coronal planes could be performed. Because the hippocampus and fornix are shown earlier than the corpus callosum, their depiction might assist in the early detection of brain abnormalities.

In conclusion, our study shows the feasibility of sonographically identifying the fetal hippocampus-fornix structure from 14 to 37 weeks’ gestation using 3D sonography, depicting curvilinear growth of the fetal hippocampus and fornix throughout pregnancy. To our knowledge, these findings have not been reported previously.

References