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Non-visualization of the cavum septi pellucidi is not synonymous with agenesis of the corpus callosum

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KEYWORDS: cavum septi pellucidi; corpus callosum; fetal brain; MRI; pericallosal lipoma; prenatal diagnosis; ultrasound

ABSTRACT

Objectives *To describe a cohort of fetuses with non-visualization of the cavum septi pellucidi (CSP) without callosal agenesis and to assess the significance of this finding with respect to postnatal development.*

Methods *We reviewed the files of all patients referred because of suspected fetal supratentorial midline anomalies, and identified those fetuses with a diagnosis of non-visualization or obliteration of the CSP.*

Results *From an initial cohort of 114 patients we identified 23 cases. Mean (± SD) gestational age at referral was 24.5 ± 1.3 weeks; referral diagnoses (with more than one in some cases) included: non-visualization or an echogenic CSP (n = 18), suspected callosal anomaly (n = 5), other findings (n = 5). The fetuses were examined for the first time at the Fetal Neurology Clinic at a mean gestational age of 26.6 ± 3.1 weeks (range, 22–34 weeks; median, 27 weeks). In all of the fetuses the zone where fluid should have been observed was echogenic. In 17 fetuses this was an apparently isolated finding and in six it was associated with other findings, but only one fetus had associated malformations. Follow-up was available for 16 children at a mean age of 17.4 months (range, 4–36 months; median, 19.5 months). Normal development was reported in 14 children. One child had infantile hypotonia but normal developmental milestones and another had mild motor delay and language delay. These two children did not have associated anomalies at the prenatal scan.*

Conclusion *Non-visualization of the CSP is not always associated with agenesis of the corpus callosum. When isolated it may be considered a variation of normal development. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The cavum septi pellucidi (CSP) is an important landmark in evaluation of the fetal brain and has become integral to both routine and detailed ultrasound examinations[1]. Development of the CSP begins at c. 10–12 weeks and it is fully formed by 17 weeks of gestation[2]. According to Rakic and Yakovlev[3], the anterior commissure and the septal area develop in the ventral part of the lamina reuniens; the CSP is formed as a subcallosal pocket of the sulcus medianus telencephali medii. The two folds (laminae) of the septum pellucidum forming the lateral walls of the cavum are initially relatively thick; later, as a result of rapid caudal growth of the cerebral hemispheres and of the corpus callosum (CC), the lateral walls of the cavum become thinner, and as the hemispheres further enlarge, the cavum becomes wider and elongates in its anteroposterior diameter[3].

Known anomalies of the septal area include pathologies of the cavum (the fluid-containing space between the laminae septi pellucidi), such as an enlarged cavum septi pellucidi et Vergae, with or without cysts, and pathologies of the septum pellucidum represented by holoprosencephaly and septo-optic dysplasia[4]. Ultrasound studies have shown that the CSP usually 'disappears' in late pregnancy or early neonatal life as the laminae septi pellucidi fuse to become the apparently single septum pellucidum composed of two apposed septa[5–8]. However, the fused septa retain the ability to once again become a fluid-containing cavity in later life, as seen especially in boxers[9].

Prenatally, the CSP should be visible until close to term. Non-visualization, particularly during the second trimester, is considered to be a marker of agenesis of the CC. Failure to visualize the CSP during pregnancy may stem from agenesis of the septa or lack of

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formation or obliteration of the space between them. The entity of absence of detectable fluid in the CSP on prenatal ultrasound examination has not been described previously.

The purpose of this study was to present our experience with a cohort of fetuses without callosal agenesis in which absence of fluid or increased echogenicity in the expected region of the CSP was observed and to evaluate the significance of this finding.

METHODS

We reviewed the files of all patients with fetuses diagnosed with cerebral midline anomalies (callosal agenesis and dysgenesis, pericallosal lipomas, agenesis of the septum pellucidum and/or non-visualization of the CSP) at the Fetal Neurology Clinic of the Edith Wolfson Medical Center between January 2006 and April 2011, identifying those fetuses with a diagnosis of non-visualization or obliteration of the CSP.

