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Cavum septi pellucidi (CSP) ratio: a marker for partial agenesis of the fetal corpus callosum

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ABSTRACT

Objective *While complete agenesis of the corpus callosum is often suspected on fetal ultrasound due to absence of the cavum septi pellucidi (CSP), suspicion of partial agenesis of the corpus callosum (pACC) is a challenge since the CSP is almost always present. The aim of this study was to measure the length and width of the CSP and calculate the length-to-width ratio (CSP ratio), and compare these between fetuses with pACC and normal fetuses.*

Methods *In this retrospective case–control study, the length and width of the CSP were measured in the axial plane of the fetal head, and the CSP length-to-width ratio calculated, in 323 normal fetuses and in 20 fetuses with pACC between 20 and 34 weeks' gestation. From the normal population we constructed reference ranges in relation to biparietal diameter (BPD). For all fetuses we calculated Z-scores for the CSP ratio.*

Results *In the normal population, the length and width of the CSP increased with increasing BPD, while the CSP ratio decreased. The CSP was short (< 5th centile) in 85% (17/20) of fetuses with pACC and wide (> 95th centile) in 65% (13/20). The CSP ratio was small (< 5th centile) in 95% (19/20) of pACC fetuses, with 16/20 (80%) having a ratio below an empirical cut-off of 1.5. Analysis of Z-scores showed that fetuses with pACC had a significantly smaller CSP ratio (*$P < 0.0001$*) compared with the normal population.*

Conclusions *Fetuses with a normal-sized corpus callosum have a rectangular-shaped CSP, with a CSP ratio > 1.5 in the second half of gestation. Most fetuses with pACC have an abnormally shaped, wide and short CSP, with a decreased CSP ratio. This simple ratio has the potential to identify fetuses at high risk for pACC. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Complete agenesis of the corpus callosum (cACC) is the most common commissural anomaly diagnosed prenatally[1,2]. In expert hands it is often suspected on imaging of the axial planes, when the cavum septi pellucidi (CSP) is absent and additional signs, such as teardrop-shaped lateral ventricles, are found[1–3]. However, in partial agenesis of the corpus callosum (pACC), often the CSP is present, which makes it difficult to suspect anomalies of the corpus callosum prenatally[4,5]. In recent years, there has been increasing interest in the assessment of changes in the size and shape of the CSP as a clue to the presence of several fetal anomalies, including numerical aneuploidies[4], 22q11 deletion[5] and pACC[6,7]. The aim of the present study, therefore, was to compare the length and width of the CSP in normal fetuses with those in fetuses with pACC, and to propose a new, simple ratio, the CSP ratio (ratio of CSP length to width), for the identification of fetuses suspected of having pACC.

PATIENTS AND METHODS

This was a retrospective case–control study performed on stored images from fetuses between 20 and 34 weeks' gestation. At our centers, the routine comprehensive scan after 20 weeks attempts to include documentation of the CSP in the axial plane of the fetal head, as recommended[8], and in addition visualization and measurement of the length of the corpus callosum. The corpus callosum is visualized either directly, in the midsagittal plane on two-dimensional (2D) ultrasound with color Doppler demonstration of the pericallosal artery, or indirectly, by acquiring a three-dimensional (3D) volume with multiplanar reconstruction. All examinations are performed using high-resolution ultrasound equipment (Voluson E8 or Voluson E10 machine, GE Medical

