Dear Editor,

According to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology, ‘in the standard transventricular plane only the hemisphere on the far side is usually clearly visualized, as the hemisphere close to the transducer is frequently obscured by artifacts. However, most severe cerebral lesions are bilateral or associated with a significant deviation or distortion of the midline echo, and it has been suggested that in basic examinations symmetry of the brain is assumed’ [1]. Nevertheless, some abnormal conditions of development can affect only one hemisphere, such as unilateral or asymmetric ventriculomegaly, vascular elastic insults (schizencephaly [2], parenchymal or subependymal haemorrhage, infarct, lenticulostriate vasculopathy and porencephaly), cerebral malformations (heterotopia [3] and polymicrogyria), subependymal pseudocysts, white matter disease, calcifications and tumours. Consequently, if the affected side is proximal to the transducer, the abnormality may not be noticed by the operator during the basic examination.

In order to improve the detection of the spectrum of central nervous system anomalies, particularly those unilaterally affecting the hemisphere proximal to the transducer, we suggest angling the transducer.

Fig. 1. Prenatal ultrasound images in a normal 25 weeks’ gestation fetus. From the thalamic axial plane, the transducer was angled towards the cephalic direction in order to display the ventricular and periventricular area, the cerebral parenchyma and the cortex.

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cranially, from the axial transthalamic plane. This manoeuvre may reduce the near-field reverberation to the bony calvarium, but also allows ultrasound access through the sphenoidal and mastoid fontanelles as well as squamosal, coronal and lambdoidal sutures. From the midtrimester onwards, using an angle of up to 45°, the proximal cerebral structures can be visualised and it is possible to check for indications of normality: the lateral ventricle walls (frontal and occipital horn and part of the body) and the periventricular zone are smooth and regular; the choroid plexus fills the cavity of the atrium and is closely opposed to both the medial and lateral walls of the ventricle; the Sylvian fissure is present and its morphology is compatible with the gestational age, and the brain surface and the homogeneity of the white matter are normal (fig. 1).

The visualisation and measurement of the near-field lateral ventricle has been reported in a small number of studies [4–6]. In our experience, observations have allowed us to visualise several other structures, in addition to the lateral ventricle, thus broadening the qualitative evaluation and enabling comparison with the distal hemisphere.

At the level of measurement of the fetal head biometry, an inclination of the probe towards the cephalic direction provides a sequence of views of proximal structures of the hemisphere usually thought to be obscured in routine examination. Therefore, we suggest integrating the investigation of the proximal hemisphere into the routine cerebral sonographic analysis in order to improve the detection of cerebral anomalies (fig. 2).

**References**


Anterior and posterior complexes: a step towards improving neurosonographic screening of midline and cortical anomalies

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KEYWORDS: anterior complex; central nervous system; fetus; posterior complex; prenatal diagnosis

ABSTRACT

Objective To describe the anatomical structures that form the anterior (AC) and posterior (PC) complexes of the fetal brain and to categorize their anomalies in fetuses with cerebral abnormalities.

Methods We analyzed retrospectively volume datasets from 100 normal fetuses between 20 and 30 weeks’ gestation. On the axial transventricular plane, our analysis of the AC included the interhemispheric fissure (IHF), the callosal sulcus (CS), the genu of the corpus callosum (CC), the cavum septi pellucidi (CSP) and the anterior horns (AH) of the lateral ventricles. The PC included the splenium of the CC, the medial wall of the lateral ventricles, the CS and the parieto-occipital fissure (POF). We then categorized AC/PC findings in 32 fetuses with agenesis of the septi pellucidi, schizencephaly, callosal dysgenesis, cortical malformation and hypoxic-ischemic brain injury.

Results The structures forming the AC and PC were visible in 100% and 92%, respectively, of normal cases. In the AC, the CSP was square-shaped in 73% of cases and it was triangular in 27%; the AH was comma-shaped in 92% of cases and triangular in the remainder. In the PC, the splenium of the CC interrupted and bridged the midline and was delimited posteriorly by the CS and the IHF. The POF was visible posteriorly. We categorized AC and PC abnormalities according to the main deviation from normality in their anatomical structures. The AC was abnormal in 30/32 cases and the PC was abnormal in 16/32 cases. In the two cases with normal AC, the PC was abnormal.

Conclusion Normal appearance of AC and PC seems to be a strong indicator of fetal central nervous system normality. Morphological abnormalities in both complexes are robust markers of midline defects, but not exclusively so. The majority of fetuses with cortical malformations showed a defect in the AC. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

In screening for fetal brain anomalies, several authors have emphasized recently the usefulness of standardizing the measurement of ventricular size, carrying out routine examination in the axial planes of specific structures, such as the Sylvian fissure, the interhemispheric fissure (IHF) and the cavum septi pellucidi (CSP) or using a combination of both techniques. The option of incorporating direct views to help visualize relevant anatomical structures, such as the corpus callosum and the cerebellar vermis, has also been discussed.

