Title
Enlarged Cavum Septi Pellucidi and Vergae in the Fetus: A Cause for Concern

Journal
Journal of Ultrasound in Medicine, 36(8)

ISSN
0278-4297

Authors
Ho, Yoona K
Turley, Michelle
Marc-Aurele, Krishelle L
et al.

Publication Date
2017-08-01

DOI
10.7863/ultra.16.06081

Peer reviewed

Enlarged Cavum Septi Pellucidi and Vergae in the Fetus

A Cause for Concern

Yoona K. Ho, MD, Michelle Turley, MD, Krishelle L. Marc-Aurele, MD, Marilyn C. Jones, MD, Elise Housman, RDMS, Dawn Engelkemier, Lorene E. Romine, MD, Paritosh C. Khanna, MD, Dolores H. Pretorius, MD

Objectives—To investigate fetal cases identified at our institution to determine whether an enlarged cavum septi pellucidi or cavum vergae is associated with other fetal abnormalities and whether its presence warrants more detailed investigation of the fetus.

Methods—In a retrospective study, 15 high- and low-risk patients undergoing prenatal sonography who had an enlarged cavum septi pellucidi or cavum vergae identified were reviewed. Data were collected for the sonographic study indication, gestation age at diagnosis of a prominent cavum, and associated anomalies. Follow-up outcome data regarding further imaging, karyotype, diagnosis of brain anomaly, and associated congenital abnormalities were obtained.

Results—Fifteen patients met the inclusion criteria. Nine patients were identified as having a prominent cavum septi pellucidi, and 6 were identified as having a prominent cavum vergae. The mean gestational age ± SD was 22.7 ± 5.9 weeks. Eleven patients made it to delivery. Of the 15 patients, 4 were thought to have trisomy 21, and 13 had congenital anomalies. Outcomes included 10 major adverse outcomes, 4 cases with normal development or minor abnormalities, and 1 lost to follow-up. An isolated dilated cavum on prenatal sonography was seen in 5 cases: 1 with lissencephaly on a neonatal examination, 3 premature deliveries (1 demise, 1 hospice, and 1 normal), and 1 unknown.

Conclusions—Our cohort had many associated clinical anomalies: 3 confirmed trisomy 21 and 1 probable trisomy 21, 2 genetic disorders, and 10 major adverse outcomes, 5 of which were grave. Although we studied a small cohort, we conclude that an enlarged cavum septi pellucidi or cavum vergae warrants consideration of genetic counseling, which may include noninvasive prenatal testing (cell-free DNA), amniocentesis with microarray testing, or both.

Key Words—cavum; cavum septi pellucidi; fetal brain; fetus; obstetric ultrasound

Received July 11, 2016, from the Maternal-Fetal Care and Genetics Center (Y.K.H., M.T., M.C.J., D.H.P.) and Departments of Radiology (Y.K.H., E.H., D.H.P.), Pediatrics (K.L.M.-A.), and Genetics (M.C.J.), University of California, San Diego, California USA; Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas USA (M.T.); Departments of Genetics (M.C.J.) and Radiology (P.C.K.), Rady Children's Hospital, San Diego, California USA; Sharp Reese Steely, San Diego, California USA (D.E.); and Department of Radiology, Cedars-Sinai Medical Center, Los Angeles, California USA (L.E.R.). Manuscript accepted for publication November 7, 2016.

We thank Olivia Hernandez for assistance with manuscript preparation.

Address correspondence to Dolores H. Pretorius, MD, Thornton Hospital, 9300 Campus Point Dr, 7756, La Jolla, CA 92037 USA.

E-mail: dpretorius@ucsd.edu

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

doi:10.7863/ultra.16.06081

The cavum septi pellucidi is a cavity filled with cerebrospinal fluid found in the normal developing fetal brain after 18 weeks' gestation. This cavity will normally close when the two leaflets of the septa pellucida come together near term.[1] The cavum vergae is a second fluid-filled structure found just posterior to the cavum septi pellucidi between the corpus callosum and the fornix.[2] In accordance with practice guidelines (now called practice parameters) released by the American Institute of Ultrasound in Medicine, American College of Radiology, American College of

Obstetricians and Gynecologists, and Society of Radiologists in Ultrasound, the cavum septi pellucidi should be imaged as part of screening fetal sonographic examinations.[3] It has been well documented that the absence of a cavum septi pellucidi on fetal sonography is associated with other intracranial abnormalities, including holoprosencephaly, septo-optic dysplasia, corpus callosum dysgenesis, and schizenchephaly.[4–6] Normal cavum septi pellucidi widths in relation to gestational age were reported by Jou et al[7] in 1998 and confirmed by Falco et al[1] in 2000, who added a correlation with the biparietal diameter. The question arises as to what should be done when fetal sonography shows an enlarged or borderline enlarged cavum septi pellucidi or cavum vergae. Is it a normal variant or an incidentaloma, as is often thought by pediatric neuroradiologists? Should additional imaging (sonography or magnetic resonance imaging [MRI]) or follow-up be recommended? The aim of this study was to investigate the fetal cases identified at our institution over the last 10 years to determine whether an enlarged cavum septi pellucidi or cavum vergae is associated with other fetal abnormalities and whether the presence of a prominent cavum septi pellucidi or cavum vergae warrants more detailed investigation of the fetus.

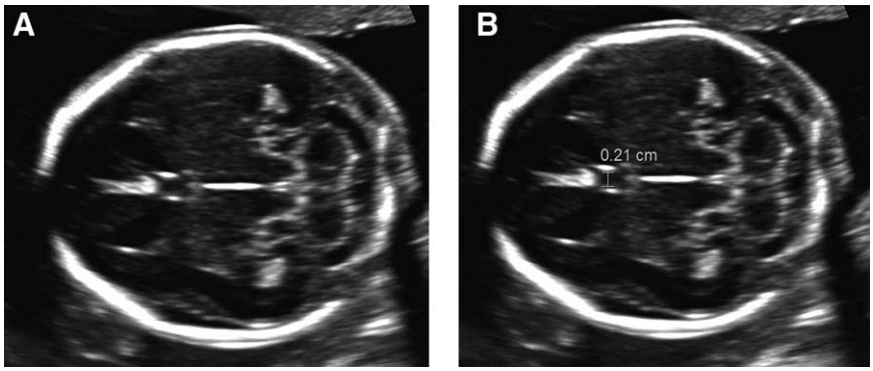
Materials and Methods

A retrospective study of images from both high- and low-risk patients undergoing routine prenatal sonography at a tertiary referral center at the University of California, San Diego, from 2004 to 2013 was conducted after Institutional Review Board approval for this study was obtained. A data log of all fetuses with anomalies identified at the University of California Maternal Fetal Care and Genetics Center was searched to identify fetuses with an enlarged cavum septi pellucidi or cavum vergae. The cavum septi pellucidi and cavum vergae were considered enlarged and prominent if the measurement exceeded the gestational age and ranges established by Jou et al,[7] Falco et al,[1] and Tao et al[2] by 2 SDs. Two-dimensional sonograms (15 cases) and 3-dimensional (3D) sonograms, when available (6 cases), were reviewed. The size of the apparently enlarged cavum septi pellucidi or cavum vergae was remeasured, and additional congenital anomalies were recorded.