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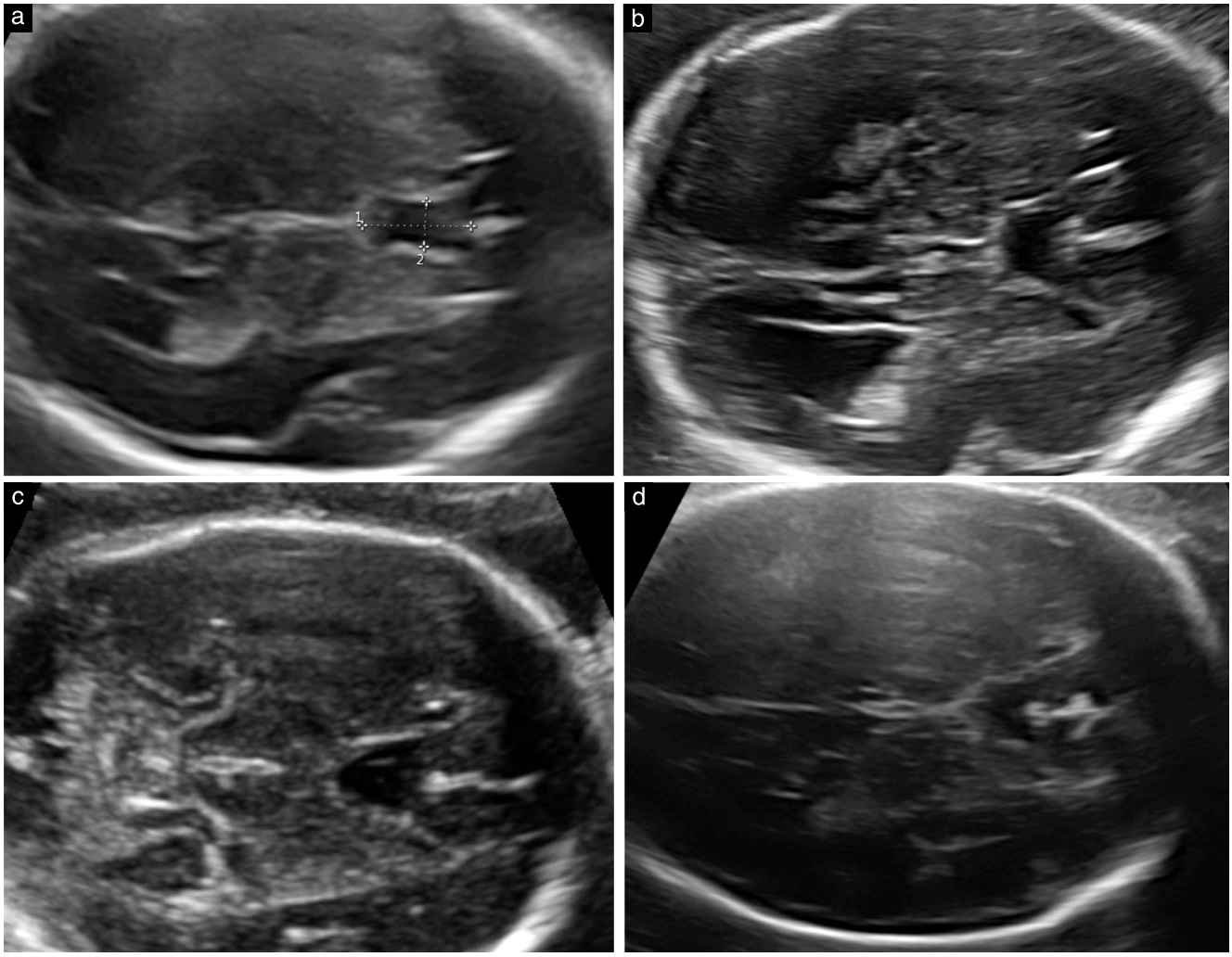

Figure 1 Axial planes of fetal head showing: (a) measurement of width and length of normal cavum septi pellucidi (CSP) at 23 weeks; and (b,c,d) cases of partial agenesis of corpus callosum between 23 and 29 weeks of gestation, with typical abnormal shape of CSP, which is shorter, wider and more square or circular in shape.

Systems, Zipf, Austria) and convex transabdominal probes (RAB 4–8, RM-6C or RAB6C transducer). All ultrasound images are stored in an image archiving system (Viewpoint®, GE Medical Systems), which allows offline measurements. As a standard requirement of our institutions, all patients provided signed informed consent for the fetal examination and agreed to storage of digital images for quality control and later data evaluation. The study included healthy fetuses and fetuses diagnosed with pACC.