This highlights the need to continue perfecting methods of ascertaining normal cerebral development, whilst ensuring such methods are potentially replicable globally. One of the most recent proposals has been to consider the anterior complex as a group of anatomical structures visible in the routine transventricular (TV) imaging plane that is useful for improving the detection of midline cerebral anomalies. The structures included in this complex suggest that the range of potential suspected lesions is broader than those related to the midline alone.

In fact, we believe that it is important to visualize not only the anterior anatomical complex of the midline but also structures located posteriorly in the midline, in particular the splenium of the corpus callosum, the medial wall of the lateral ventricles, the callosal sulcus and the parieto-occipital fissure; we refer to this group of structures as the ‘posterior complex’.

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Figure 1 (a,b) Ultrasound image and diagram of normal anterior complex in a 24-week fetus, indicating interhemispheric fissure (IHF) (1), callosal sulcus (2), genu of the corpus callosum (3), cavum septi pellucidi (4) and anterior horns (AH). (c,d) Sagittal (c) and axial (d) planes from a transvaginal three-dimensional acquisition in a normal 26-week fetus. Reference dot (arrow) is positioned at the level of the genu of the corpus callosum, a structure of the anterior complex. *, Cavum septi pellucidi.

The purposes of this study were: 1) to describe, in a normal series of fetuses, both the anatomical structures that form the anterior and posterior complexes and the sonographic axial plane in which these can be visualized; 2) to describe and categorize, in a group of fetuses covering a broad spectrum of cerebral pathologies diagnosed prenatally, the anomalies visualized in both complexes.

METHODS

In order to assess visualization of both complexes and to characterize their anatomical structures, we selected randomly from Clinica Sanatorio Aleman’s database for retrospective analysis three-dimensional (3D) volume datasets obtained routinely in 100 normal fetuses aged 20–30 (mean, 24) gestational weeks. The datasets were acquired transabdominally during 2009 using a Voluson 730 Expert (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine equipped with a RAB 4–8-MHz probe. Our center routinely keeps back-up copies of still images, videoclips and 3D volumes of the different anatomical structures from all examinations. All acquisitions were performed at the level of the TV plane, as reported previously. For the purposes of this study, all cases were followed up by telephone until 2 years of age; all displayed normal postnatal development.

The acquisition planes of the 3D volume datasets were displayed with 4DView software (GE Healthcare Ultrasound) by obtaining parallel sections from a reference slice to show several axial planes from the TV plane. Multiplanar correction of the axial cephalic plane was performed to avoid oblique-plane-induced asymmetry. The anterior complex comprised the group of structures visible in the TV plane, corresponding, from anterior to posterior, to: the IHF, the callosal sulcus, the genu of the corpus callosum, the CSP and, laterally, the anterior horns (AH) of the lateral ventricles (Figure 1). Slicing cranially from the TV plane, the posterior complex included, from anterior to posterior: the splenium of the corpus callosum, the callosal sulcus, the IHF, the parieto-occipital fissure and, laterally, the medial wall of the lateral ventricles (Figure 2). Particular attention was paid to the characteristics of each of these structures, their appearance and their anatomical relationships, in order to define a pattern of normality for this range of gestational ages.
Anterior and posterior complexes of the fetal brain

Figure 2 Ultrasound images (a,c) and diagram (b) of normal posterior complex in a 24-week fetus. Part (c) shows the oblique to midline disposition of the lateral ventricles and their choroid plexuses (lines). CP, choroid plexus; POF, parieto-occipital fissure; S and arrow, splenium of the corpus callosum; CS, callosal sulcus; IHF, interhemispheric fissure.

Table 1 Categorization of anterior and posterior complex abnormalities according to brain pathology and findings of principal anatomical structures in 32 fetuses

<table>
<thead>
<tr>
<th>Brain pathology</th>
<th>Anterior complex</th>
<th>Posterior complex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>IHF</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-lobar/alobar</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Middle interhemispheric variant</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>Agenesis of the septi pellucidi</td>
<td>4</td>
<td>N</td>
</tr>
<tr>
<td>Schizencephaly</td>
<td>2</td>
<td>N</td>
</tr>
<tr>
<td>Callosal dysgenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete agenesis</td>
<td>5</td>
<td>W</td>
</tr>
<tr>
<td>Partial agenesis</td>
<td>6</td>
<td>N/D</td>
</tr>
<tr>
<td>Hypoplasia*</td>
<td>5</td>
<td>N</td>
</tr>
<tr>
<td>Thick corpus callosum†</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>Malformation of cortical development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodular heterotopia</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>Periventricular heterotopia</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>Caudate hamartoma (TSC)</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>Hemimegalencephaly – PMG</td>
<td>1</td>
<td>D</td>
</tr>
<tr>
<td>Syndrome (Smith-Lemli–Opitz)</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>1</td>
<td>N</td>
</tr>
</tbody>
</table>