Gestational age at the time of referral ultrasound examination and diagnosis were tabulated, as well as recommendations of the referring physician. We also recorded gestational age at the time of first examination at our clinic, sex and karyotype when available, ultrasound and magnetic resonance imaging (MRI) findings, gestational age and mode of delivery, birth weight and the need for prolonged or neonatal intensive care unit (NICU) hospitalization. Families were contacted and pediatric files were reviewed when available.

Ultrasound examinations were performed according to the detailed neurosonographic examination guidelines provided by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[1] using transabdominal and/or transvaginal probes. MRI examinations were performed as previously described[10]. The study was approved by the Helsinki Committee of our institution as part of a larger study on fetuses with midline anomalies.

RESULTS

During the study period 114 fetuses were found to have supratentorial midline anomalies. Anomalies of the CC or agenesis of the laminae septi pellucidi were diagnosed in 91 fetuses. In the remaining 23 fetuses, the CC and laminae septi pellucidi were seen but there was no visible fluid between them in the expected region of the CSP (Figures 1–3). These fetuses are the subject of our study (Table 1).

The patients were referred following an ultrasound examination at a mean gestational age of 24.5 ± 1.3 weeks (range, 22–32 weeks; median, 23.5 weeks). The reasons for referral included: non-visualization or an echogenic CSP ($n = 18$), suspected callosal anomaly ($n = 5$), mild ventriculomegaly ($n = 2$), suspected macrocephaly ($n = 2$), increased nuchal translucency ($n = 1$); some patients had more than one indication for referral (Table 1). The possibility of termination of pregnancy (TOP) was discussed with five patients before referral; in four of these, other fetal anomalies were suspected.

Patients were examined initially at the Fetal Neurology Clinic at a mean gestational age of 26.6 ± 3.1 weeks (range, 22–34 weeks; median, 27 weeks). The region where fluid should have been seen in the CSP was echogenic in all fetuses (Figures 1–3) but a small amount of fluid in the cavum Vergae was observed in one fetus (Figure 3). In 17 fetuses this was an apparently isolated finding and in six it was associated with other findings (Table 1). In four of these six fetuses the associated findings raised concern regarding the prognosis. Only one had multiple malformations (Figure 3) and in this case pregnancy was terminated; autopsy was not possible, however, due to severe maceration of the brain. Associated findings included mild ventriculomegaly ($n = 2$), short CC ($n = 1$), aberrant callosal artery ($n = 1$), abnormal frontal horns ($n = 1$), bilateral choroid plexus cyst ($n = 1$) and periventricular pseudocysts ($n = 1$). In one patient a follow-up examination during the third trimester revealed a hyperechogenic pericallosal lipoma that was not visible earlier (Figure 2). There were 12 male and eight female fetuses; the sex was not recorded in three cases. A karyotype was available for 10 fetuses and was normal in all of them.

MRI was performed in seven cases, which confirmed the ultrasound findings in three, including the patient with associated fetal anomalies who underwent TOP. In the remaining four fetuses MRI raised the suspicion of presence of callosal anomalies, in one fetus the CC and CSP were not visualized at 24 weeks but ultrasound examination at 29 weeks showed a normal CC, and in three fetuses, including the fetus with the pericallosal lipoma, the CC was considered short or dysgenetic. At the time of writing, these four children were developing normally.

Adequate information regarding the outcome was obtained for 17 pregnancies (16 deliveries and one TOP) and six were lost to follow-up (Table 2). The cases with postnatal follow-up included four in which associated fetal anomalies had been observed, all of which were considered mild. All deliveries were at term and the mean birth weight was 3220 g. The results of neonatal neurological examinations were normal for all infants; two developed transient neonatal tachypnea and one developed hyperbilirubinemia requiring phototherapy. There were no NICU admissions. Only four infants underwent cranial ultrasound examination and it was considered normal in all of them. Follow-up was performed at a mean age of 17.4 months (range, 4–36 month; median, 19.5 months) and fourteen children were developing normally. One had infantile hypotonia but normal developmental milestones and had been treated by physiotherapy from the age of 6–9 months. Another had mild motor delay and mastered walking at 17 months; at the time of writing this child was 26 months old and showed language delay. These two children did not have associated anomalies on prenatal ultrasound examinations.