For the normal population, we searched the databases of both centers over the 2-year period of 2014 and 2015 for cases in which a 2D image of the corpus callosum with a length measurement was available. Fetuses with only a reconstructed corpus callosum from a 3D volume were excluded. For evaluation of the CSP, the fetal head had to be insonated in the transventricular plane. In this plane, the complete CSP had to be clearly visible (Figure 1). Additional criteria for inclusion were singleton pregnancy and gestational age $20+0$ to $34+0$ weeks of gestation, according to last menstrual period and confirmed by an early crown–rump length measurement. The following conditions were criteria for exclusion: twin pregnancy, fetal growth restriction, diabetic pregnancy and presence of any intracranial or extracranial abnormality or chromosomal aberration.

For the pACC population, the databases were searched for cases with an anomaly of the corpus callosum. Those with cACC and absent CSP, were excluded. Included were all cases with pACC and a CSP present (Figure 1). pACC was defined as interrupted or short corpus callosum, with anteroposterior length $< 5^{th}$ centile[9,10]. Fetuses with microcephaly, holoprosencephaly or a thickened but not shortened corpus callosum were excluded. Only images from the first examination in which the diagnosis was suspected were considered. When an anomaly of the corpus callosum is suspected, the patient is offered transvaginal fetal neurosonography, fetal magnetic resonance imaging (MRI), a diagnostic invasive procedure, a second opinion and counseling by a neuropediatrician. Postnatal records were analyzed in cases with continuing pregnancy and autopsy reports, if available, were evaluated in cases in which the patient opted for termination of pregnancy.

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Data collection and statistical analysis

In both control and study groups, the following data were collected: gestational age at examination, biparietal diameter (BPD, in mm), length of corpus callosum (in mm), associated intracranial signs, such as colpocephaly, ventriculomegaly or anomalies, associated extracerebral anomalies or syndromic conditions, karyotype, if available, and outcome. Length and width of the CSP (in mm) were measured on the images stored in the patient archiving system and the ratio of length to width was then calculated to obtain the CSP ratio. The width of the CSP was measured at the level of the middle of the CSP (Figure 1), as described by Abele *et al.*[4], and not at its largest point[11,12], since some fetuses may have a triangular-shaped CSP[13]. For CSP length, the calipers were placed on the echogenic borders: the callosal sulcus anteriorly and the fornix posteriorly (Figure 1). In order to minimize bias, the final diagnosis was available only at data evaluation. The examiners measuring the CSP were, therefore, unaware of the origin of the images, i.e. whether they were cases or controls. CSP length, width and ratio were then correlated to BPD and regression analysis was performed to assess a possible relationship between length, width, CSP ratio and BPD.

Intraobserver variability was calculated for both operators by having each operator perform two measurements in the same image from 30 normal cases, without seeing the results. Intraobserver agreement was quantified by calculation of the mean difference between measurement 1 and measurement 2 for both operators and using Bland and Altman's 95% limits of agreement (LOA). Interobserver variability was assessed by comparing for the same cases the means of the two measurements of Operators 1 and 2 and calculating the mean difference with 95% LOA. For fetuses with pACC, *Z*-scores were calculated using the CSP ratio equation and analyzed by *t*-test, comparing the mean values of *Z*-scores. Analysis was performed using the statistical packages GraphPad Prism and GraphPad InStat for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

The study population included a total of 343 pregnancies: 323 normal fetuses with a normal corpus callosum length and 20 fetuses with pACC. Detection of pACC was achieved mainly by routine visualization of the corpus callosum in the midsagittal plane at a median age of 22 + 2 weeks with a median BPD of 57 (range, 51–75) mm. Corpus callosum length was, by definition, shorter in cases of pACC than in normal fetuses, using published reference ranges[9]; this was also confirmed after data evaluation, using our own chart, generated from the assessment of normal fetuses (Figure 2).