*One case associated with lissencephaly and microcephaly. †Associated with nodular heterotopia. AH, anterior horn of lateral ventricle; Atyp, atypical shape; CS, callosal sulcus; CSP, cavum septi pellucidi; D, distorted; GCC, genu of the corpus callosum; IHF, interhemispheric fissure; LV, lateral ventricle; N, normal; NS, not seen; PMG, polymicrogyria; POF, parieto-occipital fissure; SCC, splenium of corpus callosum; TSC, tuberous sclerosis complex; U, underdeveloped; W, widened.

We also analyzed 32 fetuses with a broad spectrum of brain pathology (Table 1) to evaluate the anatomical abnormalities seen in both complexes. All pathological cases were studied with transabdominal and transvaginal neurosonography using a Voluson E8 ultrasound machine (GE Healthcare Ultrasound) equipped with a RAB 6D and a RIC 5–9D probe. Diagnoses were confirmed by intrauterine or postnatal magnetic resonance imaging (MRI), karyotyping and/or postmortem or neonatal follow-up, allowing us to categorize anomalies detected in our case studies according to the most obvious abnormal findings.

Definitions

The IHF was defined as ‘distorted’ if it had lost its characteristic linear form from anterior to posterior, and ‘widening’ referred to an observed interhemispheric separation. The callosal sulcus was defined as ‘distorted’ if a deviation was observed from the lateral ‘T’-shape formed with the IHF. The corpus callosum was defined qualitatively depending on whether it was not seen at all or its size seemed too thin or too thick in comparison to the normal cases studied. The AH was defined as ‘dysmorphic’ if it lacked a comma or triangular shape. Within this latter group, we further noted those cases with a quadrangular dysmorphic appearance, i.e. noting those whose AH included at least one acute angle. The parieto-occipital fissure was defined as ‘overdeveloped’ or ‘underdeveloped’ according to its appearance in comparison to normal findings in fetuses of the same gestational age. Table 1 summarizes the abnormal findings in both complexes.
Figure 3 Diagrams showing normal variation of cavum septi pellucidi (CSP) and anterior horn (AH) morphology: (a) comma shape of AH and square form of CSP; (b) comma shape of AH and triangular form of CSP; (c) triangular shape of AH and square form of CSP; (d) triangular shape of AH and triangular form of CSP. *, Genu of the corpus callosum; CS, callosal sulcus; IHF, interhemispheric fissure.

Figure 4 Sagittal (a) and axial (b) display of a transvaginal three-dimensional acquisition in a normal 26-week fetus. Reference dot (arrow) is positioned at the level of the splenium of the corpus callosum, as a structure of the posterior complex. *, Cavum vergae; CP, choroid plexus; IHF, interhemispheric fissure.

RESULTS

We found that the structures forming the anterior complex were visible in all normal cases. As shown in Figure 1, the anterior complex includes the IHF, which lies in a line perpendicular to the callosal sulcus. These echogenic structures contrast with the anechoic CSP. On the anteroposterior line from the IHF and callosal sulcus to the CSP, the genu of the corpus callosum is seen (Figure 1). Its appearance is subtle at around 20 weeks’ gestation, and it becomes increasingly evident as gestation progresses. Likewise, the callosal sulcus becomes more evident as gestation advances, with the cingulate sulcus becoming visible at around 30 weeks at the level of the IHF. At the TV plane, the CSP had a square form in 73% of the normal cases and a triangular form, with anterior base, in 27%. Lateral to the CSP, the AH had a comma shape in 92% of the normal cases and a triangular shape, with lateral base, in the remaining cases (Figure 3). The AH proximal to the transducer was not seen in only three of the normal cases, perhaps due to the low quality of 3D acquisition.

The posterior complex could be seen in 92% of the normal cases, and was not visualized when the volume acquisition was of poor quality (n = 3) or there were artifacts (n = 5). It was obtained by slicing cranially starting from the TV plane, in parallel axial sections. From anterior to posterior, the splenium of the corpus callosum had a hypoechoic sonographic appearance that interrupted and bridged the midline (Figure 4) and was delimited posteriorly by the callosal sulcus and the IHF, both of which showed a geometric layout as described above for the anterior complex. When the cavum vergae was present, the anterior delimitation of the splenium was more evident. Posterior to the callosal sulcus, the ‘diamond shape’ of the parieto-occipital
fissure was easily visible. Laterally, the medial wall of the lateral ventricle with its choroid plexus could be seen.