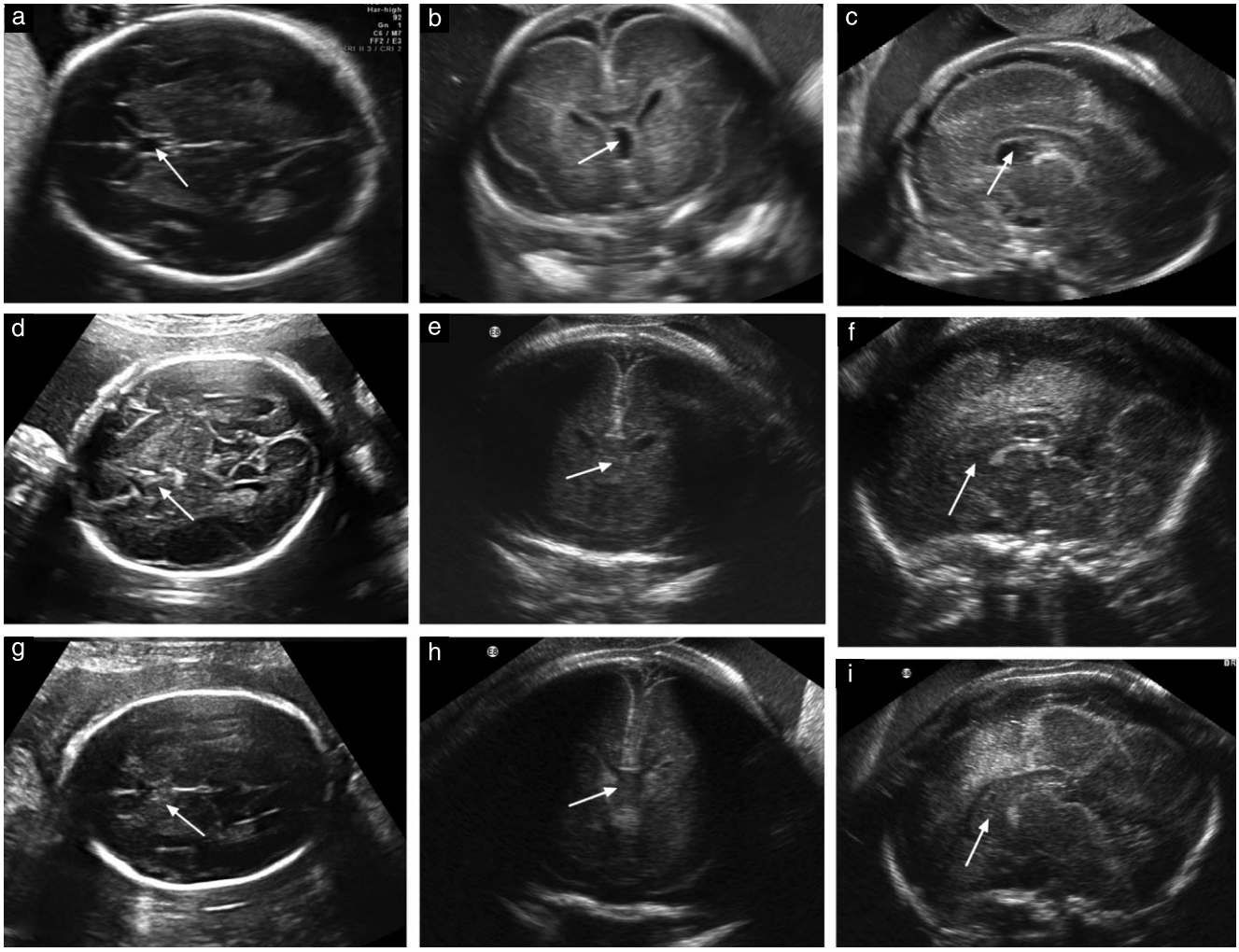

Figure 1 Ultrasound images in orthogonal planes showing the normal appearance of the cavum septi pellucidi (CSP) at 22 weeks of gestation (arrows) (a–c) and non-visualization of the CSP (arrows) in two patients, one at 26 (d–f) and one at 27 (g–i) weeks of gestation. Note that the corpus callosum is not clearly depicted in the coronal and sagittal planes when the CSP is echogenic (e, f, h, i). (a), (d) and (g) show axial views; (b), (e) and (h) show coronal views and (c), (f) and (i) show sagittal views.