In the normal population, the length of the CSP increased linearly with increasing head size: CSP length (in mm) = 0.1258 × BPD (in mm) + 2.557 ± 1.211 (Figure 3). The width of the CSP also increased linearly with increasing head size: CSP width (in mm) = 0.006738 × BPD (in mm) + 0.2597 ± 0.6269 (Figure 4). The CSP ratio for the normal population decreased linearly in comparison to head size: CSP ratio = 2.819 – 0.006969 × BPD (in mm) ± 0.3668 (Figure 5).

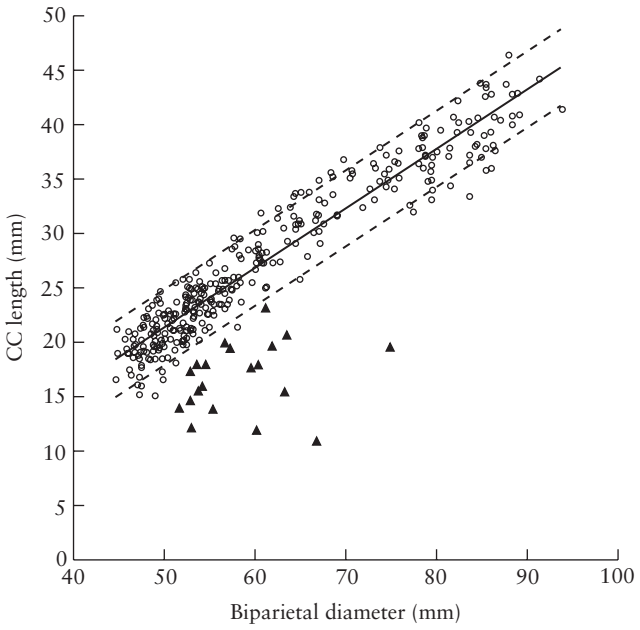

Figure 2 Individual measurements of corpus callosum (CC) length in normal fetuses (○), with reference range (median and 5th and 95th centiles), and in 20 fetuses with partial agenesis of the corpus callosum (▲), in relation to biparietal diameter.

Of the 20 fetuses with pACC, 17 (85%) had a CSP length < 5th centile (Figure 3) and 13 (65%) had a CSP width > 95th centile (Figure 4) compared with our normal population. The CSP ratio showed the best predictive performance, with 19/20 (95%) fetuses < 5th centile and, considering an empirical cut-off of 1.5, 16/20 (80%) of the fetuses had a ratio below this cut-off (Figure 5). Only 8/20 fetuses with pACC had a CSP ratio < 1, i.e. a CSP width larger than its length, the cut-off proposed by Shen *et al.*[6] as being diagnostic of pACC. We did not observe false-positive cases with a normal, long corpus callosum and a low CSP ratio. Figure 6 shows the box-and-whisker plot comparing the CSP ratio *Z*-scores of pACC and normal cases; those with pACC had a significantly smaller CSP ratio ($P < 0.0001$) compared with the normal population.

The Bland–Altman plot with 95% LOA confirmed reliable reproducibility and an absence of systematic error for measurement of CSP width and length and the CSP ratio. The interobserver reliability was found to be high, with intraclass correlation coefficients ranging from 0.904 to 0.978.

Evaluation of the 20 individual cases of pACC showed 11 fetuses with an apparently normal brain, although with a suspected abnormal CSP and anterior complex, as described by the groups of Guibaud and Vinals[13,14]. In the remaining nine cases, there were associated central nervous system (CNS) findings, some in combination, which included colpocephaly ($n = 5$), lissencephaly ($n = 2$), ventriculomegaly ≥ 10 mm ($n = 2$) and an interhemispheric

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cyst ($n = 1$). In eight cases, there were associated non-CNS anomalies, including three chromosomal aberrations, one fetus with Zellweger syndrome diagnosed postnatally, three unknown syndromes and one fetus with ventricular septal defect. There were 13 terminations of pregnancy and seven live births, with one infant death (the case with Zellweger syndrome). The remaining six children were alive and well clinically after 6 months and diagnosis