Data from 15 patients were collected for analysis, including the indication for the sonographic study, gestational age at diagnosis of a prominent cavum septi pellucidi or cavum vergae, and associated anatomic anomalies. Follow-up outcome data regarding further sonographic evaluations, fetal/neonatal MRI examinations, aneuploidy screening, fetal/neonatal karyotype, diagnosis of brain anomalies, associated congenital abnormalities, neonatal physical examination/outcome, and fetal autopsy were obtained when available.

Patients were scanned with 1 of 4 different models of diagnostic ultrasound machines: Voluson Expert (GE Healthcare, Wauwatosa, WI), Voluson E-8 (GE Healthcare), LOGIQ E-9 (GE Healthcare), and Sonoline Antares (Siemens Medical Solutions, Issaquah, WA). Images were reviewed independently by a diagnostic radiologist or perinatologist at the time of the study. All images were reviewed and remeasured at the time of this retrospective review by a fetal radiologist (D.H.P.; Figure 1). Both the cavum septi pellucidi and cavum vergae

Figure 1. Normal cavum septi pellucidi showing measurement at a gestational age of 18 weeks. **A**, Axial image of a normal cavum septi pellucidi. **B**, Measurement cursors show that the cavum septi pellucidi measures 2.1 mm.



were visualized, and the width was measured from an axial view of the brain (Figure 2). Three-dimensional sonograms were viewed from the multiplanar display (Figure 3).

Results

Fifteen patients who met the inclusion criteria were identified among approximately 25,620 patients examined by sonography during the study period. Indications for fetal sonography included abnormal serum screening results (5), evaluation for abnormalities seen on outside imaging (6), evaluation given a family history of a congenital anomaly (1), and routine follow-up (3). Nine patients were identified as having an enlarged cavum septi pellucidi by the reading radiologist or perinatologist at the time of the evaluation, and 6 were identified as having a

Figure 2. Normal cavum vergae showing measurement at a gestational age of 18 weeks. **A**, Three-dimensional image of a normal cavum vergae. **B**, Measurement cursors show that the cavum vergae measures 1.6 mm. Multiplanar images are as follows: A, axial plane; B, coronal plane; and C, sagittal plane.

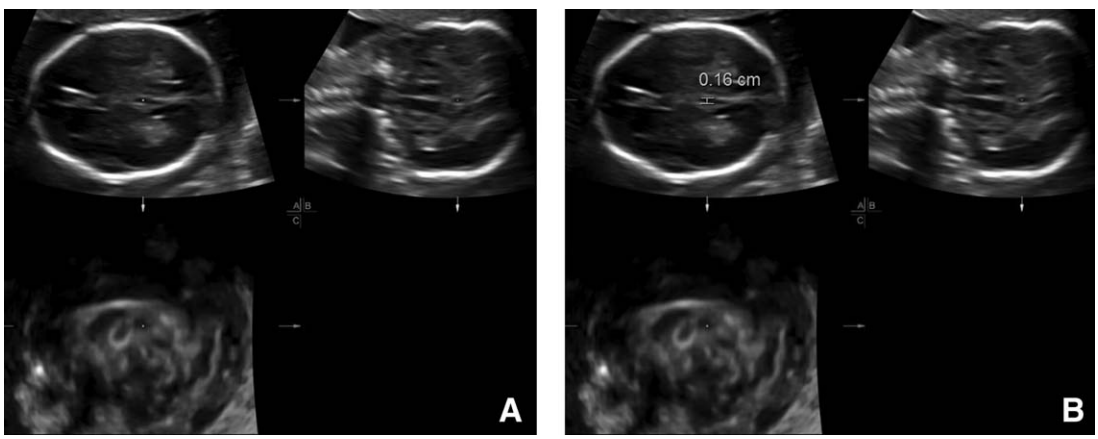
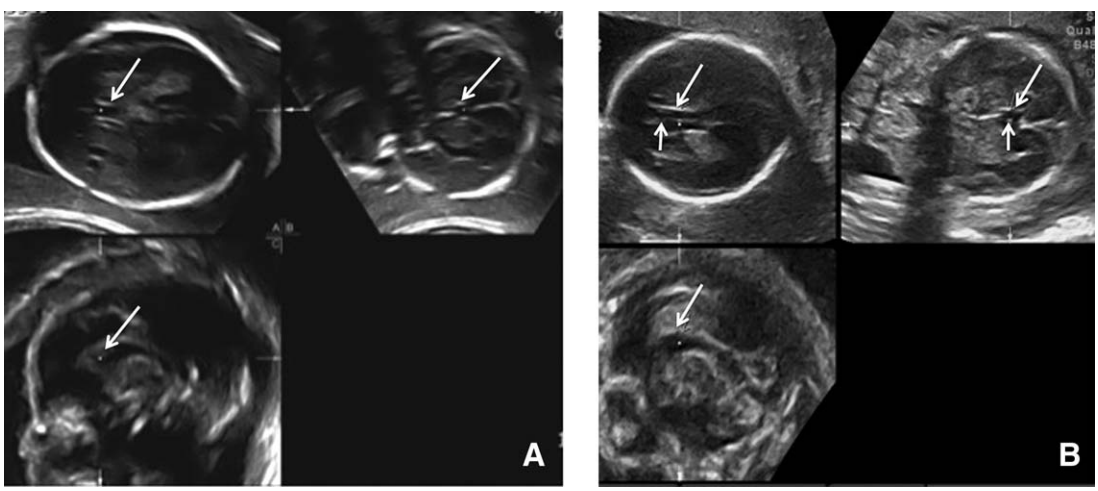


Figure 3. Normal and enlarged cavum septi pellucidi on 3D multiplanar images. **A**, Normal cavum septi pellucidi (long arrows) in a fetus at a gestational age of 20 weeks 6 days. **B**, Enlarged cavum septi pellucidi (long arrows) in fetus at a gestational age of 20 weeks 2 days. Three-dimensional axial (A) and coronal (B) planes show substantial differences between the normal and enlarged cavum septi pellucidi, whereas sagittal (C) images are similar in appearance. Of note, the septum seen within the cavum septi pellucidi of the fetus in **B** is not associated with fornices. Three-dimensional sonography shows 3 orthogonal planes depicting the septum (short arrow) within the cavum septi pellucidi and cavum vergae above the level of the fornices.



prominent cavum vergae. Overall, there were 3 cases of an isolated enlarged cavum septi pellucidi and 2 cases of an isolated enlarged cavum vergae.