DISCUSSION

The CSP is considered an important landmark in ultrasound evaluation of the fetal brain. According to current understanding, fluid should always be visible in the CSP until close to term[5–8]. Pathology and imaging studies performed in premature newborns have consistently demonstrated the presence of a patent CSP in all cases[5,11]. Three ultrasound studies, including a total of 1024 normal fetuses during the second and third trimesters, showed that the CSP could be visualized and measured in 100% of normal fetuses between 20 and 37 weeks of gestation[6–8].

Failure to visualize the CSP during the second half of the second trimester is considered to be almost synonymous with agenesis of the CC and, indeed, five of our patients were referred because of suspected fetal callosal anomalies. However, this study shows that, in some cases, the CSP may not be visualized in spite of a normal CC. Therefore, when the CSP is not visualized one should not assume automatically that the CC is abnormal or missing, but rather, should make an effort to visualize the CC directly.

Visualization of the CC under normal circumstances is greatly facilitated by the fluid contained in the cavum that clearly delineates its lower border. When the superior border represented by the callosal sulcus is blurred, as in our case with associated pericallosal lipoma, visualization of the CC becomes even more difficult.

The pathophysiology of non-visualization of the CSP is not clear. There may be two possibilities: either aberrant fetal development or later accumulation of an intracavitary substance that fills the CSP. It seems more likely that non-visualization of the CSP is due to an arrest in normal development, rather than the possibility that it forms but obliterates later in pregnancy or early childhood. This hypothesis is consistent with the description of normal formation of the CSP by Rakic and Yakovlev[3] who found that, until the second half of pregnancy, the laminae of the CSP are thick and close to each other. In our cases, absence of fluid in the CSP