The structures forming both complexes were subtle close to 20 weeks, becoming more evident as gestation progressed.

An abnormal anterior complex was seen in all five cases of complete agenesis of the corpus callosum (ACC). In each of these, widening of the IHF was observed and the callosal sulcus, the genu of the corpus callosum and the CSP were not visible. Moreover, in all five, the AH was dysmorphic, forming a sharp angle at its anterior end. In only one of the six cases of partial ACC was the IHF distorted and the genu not visible, corresponding to a fetus with Aicardi syndrome in which only the body of the corpus callosum could be seen. In five of the six cases, there was an atypical shape of the CSP (neither square- nor triangular-shaped) and there was a dysmorphic AH in three of the six cases, none of these being quadrangular. Among the five cases with hypoplastic corpus callosum, the genu was thin in two and not seen in one. Two of the five cases had a CSP atypical in shape and four had a dysmorphic AH, with one of these having a quadrangular shape. A displaced unilateral AH was seen in a case of intraventricular hemorrhage Grade 3 (Figure 5). A distorted callosal sulcus was seen in a case of hamartoma of the caudate nucleus and also in a case of nodular heterotopia. In both of these cases, the CSP had an atypical shape (Figure 6).

Regarding the posterior complex, in four of five cases with complete ACC, widening of the IHF was observed. The splenium was not seen in any of these five cases. Of the six cases with partial ACC the splenium was seen in none, while the callosal sulcus was not visualized in five. Widening of the IHF, parallelism between the lateral ventricles and ascent of the third ventricle were observed in the case of Aicardi syndrome. The splenium appeared thin in three of the five cases of hypoplastic corpus callosum and was not seen at all in one case. In these five cases the IHF was seen as normal, but in three the callosal sulcus was not seen. The body of the lateral ventricle was fused in a case of middle interhemispheric variant of holoprosencephaly (HPE) (Figures 7 and 8). The parieto-occipital fissure was not seen in two cases of complete ACC and in one case of lissencephaly, and it was defined as underdeveloped for gestational age in seven cases.

Both complexes were abnormal in the two cases of HPE. In the four cases of agenesis of the septi pellucidi, the
region of AH communication had an atypical shape, with a ‘crescent moon’ form, though the posterior complex was normal in all of these. In both cases of schizencephaly (one unilateral and the other bilateral, both frontoparietal), the CSP was atypical in shape; the AH was dysmorphic in the unilateral case (Figure 9) and was fused in the bilateral case, and the posterior complex was normal in both cases.

Figure 7 Ultrasound image (a) and diagram (b) of an abnormal posterior complex in a 24-week fetus with a middle interhemispheric variant of holoprosencephaly. Part (c) shows intrauterine magnetic resonance image (MRI) obtained at 31 weeks’ gestation. C, interhemispheric cyst; CP, choroid plexus; PH, posterior horn. There is an abnormal midline connection of the cerebral hemispheres and no separation of the parietal region of the lateral ventricles (arrows). The diagnosis was also confirmed by postnatal MRI.

Figure 8 Transvaginal sagittal (a) and coronal (b) ultrasound images at 22 weeks’ gestation in same fetus as in Figure 7. Parts (c) and (d) show corresponding magnetic resonance images at 31 weeks. Arrows indicate abnormal shape of corpus callosum. dc, dorsal interhemispheric cyst; white asterisk, medial choroid plexus; black asterisk, fusion of parietal region of the lateral ventricles.

Twelve of the 32 cases had diverse abnormalities of cortical development, 11 of which had an abnormal anterior complex. Six of these also had associated anomalies of the corpus callosum, the remaining five having an atypically shaped CSP. All six of those with abnormalities of cortical development but no associated anomalies of the corpus callosum had dysmorphic AH (Figures 10
Anterior and posterior complexes of the fetal brain

Figure 9 Diagram (a) and ultrasound image (b) of an abnormal anterior complex in a 23-week fetus with unilateral frontoparietal schizencephaly (hemisphere proximal to the transducer). A distorted interhemispheric fissure (IHF), an atypically shaped cavum septi pellucidi (CSP) and a dysmorphic quadrangular-shaped proximal anterior horn (AH) were seen. (c,d) Coronal (c) and axial (d) T2-weighted magnetic resonance images obtained at 29 weeks’ gestation.

DISCUSSION

Axial views of the fetal head are the pillars of the basic sonographic examination of the fetal central nervous system. Recently, visualization of the anterior complex in axial planes has been proposed to improve the detection of midline abnormalities; these authors went beyond the IHF and CSP to include elements of sulcation (callosal sulcus), a segment of the corpus callosum (genu) and the frontal horns of the lateral ventricles.