At the time of the sonographic evaluation, the maternal age ranged from 14 to 42 years and the mean maternal age ± SD was 30 ± 7.7 years. The mean gestational age was 22.7 ± 5.9 weeks at the time of the first sonographic evaluation in which a prominent cavum septi pellucidi or cavum vergae was noted (Table 1). The mean age at delivery was 36.4 ± 3.7 weeks and ranged from 30 to 40 weeks. Five of the 11 patients who made it to delivery were preterm, whereas 6 were term deliveries. The severity of outcomes is given in Table 2. One patient was lost to follow-up before delivery; 2 patients had intrauterine fetal demise; 2 had neonatal demise; and 1 went to hospice after intraventricular hemorrhage related to prematurity. The patient lost to follow-up had been referred from out of the country and was presumed to have returned home.

Of the 15 patients, 5 were thought to have chromosomal anomalies based on either cell-free DNA testing or amniocentesis. Of these 5, 3 were confirmed to have trisomy 21 (cases 2, 12, and 14). One patient had a complex deletion on the Y chromosome known to affect fertility but thought to be unrelated to a prominent cavum septi pellucidi (case 1). Another patient had a positive cell-free DNA test result for trisomy 13 but was found to have no abnormality at birth (case 4; Figure 4). One fetus with an unconfirmed karyotype had a positive trisomy 21 screen result (>1 in 10 risk) with cystic hygroma, pericardial effusion, an absent stomach, and ascites and was suspected to have trisomy 21 (case 11). Of the remaining 10 patients, 4 had confirmed normal amniocentesis, and the remaining 6 had unconfirmed karyotypes (Table 1).

Congenital anomalies were found in 13 patients (Table 3) in the cohort, and 1 appeared to be normal structurally. Anomalies were seen in 14 fetuses prenatally (1 had no abnormalities at delivery), and additional major anomalies were identified after delivery in 2 cases (cases 1 and 13). Anomalies confirmed in the neonates were varied and included brain anomalies (3), congenital heart disease (4), and myotonic dystrophy (1; Table 2). It should be noted that a history of maternal myotonic dystrophy was present in the case with myotonic dystrophy.

Adverse outcomes occurred in 10 cases (Table 2). Two cases had intrauterine fetal demise: 1 had a trisomy 21 karyotype with echogenic kidneys (Figure 5), and the other had a positive trisomy 21 screen result (>1 in 10 risk) with cystic hygroma, pericardial effusion, an absent stomach, and ascites (Table 1). Two cases had neonatal demise: 1 with tetralogy of Fallot and vermian hypoplasia (Figure 6) and 1 with preterm delivery at 31 weeks with chorioamnionitis. One patient was transferred to a hospice with an abnormal karyotype, inoperable pulmonary vein stenosis, and hydrocephalus from grade 3 hemorrhage. In addition, 1 patient had lissencephaly with an intellectual disability and a seizure disorder, and 1 had type 1 myotonic dystrophy with substantial physical and intellectual impairment by 5 years. Lastly, 2 had major congenital heart disease, and 1 had trisomy 21.

Isolated enlargement of the cavum on prenatal sonography was seen in 5 cases (Table 4). The outcomes were as follows: 1 was premature but normal (case 15); 1 had fetal MRI showing decreased sulcation and neonatal MRI showing lissencephaly (case 13); 1 had demise related to prematurity (case 6); 1 had hospice admission related to prematurity and congenital heart disease (case 1); and 1 was lost to follow-up (case 9).

During the review of prominent cavum septi pellucidi cases, it was found that of the 9 cases that were called "enlarged cavum septi pellucidi" on clinical reports, although all measurements of the cavum septi pellucidi were above the mean, 7 were greater than 2 SDs; 1 was near the cutoff (case 3); and 1 was within 2 SDs (case 6) according to the data published (Table 1).[1,2,7] The cavum vergae was called enlarged in 8 cases, and 5 had no reference tables available because of gestational age; 2 were greater than 2 SDs; and 1 was near the cutoff (only 25 cases in the published table by Tao et al)[2]. Note that 1 fetus (case 9) had both a prominent cavum septi pellucidi and cavum vergae. The outcomes of these patients are given in Table 1.

Discussion

Established Normal Values for the Cavum Septi Pellucidi and Cavum Vergae

Falco et al[1] reported that the cavum septi pellucidi can be seen in 40% of fetuses as early as 15 weeks, in 82% from 16 to 17 weeks, in 100% from 18 to 37 weeks, and in 79% from 38 to 41 weeks. In our clinical practice, it is common to be unable to visualize the cavum septi pellucidi before 20 weeks, and patients are asked to return at 22 weeks for a follow-up sonogram. The mean width of

Table 1. Cavum Septi Pellucidi and Cavum Vergae Measurements and Associated Outcomes