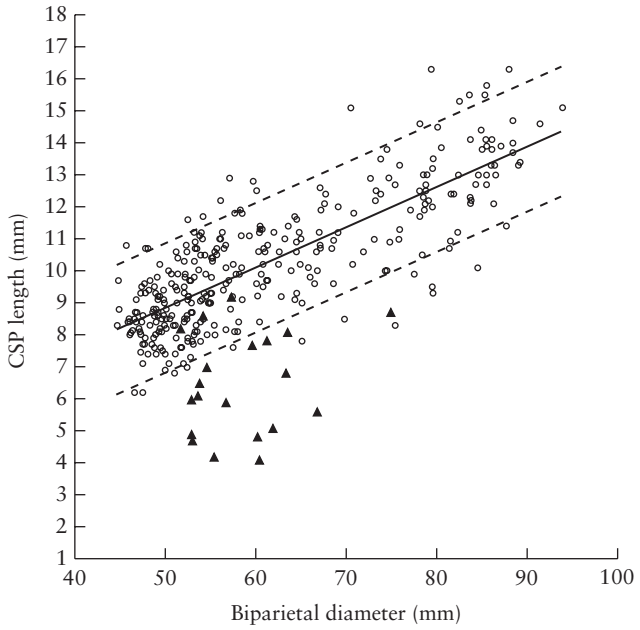

Figure 3 Individual measurements of cavum septi pellucidi (CSP) length in normal fetuses (○), with reference range (median and 5th and 95th centiles), and in 20 fetuses with partial agenesis of the corpus callosum (▲), in relation to biparietal diameter.

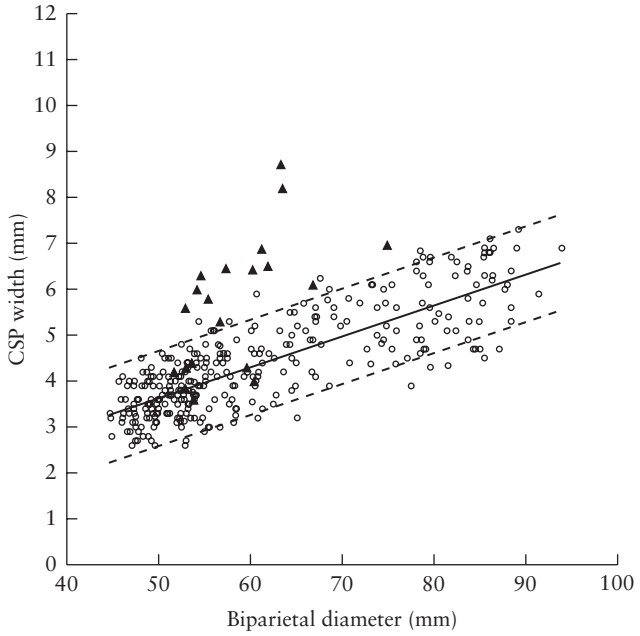

Figure 4 Individual measurements of cavum septi pellucidi (CSP) width in normal fetuses (○), with reference range (median and 5th and 95th centiles), and in 20 fetuses with partial agenesis of the corpus callosum (▲), in relation to biparietal diameter.