Our study, descriptive in nature, demonstrates the structures that form the anterior complex and their anatomical appearance in a normal population of fetuses between 20 and 30 weeks of gestation. Moving cranially from the TV plane, we also describe the posterior complex, which has additional structures that can also be considered markers for normal intrauterine brain development. At this gestational stage, determination of the ultrasonographic pattern is an essential diagnostic tool.

Several reports have demonstrated the relevance of visualization of the CSP and its different forms,
Figure 10 Ultrasound image (a) and diagram (b) of an abnormal anterior complex in a 23-week fetus with hypoplastic corpus callosum and subependymal heterotopia. A dysmorphic quadrangular-shaped proximal anterior horn (AH) was seen. Parts (c) and (d) show heterotopic gray matter nodules (arrows) protruding into the ventricles at 17 weeks (c) and at 23 weeks (d). The final diagnosis of the newborn was congenital alveolar dysplasia and nodular heterotopia, an association that has not been described in the literature.

Figure 11 Ultrasound image (a) and diagram (b) of an abnormal anterior complex in a 26-week female fetus with nodular heterotopia. The callosal sulcus (CS) was distorted, the cavum septi pellucidi (CSP) atypical in shape and both anterior horns (AH) were dysmorphic and quadrangular-shaped.
Anterior and posterior complexes of the fetal brain

Table 2 Summary of six cases of abnormal cortical development with normal corpus callosum and normal posterior complex

<table>
<thead>
<tr>
<th>Case</th>
<th>AC</th>
<th>CSP</th>
<th>AH</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>N</td>
<td>D*</td>
<td>Subependymal heterotopia; congenital alveolar dysplasia</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>Atyp</td>
<td>D</td>
<td>Bilateral frontoparietal open lip schizencephaly; PMG</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>Atyp</td>
<td>D*</td>
<td>Unilateral frontoparietal open lip schizencephaly; PMG</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>Atyp</td>
<td>D</td>
<td>Caudate and cortical hamartoma; TSC</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>Atyp</td>
<td>D*</td>
<td>Hemimegalencephaly; PMG; heterotopia</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>Atyp</td>
<td>D*</td>
<td>Nodular heterotopia</td>
</tr>
</tbody>
</table>

A, abnormal; AC, anterior complex; AH, anterior horn of lateral ventricle; Atyp, atypical shape; CSP, cavum septi pellucidi; D, dysmorphic; D*, dysmorphic – quadrangular shape; N, normal; PMG, polymicrogyria; TSC, tuberous sclerosis complex.

Figure 12 Transvaginal axial (a, b) and midsagittal (c) views of the anterior complex (a) and posterior complex (b) of a 23-week fetus with partial agenesis of the splenium and rostrum of the corpus callosum (Cc). The genu is visible (arrowhead). The splenium is not seen at the level of the posterior complex (¢). CP, choroid plexus; CSP, cavum septi pellucidi; IHF, interhemispheric fissure.

both in pathological conditions and as a variation of normal development\(^5,15\). Yet, in general, this structure is considered mainly as a marker to detect abnormalities of the corpus callosum and central nervous system organization\(^5,16,17\). In our series, the CSP was seen as square- or triangular-shaped in all normal cases and either showed an atypical shape or was not seen at all in 25/32 abnormal cases, confirming the usefulness of its visualization in detecting abnormalities. In the case of intraventricular hemorrhage, the CSP has an atypical shape, perhaps due to the midline shift produced by the hemorrhage, which causes distortion of the IHF and AH and deviation of that structure (Figure 5).

Both anterior and posterior complexes were effective in suggesting the likelihood of midline abnormalities such as HPE, including the middle interhemispheric variant, agenesis of the septi pellucidi and the broad spectrum of callosal dysgenesis. The IHF, the CSP and the segment of the corpus callosum visible in both complexes were defined as abnormal in most of these conditions. Likewise, both cases of schizencephaly had an abnormal anterior complex. Only one case of callosal dysgenesis had a normal anterior but abnormal posterior complex: a case of partial ACC with missing splenium. The callosal sulcus was also not seen at the level of the posterior complex in all cases of partial ACC. Nevertheless, a limitation of examining the posterior complex in the diagnosis of partial ACC is that, as the posterior complex displays posterior commissural fibers, this can be either the splenium in normal fetuses or the posterior part of the body of the corpus callosum in the case of short corpus callosum.