Case	GA at Scan, wk + d	CSP Width, mm	Normal CSP Range, Mm	CV Width, mm	Normal CV Range, mm (T)	Karyotype (if Known)	Prenatal Anomalies on Sonography	Head MRI Findings, wk + d	GA at Birth, wk + d	Neonatal Findings	Outcome
CSP cases											
1	20 + 2	7.1	F: 3.4–6.2 J: 2.6–5.5 T: none			46,X,der(Y) (q12). ishdel (Y)(SRY+, WCP+, DYZ1–); affects fertility	Borderline thickening of NF	20 + 0, CSP 8 mm, CC present, normal ventricles	32 + 1	Preterm delivery, mildly dilated lateral ventricles, right intraventricular hemorrhage, hydrocephalus, left pulmonary vein stenosis, pulmonary hypertension	Transferred to hospice for intraventricular hemorrhage
2	20 + 5	6.0	F: 3.2–5.8 J: 2.1–4.7 T: none			47,XY+21	Double bubble, absent NB, possible Dandy-Walker variant, VSD, overriding aorta, echogenic focus	30 + 5, CSP 12 mm, inferior vermian hypoplasia	30 + 0	Preterm delivery, TOF, Dandy-Walker variant, cortical blindness, deafness, trisomy 21	Neonatal demise
	25 + 3	9.3	F: none J: 4.0–7.2 T: 5.3–7.5								
3	24 + 0	6.0	F: 3.9–7.2 J: 3.0–6.5 T: none				Possible Dandy-walker variant		36 + 3	Late preterm delivery, Dandy-Walker variant	Normal development
4	21 + 1	5.0	F: 3.4–4.2 J: 2.6–5.5 T: none			47,XX+13–, cell-free DNA, no amniocentesis or neonatal karyotype	Ambiguous genitalia		38 + 0		Viable neonate, normal appearing
	29 + 1	8.8	F: 4.3–8.5 J: 4.8–8.1 T: 5.2–7.6								
5	34 + 5	11.0	F: 4.2–9.3 J: 4.4–8.5 T: 5.1–7.3				Abnormal foot shape, clubfoot vs posturing		40 + 0	Myotonic dystrophy, type 1, plantar-flexed feet	Mild developmental delay, dysphagia
6	18 + 5	4.3	F: 2.7–5.0 J: none T: none			46,XY with normal array	Bilateral renal pelvicaliectasis		31 + 2	Preterm delivery, chorioamnionitis	Neonatal demise

Table 1. Continued

Case	GA at Scan, wk + d	CSP Width, mm	Normal CSP Range, Mm	CV Width, mm	Normal CV Range, mm (T)	Karyotype (if Known)	Prenatal Anomalies on Sonography	Head MRI Findings, wk + d	GA at Birth, wk + d	Neonatal Findings	Outcome
7	26 + 2	8.3	F: 4.1–7.8 J: 4.0–7.2 T: 5.1–7.1			46,XY with normal array	Polydactyly left hand and right foot, clenched left hand		40 + 0	Postaxial polydactyly	Normal development
8	29 + 1	6.9	F: 4.3–8.5 J: 4.4–8.1 T: 4.7–6.9	9.1	4.4–9.2		Fetal heterotaxy syndrome	30 + 4, normal CSP 8 mm, normal CC	38 + 4	Situs inversus totalis with levocardia, transposition of great vessels, mild Ebsteinoid tricuspid valve, subpulmonary VSD-PDA, right aortic arch, normal neonatal head on sonography	Congenitally corrected heart, appropriate development
9	31 + 5	11	F: 4.4–8.8 J: 4.4–8.6 T: 5.3–7.7	9.1	6.2–8.5			29 + 0, CSP and CV enlarged, normal CC			Lost to follow-up
CV cases											
10	16 + 5	3.7	F: 2.1–4.2 J: none T: none	2.7	None	46,XY with normal array	Possible TOF vs DORV, pulmonary atresia		37 + 0	DORV	Congenital heart disease, mild speech delay, strabismus
11	16 + 6			3.8	None	Positive trisomy 21 screen, risk > 1 in 10	Anhydramnios, cystic hygroma, pleural effusion, ascites, echogenic bowel		19 + 0	Fetal hydrops	Fetal demise
12	18 + 0			3.8	None	47,XY+21	Echogenic focus left ventricle, echogenic kidneys, absent stomach		35 + 0	Trisomy 21	Fetal demise
13	27 + 3	5.4	F: 4.2–8.0 J: 4.1–8.7 T: 4.2–7.6	9.5	6.0–6.2		Lateral ventricles at upper limits of normal (9 mm)	29 + 5, mildly prominent lateral ventricles, decreased sulcation, normal CC and CSP	38 + 2	Lissencephaly, *lis*-1 gene positive	Severe developmental delay, seizure disorder

Table 1. Continued

Case	GA at Scan, wk + d	CSP Width, mm	Normal CSP Range, Mm	CV Width, mm	Normal CV Range, mm (T)	Karyotype (if Known)	Prenatal Anomalies on Sonography	Head MRI Findings, wk + d	GA at Birth, wk + d	Neonatal Findings	Outcome
14	16 + 0			2.8	None	47,XY+21	Thick nuchal fold, cystic hygroma, dysmorphic facial profile, short nasal bone, short humeri and femurs			Trisomy 21	Trisomy 21 with unknown outcome
15	18 + 1	3.3	F: 2.7–5.0 J: none T: none	2.2	None	46,XY with normal array	2-vessel cord, mildly echogenic bowel		36 + 3	Late preterm delivery, normal neonatal head on sonography, hypospadias	Normal development

CC indicates corpus callosum; CSP, cavum septi pellucidi; CV, cavum vergae; DORV, double-outlet right ventricle; F, Falco et al[1]; GA, gestational age; J, Jou et al[7]; NB, nasal bone; NF, nuchal fold; PDA, patent ductus arteriosus; T, Tao et al[2]; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

the cavum septi pellucidi has been associated with gestational age, and ranges have been established by Jou et al,[7] Falco et al,[1] and Tao et al.[2] The mean width and anteroposterior diameter of the cavum septi pellucidi have been shown to differ significantly between the second and third trimesters and to correlate with the gestational age and biparietal diameter. In a study by Serhatlioglu et al,[8] the mean second-trimester width was 3.1 mm, and the mean anteroposterior diameter was 7.7 mm; the mean third trimester width was 5 mm, and the mean anteroposterior diameter was 11.7 mm. In addition, Chaoui et al[9] reported a linear increase in the cavum septi pellucidi width relative to the biparietal diameter, with mean cavum septi pellucidi widths of 3.0 to 6.3 mm for biparietal diameters of 40 to 90 mm, respectively.

Cavum vergae visualization was examined in a study by Tao et al[2]; it was only visualized at a rate of 7.8% (25 of 322) with a width of 6.7 mm (range, 5.1–9.0 mm) in their study of 322 uncomplicated singleton pregnancies in the second and third trimesters using routine sonographic examinations. Using 3D sonography, another study was able to visualize the cavum vergae in 202 consecutive fetuses, but no measurements were reported.[10] More recently, Unal et al[11] evaluated the cavum vergae in 336 healthy third-trimester fetuses with routine transabdominal sonography and found that cavum vergae closure increased with gestational age, with 100% visualization of the cavum vergae at 28 weeks or earlier and 42% visualization at 37 to 41 weeks. The study also evaluated correlation between the biparietal diameter, cavum vergae volume, and cavum vergae thickness and found no significant correlation between the biparietal diameter and cavum vergae thickness or volume in fetuses at the same gestational age.

