Correlations of atrial diameter and frontooccipital horn ratio with ventricle size in fetal ventriculomegaly

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OBJECTIVE Fetal ventriculomegaly (FV), or enlarged cerebral ventricles in utero, is defined in fetal studies as an atrial diameter (AD) greater than 10 mm. In postnatal studies, the frontooccipital horn ratio (FOHR) is commonly used as a proxy for ventricle size (VS); however, its role in FV has not been assessed. Using image analysis techniques to quantify VS on fetal MR images, authors of the present study examined correlations between linear measures (AD and FOHR) and VS in patients with FV.

METHODS The authors performed a cross-sectional study using fetal MR images to measure AD in the axial plane at the level of the atria of the lateral ventricles and to calculate FOHR as the average of the frontal and occipital horn diameters divided by the biparietal distance. Computer software was used to separately segment and measure the area of the ventricle and the ventricle plus the subarachnoid space in 2 dimensions. Segmentation was performed on axial slices 3 above and 3 below the slice used to measure AD, and measurements for each slice were combined to yield a volume, or 3D VS. The VS was expressed as the absolute number of voxels (non-normalized) and as the number of voxels divided by intracranial size (normalized). A Pearson correlation coefficient was used to measure the strength of the relationships between the linear measures and the size of segmented regions in 2 and 3 dimensions and over various gestational ages (GAs). Differences between correlations were compared using Steiger’s z-test.

RESULTS Fifty FV patients who had undergone fetal MRI between 2008 and 2014 were included in the study. The mean GA was 26.3 ± 5.4 weeks. The mean AD was 18.1 ± 8.3 mm, and the mean FOHR was 0.49 ± 0.11. When using absolute VS, the correlation between AD and 3D VS (r = 0.844, p < 0.0001) was significantly higher than that between FOHR and 3D VS (r = 0.668, p < 0.0001; p = 0.0004, Steiger’s z-test). However, when VS was normalized, correlations were not significantly different between AD and 3D VS (r = 0.830, p < 0.0001) or FOHR and 3D VS (r = 0.842, p < 0.0001; p = 0.8, Steiger’s z-test). For GAs of 24 weeks or earlier, AD correlated more strongly with normalized 3D VS (r = 0.902, p < 0.0001) than with FOHR (r = 0.674, p < 0.0001; p < 0.0001, Steiger’s z-test). After 24 weeks, there was no difference in correlations between linear measures (AD or FOHR) and 3D VS (r > 0.9). Correlations of linear measures with VS in 2 and 3 dimensions were similar, and inclusion of the subarachnoid space did not significantly alter results.

CONCLUSIONS Findings in the study support the use of AD as a measure of VS in fetal studies as it correlates highly with both absolute and relative VS, especially at early GAs, and captures the preferential dilation of the occipital horns in patients with FV. Compared with AD, FOHR similarly correlates with normalized VS and, after a GA of 24 weeks, can be reported in fetal studies to provide continuity with postnatal monitoring.

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KEY WORDS fetal ventriculomegaly; atrial diameter; frontooccipital horn ratio; fetal magnetic resonance imaging; correlation; hydrocephalus
Fetal ventriculomegaly (FV) refers to the presence of enlarged cerebral ventricles in utero and occurs in up to 2 cases per 1000 births. Following identification of ventriculomegaly on surveillance ultrasonography, the condition's extent and etiology can be further assessed using fetal MRI. The disorder is defined based on ventricular measurements performed at the level of the ventricular atrium. Whereas normal values of the average atrial diameter (AD) range from 6.2 ± 1.2 to 7.6 ± 0.6 mm, FV is defined as greater than 3–4 SDs above the mean, with a minimum cutoff of 10 mm. Accurate measurement of ventricle size (VS) is relevant not just for inclusion or exclusion of the diagnosis of FV, but such measurements inform prognosis, prompt investigation for associated fetal anomalies, and define subgroups in clinical research studies.

Besides AD, several linear or 2D measurements exist to estimate ventricular volume based on a single axial slice obtained using various imaging modalities. Several measures, such as Evans’ index, frontal horn index, and bicaudate index, derive from the pre-CT era and focus on the size of the frontal horns. To account for overall ventricular configuration, the frontooccipital horn ratio (FOHR) was developed, representing the average of the frontal and occipital horn diameters normalized to the biparietal diameter. The FOHR is associated with excellent interobserver reliability and is more strongly correlated with ventricular volume than other linear indices. However, studies supporting its clinical use were all performed in postnatal patients with hydrocephalus, and none involved a direct comparison with AD, a measure traditionally reported for fetal studies. Furthermore, FV is characterized by preferential dilation of the occipital horns, whereas postnatal hydrocephalus commonly involves dilation of both frontal and occipital horns. Thus, we hypothesized that AD, a measure solely of the occipital horns, would be more accurate than FOHR as a proxy for VS in fetal studies. Therefore, in this study, we used advanced image analysis techniques to quantify ventricle area and volume on fetal MR images and assessed correlations between 2 linear measures (AD and FOHR) and VS in patients with FV.