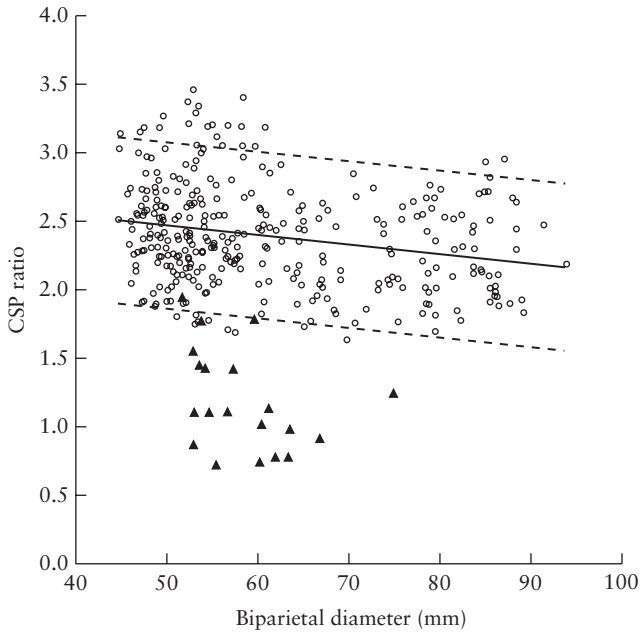

Figure 5 Individual measurements of length-to-width ratio of cavum septi pellucidi (CSP) in normal fetuses (○), with reference range (median and 5th and 95th centiles), and in 20 fetuses with partial agenesis of the corpus callosum (▲), in relation to biparietal diameter.

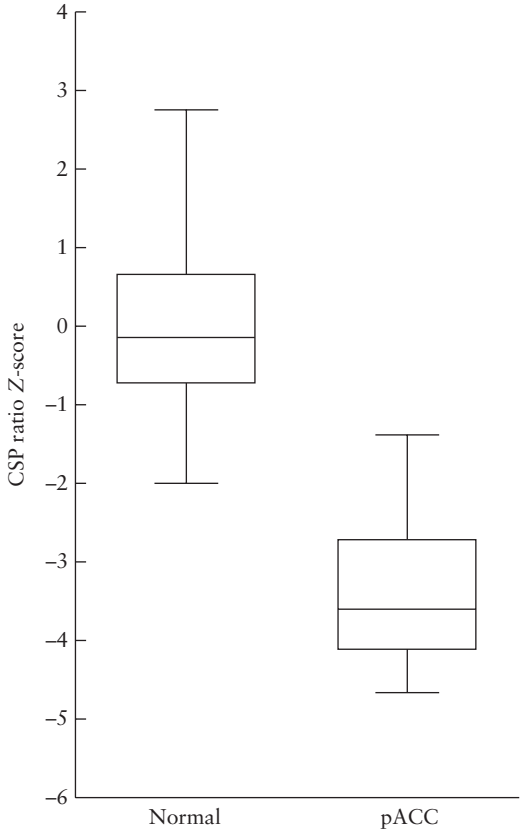

Figure 6 Box-and-whisker plot of cavum septi pellucidi (CSP) ratio (length to width) expressed as *Z*-score in normal fetuses and in study group of 20 fetuses with partial agenesis of the corpus callosum (pACC). Boxes and internal lines show median and interquartile range and whiskers represent range. Fetuses with pACC had a highly significantly smaller CSP ratio ($P < 0.0001$) compared with normal population.

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was confirmed at neonatal neurosonography. Fetal MRI was performed in 13 cases and confirmed the ultrasound diagnosis of pACC. The CSP ratio did not differ between fetuses with and those without CNS anomalies.

DISCUSSION

Visualization of the CSP is part of the International Society of Ultrasound in Obstetrics and Gynecology guidelines for the basic evaluation of the CNS (Figure 1a) and is used as a landmark for identification of the correct axial plane when measuring the BPD[8,15]. Absence of the CSP is now accepted as the main clue for suspicion of cACC, together with other signs in the axial plane of the fetal head, such as a teardrop configuration of the lateral ventricles, wide interhemispheric fissure and, occasionally, borderline ventriculomegaly and a dilated third ventricle[16]. The diagnosis is then confirmed in the midsagittal and coronal views in the context of a fetal neurosonogram[15–17]. While, in most cases, the signs suggesting cACC are well known and the detection rate in experienced hands is high[16], detection of pACC is, according to Ghi *et al*., 'extremely difficult because the corpus callosum is detectable and the axial view of the fetal head is often unremarkable'[18]. Our data show, however, that the measurements of CSP length (Figure 3) and width (Figure 4), and the length-to-width ratio (i.e. CSP ratio) (Figure 5), are important hints with the potential to improve the antenatal detection of pACC.