The presence of the cavum septi pellucidi decreases with postnatal age; however, the reported prevalence in the literature is widely variable, likely because of differences in imaging modalities and study populations. There is a dramatic decrease in the presence of the cavum septi pellucidi detected on autopsy during the first few months of life, from 97% during the first week of life to 15% at 3 to 6 months of life.[12] The cavum septi pellucidi size in the term neonate is similar to that in the second- to third-trimester fetus, with a mean width of 5.1 mm; widths of greater than 9.5 mm and depths of greater than 8.1 mm are considered outside the normal range.[13] In adults, the cavum septi pellucidi is typically measured

anterior to posterior based on the number of MRI slices on which it is visible, with a length of greater than 6 mm considered abnormal.[14] Criteria for a normal versus abnormal cavum septi pellucidi in the young pediatric population are not well established, although a similar anteroposterior measurement threshold of 6 mm has been used for studying the association between childhood-onset schizophrenia and 22q11 deletion syndrome.[15,16]

Prominent Cavum Septi Pellucidi in the Fetus

Chromosomal anomalies are associated with a prominent cavum septi pellucidi. Recently, significantly larger cavum septi pellucidi widths were found in 139 fetuses with autosomal trisomies compared to 267 euploid fetuses.[17] Ninety-two percent of fetuses with trisomy 18, 42% of fetuses with trisomy 21, and 37.5% of fetuses with trisomy 13 had a cavum septi pellucidi width above the 95th percentile compared to euploid fetuses. However, the actual difference in width measurements was small, with a substantial overlap of ranges for aneuploid and euploid fetuses. Similarly, our cohort had 3 fetuses with trisomy 21, another with a high suspicion of trisomy 21 with a positive screen result and anomalies commonly seen with trisomy 21 (case 11), and 1 with a positive screen results and risk of greater than 1 in 10 who was lost to follow-up; all 5 cases had a cavum septi pellucidi exceeding the normal range. In addition, 4 of these 5 patients had an enlarged cavum vergae detected on sonography. An enlarged cavum septi pellucidi has also been reported prenatally in fetuses with 22q11 deletion syndrome. In a study of 37 fetuses with 22q11

Table 2. Outcomes Based on Severity

Normal Development +/− Minor Anomalies			Major Anomalies			Grave Outcomes			Unknown	
Case 3	P	Dandy-Walker variant	Case 5	T	Myotonic dystrophy	Case 1	P	Intraventricular hemorrhage, congenital heart disease, hospice	Case 9	Lost to follow-up
Case 4	T	Normal	Case 8	T	Congenital heart disease, trisomy 21	Case 2	P	Congenital heart disease, possible Dandy-Walker variant, trisomy 21, neonatal demise		
Case 7	T	Polydactyly	Case 10	T	Congenital heart disease	Case 6	P	Chorioamnionitis, neonatal demise		
Case 15	P	Hypospadias	Case 13	T	Lissencephaly	Case 11		Suspected trisomy 21, fetal demise		
			Case 14		Trisomy 21	Case 12		Trisomy 21, fetal demise		
Total		4			5			5		1

P indicates preterm; T, term.

Figure 4. Changes in cavum septi pellucidi size with fetal growth. **A**, Axial image of a 21-week fetus shows a normal cavum septi pellucidi measuring at the mean for gestational age. **B**, This same fetus at 29 weeks now has an enlarged cavum septi pellucidi measuring between 1 and 2 SDs above the mean for gestational age. This fetus had ambiguous genitalia and 47,XX+13 on cell-free DNA testing. The neonate appeared normal at delivery.

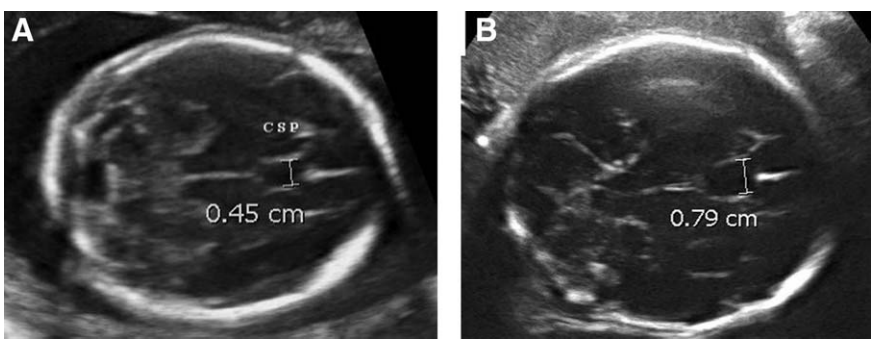


Table 3. Reported Prenatal and Postnatal Anomalies in Patients

Anomalies in Viable Patients	Anomalies in IUFD Patients
Cortical blindness	Absent stomach
Dandy-Walker variant	Anhydramnios
Hearing loss	Ascites
Intraventricular hemorrhage	Cystic hygroma
Lissencephaly	Echogenic focus in left ventricle
Macrocephaly	Echogenic kidneys
Myotonic dystrophy	Lagging long bone growth
Polydactyly	Nuchal cyst
Pulmonary hypertension	Pericardial effusion
Pulmonary vein stenosis	Pleural effusion
Situs inversus totalis	Trisomy 21
Tetralogy of Fallot	
Transposition of great arteries	

IUFD indicates intrauterine fetal demise.

deletion syndrome, 67.5% had a dilated cavum septi pellucidi in the second half of gestation.[9] Although further investigations examining the importance of incidental cavum septi pellucidi enlargements and associations with other anomalies are needed, genetic counseling and a discussion of noninvasive and diagnostic prenatal testing should be considered during pregnancy

Fetal anomalies and poor neonatal outcomes have been associated with a prominent cavum septi pellucidi and cavum vergae. Several studies and case reports have suggested the association of a prominent cavum septi pellucidi and cavum vergae on prenatal sonography with fetal anomalies and poor outcomes. Our study cohort had major adverse outcomes in 10 cases and clinical

Figure 5. Abnormal cavum vergae at a gestational age of 18 weeks in a fetus with 47,XY+21 and intrauterine demise at 35 weeks. **A**, Three-dimensional image of an abnormal cavum vergae. **B**, Measurement cursors show that the cavum vergae measures 3.8 mm. Multiplanar images are as follows: A, axial plane; B, coronal plane; and C, sagittal plane.