Methods

Study Design and Patient Population

We performed a cross-sectional study of FV patients drawn from a prospectively collected institutional fetal database. The study was approved by the institutional review board of the Children’s Hospital of Philadelphia (CHOP). All patients had been referred for surveillance fetal ultrasonography and occurred in up to 2 cases per 1000 births. The data set was originally created for another study in patients with hydrocephalus and none involved a direct comparison with AD, a measure traditionally reported for fetal studies. Furthermore, FV is characterized by preferential dilation of the occipital horns, whereas postnatal hydrocephalus commonly involves dilation of both frontal and occipital horns. Thus, we hypothesized that AD, a measure solely of the occipital horns, would be more accurate than FOHR as a proxy for VS in fetal studies. Therefore, in this study, we used advanced image analysis techniques to quantify ventricle area and volume on fetal MR images and assessed correlations between 2 linear measures (AD and FOHR) and VS in patients with FV.

Image Acquisition and Linear Measurements

Half-Fourier acquisition single-shot turbo spin echo (HASTE) MRI was performed in multiple planes in all patients. The majority of studies were performed on a 1.5-T Siemens Avanto MRI scanner with 3-mm slice thicknesses (TR 1400 msec, TE 64 and 78 msec). Axial T2 slices were selected for analysis. Atrial diameter was measured on fetal MR images in the axial plane, as is convention at CHOP, at the level of the atria of the lateral ventricles and the glomus of the choroid plexus. Atria were measured from the inner margin of the medial ventricular wall to the inner margin of the lateral ventricular wall. The ADs for the right and left ventricles were obtained and a mean was calculated. The FOHR, determined using the same axial slice used to measure AD, was calculated as the average of the maximal frontal and occipital horn diameters divided by the biparietal diameter. Figure 1 demonstrates the method used for obtaining linear measurements. The AD was obtained by a neuroradiologist and was independently measured again by a senior neurosurgery resident blinded to the prior measurement and additional clinical data. The axial slice level at which AD was measured was also selected independently. The FOHR was measured separately by 2 senior neurosurgery residents. Linear measurements were manually performed using EasyViz (Karos Health, Medical Insight).

Image Analysis

To isolate the brain from extracranial maternal tissues and to highlight the intracranial contents, all raw fetal MR images (Fig. 2A) were skull stripped by applying a
and bias correction. 16

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manually generated mask to each image (Fig. 2B). All images were then preprocessed, which included smoothing4 and bias correction.16 Automatic segmentation of the CSF spaces (Fig. 2C) was performed in Matlab (MathWorks) using the Otsu method of thresholding.17 In a grayscale image, a histogram of intensities was created, and a threshold value was selected such that the variance on each side of the chosen threshold was minimized. In other words, the method was used to separate the lower-density CSF spaces from the higher-density brain compartment. Segmentation of CSF was initially performed on the axial slice used to measure AD. The total number of voxels within the segmented CSF space, referred to as the “2D CSF area,” was computed using Matlab. The “CSF space” refers to the voxels representing CSF within the ventricle and subarachnoid space. In a separate analysis, the ventricle and subarachnoid spaces were segmented separately. Because of the poor image quality of the most cranial and most caudal axial slices encountered in fetal MRI, a 3D or volumetric approximation was obtained by also segmenting the CSF spaces on slices 3 above and 3 below the axial slice used to measure AD. Image quality was poor in selected cases primarily because of fetal movement, despite multiple imaging attempts. The 2D CSF area of each of the maximum of 7 total segmented axial slices per patient was automatically computed and summed to yield a 3D CSF volume. Brain parenchyma volume was calculated by subtracting the known total CSF volume from the known total intracranial volume. All segmentations were manually confirmed and corrected as needed by using the image analysis software ITK-SNAP 3.4.0.18 Although infrequent, up to 3 of the 7 axial slices per patient were excluded from analysis because of poor image quality. Measurements of the 2D area and the 3D volume were obtained as the absolute number of voxels (non-normalized), as well as the number of voxels divided by the intracranial area for each slice (normalized). The presence of pathological entities on imaging, such as germinal matrix hemorrhage, posterior fossa abnormality, or cyst, was noted. In addition, the presence of lateral ventricle asymmetry was recorded. The standard deviation of the differences between right and left ventricle AD for each patient was calculated, and asymmetry was defined as a difference of more than 1 SD between right and left AD measurements in a single patient.