Our study confirms that the morphology of the AH of the lateral ventricles in the anterior complex is comma-shaped\(^14\) or triangular-shaped in normal cases. This triangular pattern has already been reported as normal in other studies\(^18,19\). We observed three possible abnormal variants, which we defined as fused, dysmorphic or displaced. The AHs were fused in agenesis of the septi pellucidi, in schizencephaly and in HPE, an observation compatible with other studies\(^15,20\). A dysmorphic pattern, i.e. one lacking the comma-shaped or triangular morphology, was seen in 19/32 abnormal cases. Of the 12 cases with abnormal cortical development, there was some alteration of the anterior complex in 11 and the posterior complex in seven. Nine of the twelve cases presented dysmorphism of the AH, five of them with normal corpus callosum; in the other four cases this dysmorphism involved a quadrangular shape (Table 2). This shape has been described by other authors, especially in the context of MRI findings, in cases of white-matter lesions in preterm infants\(^21\) and neural tube defects\(^22\). It was also visualized in a case of subependymal heterotopia\(^23\), concordant with our findings. Although further studies are needed, we suggest that ventricular anterior dysmorphism, including the quadrangular appearance, should be seen as an indication to carry out fetal neurosonography or MRI for a more

detailed study of the fetal brain, with special focus on the cortical development. This novel observation is limited by the lack of an exact definition of cortical development malformations and the wide range of associated structural brain abnormalities. Making an accurate diagnosis is difficult when focusing exclusively on the imaging pattern. The third abnormal appearance of the AH, displacement, was observed in a case of intraventricular hemorrhage. Figure 5 shows the external compression of the AH and CSP and subsequent displacement. The presence of ‘midline shift’ in severe brain hemorrhage is fairly well known in neonates, being a frequent cause of neurosurgical intervention. Yet, it should be remembered that asymmetrical AH is a frequent finding in normal fetuses. Besides ventricular measurement, preservation of the AH triangular configuration in coronal views, thin ventricular walls showing only faint echogenicity and lack of increase in size on follow-up scans are clues suggesting normality.

Recently, it has been shown that accurate grading of cortical development is feasible and quick on transabdominal two-dimensional (2D) and 3D ultrasound; in more than 90% of the examinations performed by Pistorius et al., it was possible to visualize the parieto-occipital fissure on both sides in an axial plane, cephalad to the TV plane. This plane is slightly cephalad from the plane of the posterior complex. The plane in which all the structures included in the anterior complex can be visualized is proposed in several practice guidelines for sonographic examination of the fetal central nervous system.

This study revealed four major findings. First, a customary appearance of both anterior and posterior complexes seems to be a strong indicator of fetal central nervous system normality. Second, morphological abnormalities in both complexes seem to be strong markers of midline defects, particularly affecting the corpus callosum. Third, morphological abnormalities in either or in both complexes are not an exclusive hallmark of callosal dysgenesis. The majority (11/12) of fetuses with cortical malformations had defects in the anterior complex and in about 50% the anterior horns had a quadrangular shape. Fourth, systematic evaluation of the anterior and posterior complexes could permit more robust ultrasonographic screening and increase the chance of detecting fetuses with brain abnormalities. Although in our study we used 3D ultrasound for the normal group, both complexes are simple and useful tools that can in fact be integrated into 2D real-time axial routine examination. Further prospective studies involving the general population are needed to confirm these conclusions.

REFERENCES

2D visualization and measurement of the fetal optic chiasm. Improving the counselling of antenatal diagnosis of agenesis of the septi pellucidi

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Abstract

Objective To develop an objective method to visualize and measure the optic chiasm (OC) through a 2D coronal vaginal plane and to report measurements in fetuses with agenesis of the septi pellucidi (SP).

Methods This was a prospective cross-sectional study of 115 morphologically normal fetuses in low-risk pregnancies, between 21 and 30 weeks’ gestation. OC was measured in a coronal plane at the level of the third ventricle and was seen as a horizontally aligned dumbbell-shaped structure of moderate echogenicity. In addition, OC measurements from eight fetuses with agenesis of the SP and complete follow-up were compared to the reference range.

Results OC measurements were obtained in 110 of 115 normal fetuses. OC growth occurred linearly with gestational age. Our method demonstrated good intraobserver repeatability and excellent interobserver reproducibility. Among the eight fetuses with agenesis of the SP, four had normal measurements, and five normal vision postnatally. Pregnancy continued to term in all cases and the follow-up period varied from six months to seven years.

Conclusion Our study demonstrates that it is possible to visualize and measure the OC directly through a 2D ultrasound coronal plane. In fetuses with agenesis of the SP, the morphology and width of the OC visual pathway could prove a relevant tool in assessing its development. It would also provide support to the difficult antenatal counselling when faced with the diagnosis of agenesis of the SP.