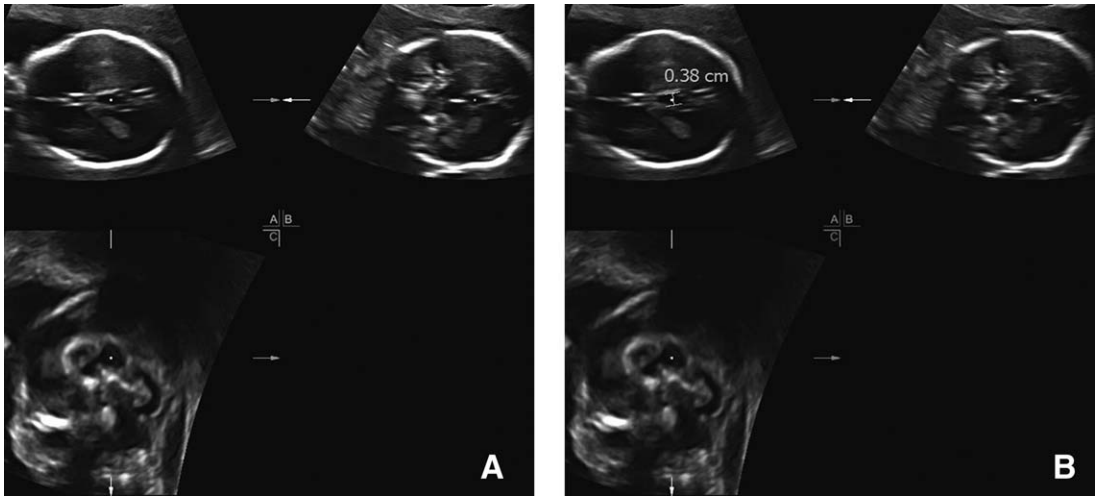
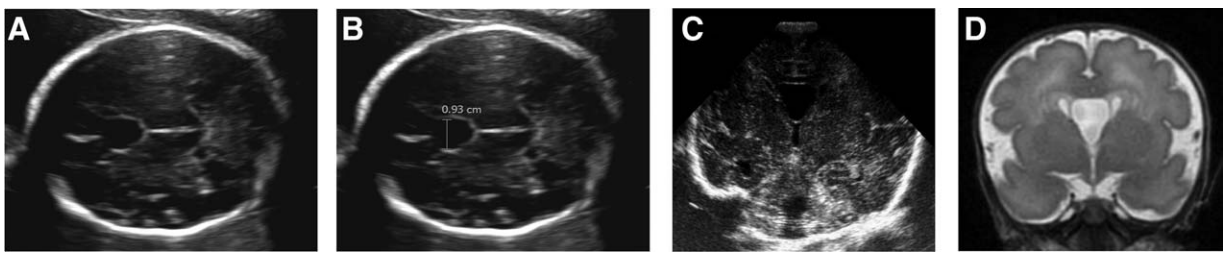


Figure 6. Enlarged cavum septi pellucidi in a fetus at a gestational age of 25 weeks 3 days who had multiple anomalies, 47,XY+21, and neonatal demise. **A**, Axial image showing an enlarged cavum septi pellucidi. **B**, Measurement cursors show that cavum septi pellucidi measures 9.3 mm. Other fetal sonographic findings included a double bubble, an absent nasal bone, a ventricular septal defect, an overriding aorta, an intracardiac echogenic focus, and a possible Dandy-Walker variant. **C** and **D**, Coronal sonogram (**C**) and coronal T2-weighted MRI (**D**) of the neonate at 1 day old (adjusted gestational age, 30 weeks 5 days) showing an enlarged cavum septi pellucidi measuring 9 mm. Neonatal findings included tetralogy of Fallot, a Dandy-Walker variant with vermian hypoplasia, cortical blindness, deafness, and 47,XY+21. This patient had neonatal demise.



anomalies in 13, which were further discussed in the "Results" section. Outcomes included fetal demise, neonatal demise, and major anomalies such as lissencephaly, myotonic dystrophy, and congenital heart disease. In a large study of 11,200 pregnant women reported by Bronshtein and Weiner[18] in 1992, only 8 cases of a cavum vergae measuring 5 mm or greater were identified; the size of the cavum septi pellucidi was not discussed in that cohort. Only 1 of these 8 cases showed a normal karyotype, lack of associated anomalies, and normal development at 6 months. One had a chromosomal translocation, and the others had normal karyotypes with a range of abnormalities, including fetal growth restriction with subsequent normal development at 12 months, an Ebstein anomaly, arthrogryposis, polycystic kidneys, cystic hygroma, short stature, hydrocephalus, and periventricular calcifications. In another report of 3 cases looking at midline cystic structures larger than 10 mm diagnosed prenatally as an enlarged cavum vergae, 1 had associated ventriculomegaly and lumbar meningocele; 1 required shunting postnatally for intracranial hypertension; and 1 was asymptomatic.[19] A single report was made of a fetus with a large cavum septi pellucidi and cavum vergae (12.6 mm) who was found to have midgut malrotation postnatally.[20]

An enlarged cavum septi pellucidi or cavum vergae without other anomalies is of unclear importance. In our study, 2 major adverse outcomes were identified: 1 case had relatively normal sonographic findings (lateral ventricles at the upper limits of normal) that was later found to have lissencephaly, and 1 case had congenital heart disease that went to a hospice for complications of prematurity. Another case had neonatal demise from premature abruption. Only 1 case had a normal outcome.

Table 4. Isolated Cases of Enlarged Cavum Septi Pellucidi and Cavum Vergae

Case	Term vs Preterm Delivery	Clinical Outcome
1	Preterm	Hospice for intraventricular hemorrhage related to prematurity and congenital heart disease
6	Preterm	Neonatal demise from premature abruption
9	Unknown	Lost to follow-up
13	Term	Lissencephaly
15	Preterm	Normal development