Correlations and Statistical Analysis

The Pearson correlation coefficient was used to measure the strength of the relationship between linear measurements (AD and FOHR) and the CSF area or volume. Correlations with AD and with FOHR were also evaluated specifically for VS, in which the subarachnoid compartment was excluded. To investigate the relationship between GA and the correlation between linear measures and 3D ventricle volume, correlation coefficients were compared between younger and older patients using various GA thresholds to stratify subjects. We determined the GA beyond which the correlations between 1) AD and VS and 2) FOHR and VS were no longer significantly different. Correlations between linear measures (AD and FOHR) and brain area and volume were also assessed. Because FOHR incorporates both right and left atria, the mean AD, or the average of the right and left AD measurements, rather than the maximum AD, was used for assessing correlations. The threshold for statistical significance was set as p = 0.05. Lin’s concordance correlation coefficient was used to evaluate the interrater reliability among linear measurements. Steiger’s z-test was used to test for significant differences between the correlation coefficients for comparisons of AD and FOHR with CSF and ventricle volume (http://quantpsy.org/corrtest/corrtest2.htm). The statistical test has been used previously to assess for significant differences among correlations between linear and ventricular volume measures in postnatal hydrocephalus.14 A power analysis for the study of correlations was performed to determine the adequacy of the sample size using the following parameters: alpha (2-tailed) = 0.05, beta = 0.2, and r = 0.4.8 As our study is the first to assess the correlations of linear measures in the fetal population, our expected correlation coefficient was obtained using the minimum correlation coefficients reported in a recent study of correlations between linear measures and VS in postnatal hydrocephalus.14 All other calculations were performed in Matlab.

Results

Patient and Imaging Characteristics

From a fetal database of 289 patients, we used a previously selected data set that consisted of 50 FV patients, half of whom had undergone postnatal CSF diversion. All patients underwent fetal MRI between 2008 and 2014. The mean GA was 26.3 ± 5.4 weeks (range 20–37 weeks). Additional pathology noted on imaging included germinal matrix hemorrhage (16 patients [32%]), posterior fossa

FIG. 2. Image analysis and segmentation. Using raw fetal MR images (A), a mask was applied to highlight the intracranial contents (B). After images were preprocessed, automated segmentation was performed to highlight the CSF spaces based on differences in intensity between brain tissue and CSF (C). Figure is available in color online only.
abnormality (7 patients [14%]), and posterior fossa cyst (4 patients [8%]). The mean AD was 18.1 ± 8.3 mm and the maximum value was 42.0 mm. Taking the maximum AD for each patient, we calculated the average of these measurements at 19.9 ± 8.9 mm with a maximum of 42.5 mm. The SD of the differences between right and left AD measurements was 4 mm. Ventricle asymmetry was present in 14 patients (28%). The mean FOHR was 0.49 ± 0.11 and ranged from 0.29 to 0.76. Imaging data from each of the 50 patients were included in the study; however, because of poor image quality, 1–2 of 7 axial slices were excluded in each of 11 patients, and 3 of 7 slices were excluded in each of 2 patients. Lin’s concordance correlation coefficient was 0.98 (confidence limit 0.98–0.99) for AD and 0.92 (confidence limit 0.87–0.95) for FOHR. A power analysis yielded 47 patients.

Correlations
The Pearson correlation coefficient between linear measurements (AD and FOHR) and segmented regions (2D areas and 3D volumes for CSF, ventricle, and brain) are shown in Table 1. The use of 2D area versus 3D volume measurements did not result in significant differences in correlations between linear measures (AD or FOHR) and CSF, ventricle, or brain sizes. Correlations between linear measures (AD or FOHR) and VS were no different from those between linear measures and CSF size (which included the subarachnoid space). Negative correlations were noted between linear measures and normalized 2D area and 3D volume for brain. Both AD and FOHR were weakly correlated with non-normalized measures of brain parenchyma size. In Table 1, all correlations reached statistical significance, except the correlations between AD and 2D brain (p = 0.36) and AD and 3D brain (p = 0.32). With voxel counts, or non-normalized measures (Fig. 3A and B), the correlation between AD and 3D VS (r = 0.844, p < 0.0001) was significantly higher than that between FOHR and 3D VS (r = 0.668, p < 0.0001; p = 0.0004, Steiger’s z-test). However, when using normalized data in which voxel counts were divided by intracranial size (Fig. 3C and D), correlations were similar between AD and 3D VS (r = 0.830, p < 0.0001) and between FOHR and 3D VS (r = 0.842, p < 0.0001; p = 0.8, Steiger’s z-test). In other words, each linear measure correlated strongly with ventricle volume as a proportion of intracranial volume. For a GA ≤ 24 weeks, AD correlated more strongly with normalized 3D VS (r = 0.902, p < 0.0001) than with FOHR (r = 0.674, p < 0.0001; p = 0.0001, Steiger’s z-test; Fig. 4A and B). At GA > 24 weeks, correlations between linear measures and 3D VS were both > 0.9 (Fig. 4C and D).