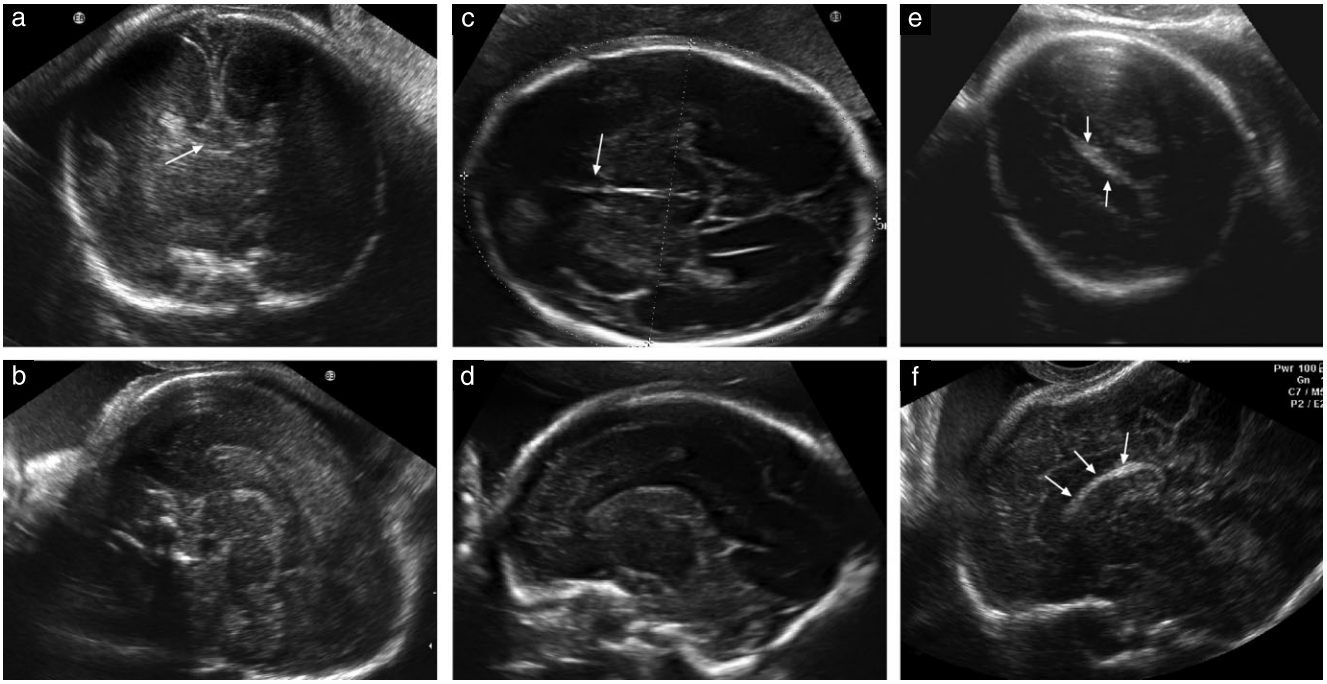

Figure 2 Ultrasound images documenting non-visualization of the cavum septi pellucidi (CSP) in a fetus with pericallosal lipoma diagnosed at 32 weeks. (a) Coronal and (b) median planes at 24 weeks of gestation. The corpus callosum and CSP are not clearly depicted in the coronal plane (arrow). The median plane shows the normal appearance and echogenicity of the corpus callosum but there is no fluid present in the CSP. (c) Axial and (d) median planes at 27 weeks of gestation. The CSP is not present in the axial plane (arrow) and the corpus callosum is less well defined in the median plane. (e) Axial and (f) median planes at 32 weeks of gestation. The midline hyperechogenicity (arrows) is diagnostic of a curvilinear pericallosal lipoma.

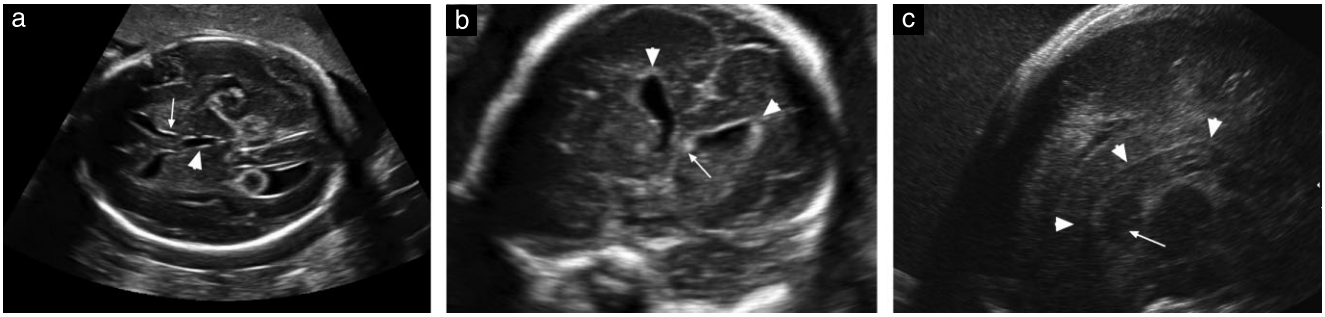

Figure 3 Non-visualization of the cavum septi pellucidi (arrows) at 29 weeks of gestation in a fetus with mild asymmetric ventriculomegaly, dilatation of the third ventricle (arrowhead in a), macrocephaly and bilateral choroid plexus cysts. Note the abnormal shape of the anterior horns of the lateral ventricles (arrowhead in b) and difficult visualization of the corpus callosum (arrowhead in c). A small amount of fluid is present in the cavum Vergae.

was observed as early as 22 weeks' gestation. We feel that this is more likely due to non-formation or non-cavitation of the CSP rather than formation and rapid 'obliteration'. Furthermore, the appearance of the CSP is similar to the rectangular shape observed in normal fetuses at 17–19 weeks and not to the 'Y' shape observed postnatally. However, we cannot absolutely exclude the possibility that, in some cases, non-visualization of the CSP is due to accumulation or deposition of some kind of intracavitary substance or to bleeding. It would be possible to demonstrate this sequence of events only if a fetus were to undergo serial ultrasound examinations that first showed normal formation of the CSP in the first half of gestation and then obliteration in the second half.

Although the number of cases presented is relatively small, it can be concluded that the finding of non-visualization of the CSP in isolation is most probably benign and reflects a subtle brain anomaly that does not affect development. Only one out of 16 children (6%) showed developmental delay. It is important to take into consideration the fact that we did not use a formal developmental test and that this may have prevented recognition of subtle abnormalities. In the presence of associated anomalies the prognosis depends on other brain anomalies. We cannot establish whether the combination of multiple subtle brain anomalies with lack of formation of the CSP increases the risk of abnormal development, particularly in the context of the possible connection between abnormal CSP and psychiatric problems[12].