Occasionally, differentiation of a prominent cavum septi pellucidi from other cystic cerebral lesions on fetal sonography may be challenging. We have found that 3D sonography is particularly helpful in differentiating a normal cavum septi pellucidi and cavum vergae from pathologic lesions. The cursor dot or reference dot can be positioned in the lesion and seen on all 3 orthogonal planes to identify the structure (Figure 1). Differential considerations of a midline cystic lesion include an arachnoid cyst, an enlarged third ventricle, a vein of Galen malformation, an interhemispheric cyst with agenesis of the corpus callosum, agenesis of the corpus callosum with the subarachnoid space extending into the region of the cavum septi pellucidi, a porencephalic cyst, a glioependymal cyst, schizencephaly, intracranial hemorrhage, and a cystic neoplasm. Careful evaluation of the location of the lesion and adjacent abnormalities and the use of color Doppler facilitate correct diagnosis. Occasionally, serial follow-up examinations to evaluate interval changes or MRI may be necessary for definitive diagnosis. In a series of 19 cases of interhemispheric cystic lesions on prenatal sonography, 12 were related to an enlarged physiologic structure (cavum septi pellucidi, cavum vergae, and velum interpositum cysts) with a median size of 10 mm.[21] These lesions were stable or resolved. Only borderline ventriculomegaly was present in 2 cases, and pediatric follow-up showed normal neurodevelopment. Conversely, pathologic cystic lesions were larger (median size of 40 mm), and most showed associated anomalies of callosal agenesis or hypogenesis with hydrocephalus.[21]

Prominent Cavum Septi Pellucidi Postnatally

Although a persistent cavum septi pellucidi beyond infancy may be a normal variant, an enlarged cavum septi pellucidi may indicate abnormal neurodevelopment. The septum pellucidum is part of the limbic system, which affects memory, behavior, and emotion. Aberrations in the limbic system have been associated with neuropsychiatric diseases.[22] Multiple studies have shown increased cavum septi pellucidi prevalence and size in neuropsychiatric disorders, particularly schizophrenia.[14,23–25] In a large meta-analysis, the incidence of a large cavum septi pellucidi was significantly higher in schizophrenia spectrum disorders compared to controls (odds ratio, 1.59).[14] Schizophrenia has also been highly associated with 22q11 deletion syndrome; in a study of 78 adults with 22q11 deletion syndrome, 22.6% were

found to have schizophrenia.[26] Children with chromosome 22q11.2 deletion syndrome have been found to have a greater cavum septi pellucidi anteroposterior length (mean of 12.58 mm compared to mean of 2.31 mm in controls) and volume (916.13 mm^3 compared to 12.83 mm^3 in controls).[16] An enlarged cavum septi pellucidi has also been associated with disruptive behavior disorder in youth, bipolar disorder, posttraumatic stress disorder, adolescent-onset opiate dependence, and lower IQ scores.[27–31] During our study period, we had 2 cases of an enlarged cavum septi pellucidi diagnosed in neonates, 1 of which was the index case that prompted this study. Both neonates were born preterm, and 1 developed chronic lung disease as a complication of prematurity. The other case had a normal clinical outcome with appropriate development.

The presence of the cavum septi pellucidi in adults has been linked to traumatic brain injury, and the cavum septi pellucidi size has been shown to correlate with the injury severity in pediatric brain trauma.[32] Injury to the right entorhinal cortex and bilateral hippocampi is strongly correlated with the cavum septi pellucidi size.[32] Similarly, in adults with schizophrenia, decreased volumes in the left temporal lobe (specifically the left amygdala and anterior hippocampus), left parahippocampal gyrus, and bilateral amygdala have been associated with a large cavum septi pellucidi.[33–36] Although the mechanisms may be different, an enlarged cavum septi pellucidi postnatally may reflect developmental or acquired abnormalities of bordering structures in the limbic system.[32,37]

Limitations

Limitations of this study included the following: (1) limited long-term follow-up on a prenatally diagnosed large cavum septi pellucidi has been done to date—in our study or in the literature; (2) substantial overlaps in the ranges of normal and abnormal measurements of the cavum septi pellucidi and cavum vergae have been reported; (3) a limited number of patients were included in the study; and (4) 1 patient was lost to follow-up.

Conclusions

This study examined an enlarged cavum septi pellucidi and cavum vergae in routine prenatal sonographic examinations and their association with prenatal and neonatal anomalies. In our study, 13 of 15 cases had associated clinical anomalies; 4 had abnormal karyotypes; 2 had genetic disorders; and 10 had major adverse outcomes. Overall, our cohort had 3 confirmed cases of trisomy 21 and 1 additional suspected case, which corresponds to the supporting literature. The importance of an isolated enlarged cavum vergae or cavum septi pellucidi is unclear. We had 5 cases of an isolated enlarged cavum septi pellucidi or cavum vergae: 1 had congenital heart disease; 1 had lissencephaly; and 1 had normal development. Although further studies are needed to investigate this association of an enlarged cavum septi pellucidi or cavum vergae with anomalies, we conclude that these findings on routine sonograms warrant consideration of genetic counseling, which may include noninvasive prenatal testing (cell-free DNA), amniocentesis with microarray testing, or both. Future studies with larger cohorts are needed to examine whether fetal brain MRI should be recommended in isolated cases of an enlarged cavum.

References

1. Falco P, Gabrielli S, Visentin A, Perolo A, Pilu G, Bovicelli L. Transabdominal sonography of the cavum septum pellucidum in normal fetuses in the second and third trimesters of pregnancy. *Ultrasound Obstet Gynecol* 2000; 16:549–553.
2. Tao G, Lu G, Zhan X, et al. Sonographic appearance of the cavum septum pellucidum et vergae in normal fetuses in the second and third trimesters of pregnancy. *J Clin Ultrasound* 2013; 41:525–531.
3. American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of obstetric ultrasound examinations. *J Ultrasound Med* 2013; 32:1083–1101.
4. Barkovich AJ, Kjos BO, Norman D, Edwards MS. Revised classification of posterior fossa cysts and cystlike malformations based on the results of multiplanar MR imaging. *AJR Am J Roentgenol* 1989; 153: 1289–1300.
5. Oh KY, Kennedy AM, Antonio E. Frias J, Byrne JLB. Fetal schizencephaly: pre- and postnatal imaging with a review of the clinical manifestations. *Radiographics* 2005; 25:647–657.
6. Winter TC, Kennedy AM, Byrne J, Woodward PJ. The cavum septi pellucidi: why is it important? *J Ultrasound Med* 2010; 29:427–444.
7. Jou HJ, Shyu MK, Wu SC, Chen SM, Su CH, Hsieh FJ. Ultrasound measurement of the fetal cavum septi pellucidi. *Ultrasound Obstet Gynecol* 1998; 12:419–421.
8. Serhatlioglu S, Kocakoc E, Kiris A, Sapmaz E, Boztosun Y, Bozgeyik Z. Sonographic measurement of the fetal cerebellum, cisterna magna, and cavum septum pellucidum in normal fetuses in the second and third trimesters of pregnancy. *J Clin Ultrasound* 2003; 31:194–200.
9. Chaoui R, Heling KS, Zhao Y, Sinkovskaya E, Abuhamad A, Karl K. Dilated cavum septi pellucidi in fetuses with microdeletion 22q11. *Prenat Diagn* 2016; 36:911–915.