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INTRODUCTION

Absence of the septi pellucidi (SP) is considered to be a rare congenital brain malformation. In recent years, identification of this condition is increasing due to the progress in prenatal and neonatal diagnosis. Counselling these patients represents one of the challenges in fetal medicine, once it can be isolated or associated with a wide spectrum of brain defects. Some of these associated anomalies, such as open lip schizencephaly, severe holoprosencephaly, complete agenesis of the corpus callosum and ventriculomegaly can be easily diagnosed with sonography. Others, such as septo-optic dysplasia (SOD) can be difficult to identify by fetal imaging. This condition presents a highly heterogeneous phenotype and is defined by the variable association of hypoplasia of the visual connecting pathways, agenesis of the SP, and/or pituitary endocrine impairment. A wide spectrum of neurological abnormalities associated with SOD has been reported.

Septo-optic dysplasia is usually diagnosed postnatally. Magnetic resonance imaging (MRI) criteria for postnatal diagnosis are direct evaluation of the optic nerves and the optic chiasm (OC). The latter is visualized through the coronal plane. Since agenesis of SP is highly indicative of SOD during fetal life, it would be extremely helpful to evaluate the OC in such cases. Although a normal sized OC does not rule out SOD, a hypoplastic OC associated with absence of the SP gives cause to suspect SOD.

To date, few prenatal studies have carried out evaluations focused exclusively on the posterior optic tracts using three-dimensional (3D) ultrasound. The aim of this study was to develop an objective method for visualizing and measuring OC through a 2D pre-established coronal plane and to document its normal size range throughout gestation. Additionally, the study sought to assess the value of analysing the measurements of a series of fetuses affected by agenesis of the SP.

SUBJECTS AND METHODS

This was a prospective cross-sectional study of 115 morphologically normal vertex fetuses in low-risk pregnancies undergoing routine ultrasound examination at 21–30 weeks. All cases were studied with 2D transvaginal neurosonography performed by a single trained sonographer using Voluson E8 BT13 ultrasound machine (GE Healthcare Ultrasound, Kretz, Austria) equipped with RIC 5-9D vaginal probe. Fetuses with congenital malformations, abnormal karyotype, growth restriction or multiple pregnancies were excluded from the study. All patients gave their informed consent for participation in the study. Gestational age was determined from measurements of the fetal crown-rump length at 11-13 weeks. Fractions of weeks were corrected up to the nearest week, with fractions of ≤4 days assigned to the lower week and ≥5 days to the higher week.

During the coronal approach through the anterior fontanelle, the OC was identified as a horizontally aligned dumbbell-shaped structure of moderate echogenicity located at the midline, occupying a central place in the suprasellar cistern at the level of the anterior-inferior wall of the third ventricle, below the optic recess (Figure 1). Transvaginal fetal neurosonography was standardized by Timor-Tritsch and Monteagudo and the coronal...
plane used in our study corresponds to the mid-coronal-2 plane in their description. Visualising the pulsation of the supracavernous segment of the internal carotid artery immediately below the borders of the OC and the anterior cerebral artery which passes cranially to the OC provided clear anatomical reference points to help define the lateral and superior boundaries of the OC. (Figure 1). The width of the OC was measured by an experienced sonographer in a coronal plane with the callipers touching the inner edge of the slightly echogenic chiasma wall (Figure 2). A three-second clip was stored digitally at this level. All measurements were repeated by a second sonographer, blinded to the first measurements, using the cineloop saved on the ultrasound machine.

Additionally, all fetuses defined as "absence of the cavum SP" or "agenesis of the SP" were selected retrospectively from our single-center database. After excluding anomalies such as holoprosencephaly, callosal agenesis, ischemic-hemorrhagic lesions and severe ventriculomegaly, eight patients scanned between June 2009 and June 2015 with complete follow-up were included in the study. Postnatal ophthalmological examination was available in all cases. Digital video clips and three-dimensional volume datasets from coronal transvaginal neurosonography performed with a similar ultrasound system described previously were used to measure the OC. Measurement of the OC was also compared with its aspect seen in coronal magnetic resonance imaging (MRI) images, whenever this was available.

Statistical analysis

Analysis was performed using measurements of central tendency, dispersion and position for quantitative variables, and frequency distribution for qualitative variables. Centile ranges were calculated and tabulated for consecutive gestational ages (GA) and regression fitness with GA was determined. Linear regression analysis was performed to determine the association of outcome variable with respect to GA, describing the value of coefficient of determination (R2). The level of statistical significance was set at p<0.05.

The agreement between the measurements results of two raters and between two consecutive assessments by the expert assessor were analyzed using the intraclass correlation coefficient (ICC). They were then described using the Bland-Altman plot along with the mean and 95% confidence interval of the difference. The intraobserver variation was calculated from 20 cases, with a week of difference between them. Data was analyzed using the V15 SPSS statistical software and 3.1 Epidat.