Discussion
Although linear indices as a proxy for ventricular volume have been well studied in the postnatal population, our study is the first to assess correlations between AD or FOHR and VS in the prenatal period among patients with FV. Whereas other groups have studied postnatal MRI and ultrasonography, our study involved prenatal or fetal MRI. Quantitative image analysis techniques were applied to fetal MR images to obtain the absolute and relative VS as 2D and 3D measures. Compared with FOHR, mean AD was more strongly correlated with absolute VS, although this difference was not observed when ventricle measurements were normalized to intracranial size. Mean AD was more strongly correlated with normalized VS up to 24 weeks’ gestation, after which time AD and FOHR showed similarly strong correlations with ventricle volume. Thus, although FOHR is increasingly used in postnatal studies, our findings have clinical implications in that they support a continued role for AD in the study of fetal patients. Furthermore, applying the most accurate proxy of VS is clinically relevant when such data are used as a component in determining postnatal prognosis or as a basis for decisions related to continuation of the pregnancy, especially early in gestation, and our findings support the use of AD over FOHR before 24 weeks’ gestation.

The strength of the correlation with VS for AD, as compared with FOHR, especially among younger subjects, is supported by the general pattern of ventricular enlargement in fetal patients. In FV, the occipital horn of the lateral ventricle is the first area to dilate,1,3 and the atrium dilates to a greater extent than other ventricle regions, such as the frontal horns.2 A similar finding was noted in a study of preterm infants with posthemorrhagic hydrocephalus in which a segmental volume analysis showed disproportionate enlargement of the occipital region of the lateral ventricles.2 Atrial diameter exclusively measures the width of the posterior horn of the lateral ventricle, whereas FOHR reflects the size of both the frontal and occipital horns. Although FOHR does incorporate the occipital horns, AD does so to a greater extent, which may explain why it was found in the present study to correlate more strongly with ventricular volume in fetal patients. Over the course of gestation, the frontal horns change in size and shape because of the growing head and body of the caudate.4 Therefore, at later time points when the frontal horns contribute more to overall VS, equivalent correlations were noted between both linear measures (AD and FOHR) and VS after a GA of 24 weeks in our study. The correlation between AD and VS remained strong throughout the fetal period. Although not assessed in the current study, we would expect FOHR to outperform AD in postnatal studies.

### Table 1. Pairwise Pearson correlation coefficients between AD or FOHR and CSF, ventricle, or brain sizes using normalized and non-normalized 2D and 3D data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2D</th>
<th>3D</th>
<th>2D</th>
<th>3D</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>0.796</td>
<td>0.793</td>
<td>0.827</td>
<td>0.830</td>
<td>-0.796</td>
<td>-0.793</td>
</tr>
<tr>
<td>FOHR</td>
<td>0.741</td>
<td>0.792</td>
<td>0.835</td>
<td>0.842</td>
<td>-0.741</td>
<td>-0.792</td>
</tr>
<tr>
<td>Non-normalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>0.836</td>
<td>0.845</td>
<td>0.875</td>
<td>0.886</td>
<td>0.133*</td>
<td>0.144*</td>
</tr>
<tr>
<td>FOHR</td>
<td>0.519</td>
<td>0.529</td>
<td>0.667</td>
<td>0.668</td>
<td>-0.323</td>
<td>-0.314</td>
</tr>
</tbody>
</table>