Table 1 Ultrasound findings and gestational age at time of diagnosis in fetuses with absence of fluid in the cavum septi pellucidi (CSP)

		GA (weeks) at:			
Case	*Referral indication*	*Referral US*	*Index US*	*Failure to visualize**	*US findings*
1	MV	29	29	35	NV-CSP; MV
2	ACC; susp SOD or HPE	24	29	29	NV-CSP
3	Small and echogenic CSP; susp short CC; HC, 5th centile; abnormal optic nerve	23	25	25	NV-CSP
4	NV-CSP	23	26	26	NV-CSP
5	NV-CSP; susp macrocephaly; MV	26	27	27	NV-CSP; HC, 1.8 SD; CPCs; MV; abnormal frontal horns
6	NV-CSP	22	30	30	NV-CSP; aberrant callosal artery
7	NV-CSP; susp ACC	22	33	33	NV-CSP
8	Susp macrocephaly	32	34	34	NV-CSP
9	NV-CSP	23	28	28	NV-CSP; bilateral PVPC
10	Susp PACC; NV-CSP	23	24	24	NV-CSP; poor visualization of splenium; pericallosal lipoma (visualized at 31 weeks)
11	NV-CSP	24	26	26	NV-CSP
12	NV-CSP	27	27.4	27.4	NV-CSP
13	NV-CSP	27	27	27	NV-CSP
14	NV-CSP	27	27.2	27.2	NV-CSP
15	NV-CSP	26	26	26	NV-CSP
16	NV-CSP	23	23	23	NV-CSP
17	NV-CSP	27	27	27	NV-CSP
18	Increased NT (9 mm)	22	22	22	NV-CSP
19	NV-CSP	22	22	22	NV-CSP
20	NV-CSP	24	26	26	NV-CSP
21	NV-CSP	23	27	27	NV-CSP
22	PACC	22	24	27.2	Short CC (below 2 SD)
23	NV-CSP	22	23	23	NV-CSP

*Failure to visualize fluid in the CSP occurred at the time of the index scan in all but two cases (Cases 1 and 22), in which fluid was initially visible but subsequently disappeared. ACC, agenesis of the corpus callosum; CC, corpus callosum; CPC, bilateral choroid plexus cyst; GA, gestational age; HC, head circumference; HPE, holoprosencephaly; MV, mild ventriculomegaly; NT, nuchal translucency thickness; NV-CSP, non-visualization of the cavum septi pellucidi; PACC, partial agenesis of the corpus callosum; PVPC, periventricular pseudocyst; SOD, septo-optic dysplasia; susp, suspected.

Table 2 Delivery characteristics and postnatal follow-up in cases of absence of fluid in the fetal cavum septi pellucidi

Case	*GA at delivery (weeks)*	*Birth weight (g)*	*Neonatal follow-up*	*Age at follow-up (months)*	*Developmental follow-up*
1	40	2840	Normal	23	Normal
2	40	3000	Transient tachypnea	36	Normal
3	40	2800	Normal	19	Infantile hypotonia (resolved)
4	40	3580	Normal	12	Normal
5	30	—	TOP	—	—
6	37	2600	Normal	16	Normal
7	40	3500	Normal	23	Normal
8	38	3500	Normal	21	Normal
9	39	3165	Normal	29	Normal
10	41	4015	Normal	20	Normal
11	38	2400	Normal	26	Motor and language delay
13	39	3125	Normal	4	Normal
15	38	3025	Normal	18	Normal
20	39	3690	Hyperbilirubinemia	14	Normal
21	39	3545	Normal	6	Normal
22	38	3470	Transient tachypnea	7	Normal
23	40	3260	Normal	4	Normal

GA, gestational age; TOP, termination of pregnancy.

In conclusion, we have demonstrated that failure to see fluid in the CSP or seeing increased echogenicity in the region of the CSP is not always associated with callosal abnormalities. However, this finding should elicit detailed imaging and evaluation of the CC, other cerebral structures and the remaining fetal anatomy. When isolated, such a finding may be considered a variation of normal development.

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