Herrera *et al*.[7] reported on the increased width of the CSP in 26 fetuses, in 19 (73%) of which there was dysgenesis of the corpus callosum. In a study published recently in this Journal, on fetuses with pACC, Shen *et al*. found that a new hint for pACC was an abnormal, wide CSP, with 'its width larger than its length'[6]. Our study on 20 fetuses with pACC support these observations, showing, in the majority of cases, an abnormal size and shape of the CSP, visualized in the axial view of the fetal head (Figure 1b–d). We found that the CSP was wide in 13 (65%) and short in 17 (85%) of the 20 cases, and the CSP length-to-width ratio was below the reference range in all except one case (19/20, 95%). We believe that the shape and size of the CSP in the axial plane of the fetal head are simple hints for suspicion of an abnormal corpus callosum, which can be confirmed or excluded on visualization and measurement of the corpus callosum itself in the midsagittal view. We found the sign reported by Shen *et al*.[6], of a CSP wider than it is longer, corresponding to a ratio ≤ 1, in only eight (40%) of our 20 cases. Interestingly, this rate of 40% with a CSP ratio < 1 is similar to the 34% rate of abnormal CSP reported by Shen *et al*.[6], while the remaining 66% of their 56 pACC cases were described as being 'normal'. We hope that an improved detection rate of pACC can be achieved by observation of the associated abnormal shape of the CSP and its objective quantification using the CSP ratio. In all suspicious cases, the examiner should obtain a midsagittal view of the corpus callosum to confirm or exclude its abnormal size and appearance. pACC with absence of a CSP has been reported with various different frequencies, including 10%[18], 16%[19] and 21%[6]. In our study, we excluded *a priori* fetuses with pACC in which the CSP was not visualized, as the study focused on the dimensions of the CSP.

It is important to discuss the technique and the level at which CSP is measured, since incorrect measurement may lead to false positives or false negatives with regard to suspicion of pACC. We measured the width of the CSP at the middle, similar to the reported measurements of Abele *et al*.[4], so our charts are comparable to theirs. In two other studies reporting on normal values, the measurements were obtained at the largest part[11,12], which increases the confidence interval. It should be borne in mind that the shape of the CSP is variable between fetuses; a recent evaluation showed that in the transventricular plane, the CSP had a square form in 73% of the normal cases and a triangular form, with anterior base, in 27%[13]. We think that measuring the CSP at the largest part may increase the rate of false-positive diagnosis in normal cases. Interestingly, we found that all except one case in our study had a CSP that was more circular than triangular in shape, so we believe the best level at which to measure its width is the middle.

pACC is diagnosed more frequently in postnatal life than prenatally due to its high association with neurodevelopmental delay[2,20]. However, these studies may have been affected by selection bias, since they included mainly patients with neurological findings. Several prenatal studies have reported similar neurodevelopmental outcome in fetuses with pACC and those with cACC, with delay in about 25–30% of cases; however, there was a lack of long-term follow-up of the surviving children[18,19,21,22]. The high rate of termination reflects the strong association of both forms of callosal anomaly with other structural defects and chromosomal or genetic anomalies[21].

A strength of our study is that we have proposed reference ranges for the CSP width, length and length-to-width ratio, in fetuses with a confirmed normal length and shape of the corpus callosum, and we showed that the majority of fetuses with pACC had abnormal values, particularly of the CSP ratio.

Our study has, however, limitations, especially its retrospective nature and the lack of complete long-term follow-up of the survivors. Another limitation is that it is unknown whether normal fetuses, with a normal-sized corpus callosum, can have a low CSP ratio, a question regarding false positives which can only be assessed in a longitudinal prospective study.

In conclusion, we have shown that evaluation of the CSP in a basic screening examination should include determination not only of its presence or absence but also its shape. An abnormal length-to-width ratio of the CSP, which can be quantified easily, is a simple hint for the possible presence of pACC and should lead to direct insonation of the corpus callosum in the midsagittal view. However, prospective studies are needed in order to show the feasibility of applying this ratio in clinical practice, for the detection of pACC as well as other callosal anomalies.

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