10. Correa FF, Lara C, Bellver J, Remohí J, Pellicer A, Serra V. Examination of the fetal brain by transabdominal three-dimensional ultrasound: potential for routine neurosonographic studies. *Ultrasound Obstet Gynecol* 2006; 27:503–508.
11. Unal O, Ipek A, Keskin HL, Idilman I, Cay N, Balaban M. Transabdominal sonographic study of the cavum vergae detection rate in healthy third-trimester fetuses. *J Ultrasound Med* 2015; 34:1407–1414.
12. Shaw CM, Alvord EC Jr. Cava septi pellucidi et vergae: their normal and pathological states. *Brain* 1969; 92:213–223.
13. Mott SH, Bodensteiner JB, Allan WC. The cavum septi pellucidi in term and preterm newborn infants. *J Child Neurol* 1992; 7:35–38.
14. Trzesniak C, Oliveira IR, Kempton MJ, et al. Are cavum septum pellucidum abnormalities more common in schizophrenia spectrum disorders? A systematic review and meta-analysis. *Schizophr Res* 2011; 125:1–12.
15. Nopoulos PC, Giedd JN, Andreasen NC, Rapoport JL. Frequency and severity of enlarged cavum septi pellucidi in childhood-onset schizophrenia. *Am J Psychiatry* 1998; 155:1074–1079.
16. Beaton EA, Qin Y, Nguyen V, Johnson J, Pinter JD, Simon TJ. Increased incidence and size of cavum septum pellucidum in children with chromosome 22q11.2 deletion syndrome. *Psychiatry Res* 2010; 181:108–113.
17. Abele H, Babiy-Pachomow O, Sonek J, Hoopmann M, Schaelike M, Kagan KO. The cavum septi pellucidi in euploid and aneuploid fetuses. *Ultrasound Obstet Gynecol* 2013; 42:156–160.
18. Bronshtein M, Weiner Z. Prenatal diagnosis of dilated cava septi pellucidi et vergae: associated anomalies, differential diagnosis, and pregnancy outcome. *Obstet Gynecol* 1992; 80:838–842.
19. Sahinoglu Z, Uludogan M, Delikara MN. Prenatal sonographic diagnosis of dilated cavum vergae. *J Clin Ultrasound* 2002; 30: 378–383.
20. Sherer DM, Sokolovski M, Dalloul M, Santoso P, Curcio J, Abulafia O. Prenatal diagnosis of dilated cavum septum pellucidum et vergae. *Am J Perinatol* 2004; 21:247–251.
21. Vergani P, Locatelli A, Piccoli MG, et al. Ultrasonographic differential diagnosis of fetal intracranial interhemispheric cysts. *Am J Obstet Gynecol* 1999; 180:423–428.
22. Granziera C, Hadjikhani N, Arzy S, Seeck M, Meuli R, Krueger G. In-vivo magnetic resonance imaging of the structural core of the Papez circuit in humans. *Neuroreport* 2011; 22:227–231.
23. Dickey CC, McCarley RW, Xu ML, et al. MRI abnormalities of the hippocampus and cavum septi pellucidi in females with schizotypal personality disorder. *Schizophr Res* 2007; 89:49–58.
24. Raine A, Lee L, Yang Y, Colletti P. Neurodevelopmental marker for limbic maldevelopment in antisocial personality disorder and psychopathy. *Br J Psychiatry* 2010; 197:186–192.
25. Chon MW, Choi JS, Kang DH, Jung M, Kwon J. MRI study of the cavum septum pellucidum in obsessive-compulsive disorder. *Eur Arch Psychiatry Clin Neurosci* 2010; 260:337–343.
26. Bassett AS, Chow EWC, Husted J, et al. Clinical features of 78 adults with 22q11 deletion syndrome. *Am J Med Genet A* 2005; 138:307–313.
27. White SF, Brislin S, Sinclair S, Fowler KA, Pope K, Blair RJ. The relationship between large cavum septum pellucidum and antisocial behavior, callous-unemotional traits and psychopathy in adolescents. *J Child Psychol Psychiatry* 2013; 54:575–581.
28. Kim MJ, Lyoo IK, Dager SR, et al. The occurrence of cavum septi pellucidi enlargement is increased in bipolar disorder patients. *Bipolar Disord* 2007; 9:274–280.
29. May FS, Chen QC, Gilbertson MW, Shenton ME, Pitman RK. Cavum septum pellucidum in monozygotic twins discordant for combat exposure: relationship to posttraumatic stress disorder. *Biol Psychiatry* 2004; 55:656–658.
30. Hwang J, Kim JE, Kaufman MJ, et al. Enlarged cavum septum pellucidum as a neurodevelopmental marker in adolescent-onset opiate dependence. *PLoS One* 2013; 8:e78590.
31. Flashman LA, Roth RM, Pixley HS, et al. Cavum septum pellucidum in schizophrenia: clinical and neuropsychological correlates. *Psychiatry Res* 2007; 154:147–155.
32. Silk T, Beare R, Crossley L, et al. Cavum septum pellucidum in pediatric traumatic brain injury. *Psychiatry Res* 2013; 213:186–192.
33. Nopoulos P, Swayze V, Andreasen NC. Pattern of brain morphology in patients with schizophrenia and large cavum septi pellucidi. *J Neuropsychiatry Clin Neurosci* 1996; 8:147–152.
34. Rossi A, Stratta P, Mancini F, et al. Magnetic resonance imaging findings of amygdala-anterior hippocampus shrinkage in male patients with schizophrenia. *Psychiatry Res* 1994; 52:43–53.
35. Kasai K, McCarley RW, Salisbury DF, et al. Cavum septi pellucidi in first-episode schizophrenia and first-episode affective psychosis: an MRI study. *Schizophr Res* 2004; 71:65–76.
36. Takahashi T, Suzuki M, Hagino H, et al. Prevalence of large cavum septi pellucidi and its relation to the medial temporal lobe structures in schizophrenia spectrum. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31:1235–1241.
37. Nopoulos P, Krie A, Andreasen NC. Enlarged cavum septi pellucidi in patients with schizophrenia: clinical and cognitive correlates. *J Neuropsychiatry Clin Neurosci* 2000; 12:344–349.