2D = area of single slice used to calculate AD; 3D = summed areas for up to 7 slices, centered at the slice used to measure AD; CSF = refers to ventricle and subarachnoid space. * Nonsignificant correlation (p > 0.05); all other correlations are statistically significant.
In addition to measuring different parts of the ventricular system, AD and FOHR have intrinsic differences, in accordance with our overall findings. Although both measures can be obtained using an axial MRI slice, AD is a single linear measure associated with units, whereas FOHR consists of multiple measures and is without units. Caution must be used when directly comparing a number and a ratio. In a study of correlations between FOHR and ventricle volume in postnatal hydrocephalus patients, Ragan et al. were sensitive to this issue and reported ventricle volume in both absolute (non-normalized) and relative (normalized) terms. Likewise, we reported correlations for VS computed both as the number of voxels (non-normalized) and as the number of ventricle voxels divided by...
the total number of intracranial voxels (normalized). Normalized ventricle volume is equivalent to the proportion of intracranial volume taken up by the ventricle. Atrial diameter correlated better with VS regardless of whether or not VS was normalized, whereas FOHR was strongly correlated to normalized VS only. Thus, AD is representative of both absolute and relative volume in FV, whereas FOHR, a ratio, achieves the same correlation as AD in relation to VS only when the intracranial size is taken into account.

Although volumetric techniques are probably most representative of true ventricular volume, linear measures are primarily used in current clinical practice. Nonetheless, image analysis techniques used in our study revealed patterns related to ventriculomegaly that may inform future investigations. For instance, enlargement of the subarachnoid space in pediatric patients has been cited as a potential confounder when determining true intracranial volume. Following segmentation of the ventricle, the remaining intracranial volume can mistakenly be labeled as brain parenchyma when, in fact, a component consists of subarachnoid space. In our study, the subarachnoid space was separately segmented from the ventricles. Correlations between linear measures and VS alone (excluding the subarachnoid space) were only slightly higher than those between linear measures and total CSF size (ventricle plus subarachnoid space). The lack of a statistically significant difference corroborates assumptions in prior studies that the size of the subarachnoid space did not confound results. In another example, similar correlations between linear measures and VS when comparing 2D versus 3D approaches indicate that substantial data can be derived from the single axial slice used to calculate AD. For centers in which computerized segmentation is not available, linear measures in 2 dimensions still provide useful clinical data. Conversely, correlations between linear measures and brain size were lower than correlations with ventricle measurements, suggesting that volumetric techniques, rather than linear measures, are required for further study or tracking of this intracranial compartment.

Despite its strengths—sophisticated image analysis techniques, segmentation of the subarachnoid space, use of normalized and non-normalized VS, and direct statistical comparisons between correlations—our study does have several limitations. First, poor-quality fetal MRI data, most commonly at the upper- and lower-most axial slices, primarily due to motion artifact, precluded incorporation of all axial slices in our volumetric approach. Still, no significant differences were noted when comparing correlations in 2D versus 3D approaches. Second, our study was retrospective and linear measurements were drawn by hand, during which time raters were able to obtain a subjective estimate of ventricular size. However, subjective ratings have been shown to be inaccurate when estimating ventriculomegaly, especially for borderline cases, and all raters were blinded to VS when performing the linear measurements. Third, half of the FV patients in our data set underwent postnatal CSF diversion, which is a higher proportion than would be expected from a random sample of patients with FV. Patients who required CSF diversion after birth would be expected to have larger ventricles in utero, which in turn could be more easily detected by AD measurements than by FOHR. In addition, ascertainment bias may have resulted in the selection of FV patients with larger ventricles compared with other samples, as cases of borderline FV are less likely to be referred to our center. Finally, our study was performed at a single center, and future studies are needed to determine the relationship between linear measures and volumetric studies using data obtained across different MR scanners with different acquisition parameters.

Conclusions

Until volumetric approaches are widely available and well integrated into clinical practice, linear measures with the highest correlation to VS are desired for defining disease and prognosis in FV. Although FOHR is commonly used in postnatal patients, findings in the current study support the continued use of AD in the evaluation of patients with FV. Mean AD was highly correlated with 2D and 3D VS throughout gestation, whereas FOHR only reached the same strength of correlation after 24 weeks. Atrial diameter captures the preferential dilation of the occipital horns in fetal patients to a greater extent than FOHR. Nonetheless, FOHR can be used at later GAs since it performs as well as AD in estimating normalized VS after 24 weeks and can offer continuity with postnatal measurements.

Acknowledgments

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Pisapia, Heuer. Acquisition of data: Pisapia, Thawani. Analysis and interpretation of data: Pisapia, Rozycki, Akbari, Davatzikos, Heuer. Drafting the article: Pisapia. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Pisapia. Statistical analysis: Pisapia, Rozycki, Akbari. Administrative/technical/material support: Rozycki, Zarnow. Study supervision: Davatzikos, Heuer.

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