RESULTS

Optic chiasm width measurements could be obtained in 110 of 115 (95.6%) normal fetuses from 21-30 weeks gestation. Fetal OC diameter measurements were fitted adequately with a regression linear model as follows: optic chiasm width (OCW) (mm) = 0.078 + (0.275 × GA) where GA is the gestational age closest to the nearest week. There was evidence of increased variability with increasing GA (P <0.001). The increase rate according to GA was equal to 0.275.

There was a linear relationship between GA and OC width (Figure 3). GA explains 32.4% of parameter variability (R2=0.324). Table 1 shows the mean and 3rd, 5th, 95th and 97th centiles for chiasm width measurements at 21–30 weeks. Optical chiasm width in the
50th centile increased throughout gestation (from 5.6 mm at 21 weeks to 10 mm at 30 weeks).

The intraclass correlation coefficients (ICC) were 0.784 (95% CI, 0.45–0.91) for intraobserver and 0.917 (0.88–0.94) for interobserver measurements. The mean was 0.28 (95% CI, −0.11–0.67) for intra-observer and 0.0082 (95% CI, −0.079–0.095) for interobserver and the SD were 0.84 and 0.46 repeatability. Figure 4 represents the Bland–Altman plot for interobserver variability. This plot shows that the difference between two observers of the optic chiasm measurements is close to the mean.

We were able to obtain a complete follow-up for all eight cases with agenesis of the SP. The OC measurement for these cases was carried out retrospectively by an experienced operator, but in three of these it had also been measured during the transvaginal neurosonography, following the same technique described above. Two patients were assessed at different stages of gestation, with OC measurements taken three and six weeks apart respectively (Figure 5). The OC width was lower than the 3rd centile in three fetuses affected by schizencephaly (Figure 6) and in one fetus with severe growth restriction and agenesis of the SP (Figure 7). In the four remaining cases of agenesis of the SP, the width of the OC fell within the normal range for the gestational age (Figure 8). None of these four cases had poor vision and/or nystagmus or clinical signs of both anterior and posterior hypopituitarism. The follow-up periods for these cases ranged from two to six years. The results are summarized in Table 2.

**DISCUSSION**

The optic chiasm is a commissure formed by converging optic nerves anteriorly and diverging optic tracts posteriorly. Its development begins between the fourth and sixth week of gestation forming a later structure with meeting and partial decussation of the optic nerves. Subsequently, the optic tracts grow backward from the OC, terminating in the diencephalon and midbrain. The OC is in direct contact with cerebrospinal fluid (CSF) anteriorly within the subarachnoid space, and posteriorly within the third ventricle, features easily identified with postnatal MRI\textsuperscript{11,12}. The floor of the third ventricle is located above the OC and below it lies the body of the sphenoid bone, typically above the sella turcica\textsuperscript{14}, although the relative position of the chiasm over the sella turcica is variable. In 12% of the population the chiasm is above the tuberculum sellae (i.e. “prefixed”); in 79% it is above the diaphragma sellae; and in only 4% of cases it lies above the dorsum sellae (i.e. “postfixed”)\textsuperscript{11}. However, in MRI studies, these differences in position are not mentioned as interferences in measuring the width of the optic chiasm coronally\textsuperscript{15–18}.

The OC is an important landmark for interpreting MRI examinations of adult and child brains\textsuperscript{16}. A small chiasm can be an indication of several disorders, the most common of which is SOD. The diagnosis of postnatal atrophy or enlargement of the chiasm has mainly been made by qualitative interpretation on MRI; few studies have published normal range size values of OC area and width on coronal MRI images. Wagner et al report that in adults the MRI width of the OC ranged between 10.3mm and 18.3mm\textsuperscript{16}. According to this same study, coronal images provide the most accurate OC measurements\textsuperscript{16}, while coronal images of the brain are a standard sequence for imaging the chiasm and sella. There may be some variation between studies due to section differences, but Wagner et al
study postulates that errors can be minimized by using the section with the largest chiasm measurement\textsuperscript{16}. Measuring OC width is justified by the fact that MRI postnatal studies found that the chiasm height was so small that it led to significant intraobserver and interobserver error\textsuperscript{16}.

Bault et al described the visualization and development of the fetal optic tact using 3D ultrasound, mainly through transabdominal axial acquisition\textsuperscript{10}. Our ultrasound technique showed good intraobserver repeatability and excellent interobserver reproducibility. We believe that visualization of the OC and knowledge of its size can help determine whether an optic chiasm measurement is outside the normal range, thus potentially increasing the likelihood of SOD in utero. A normal OC size does not guarantee normal vision and does not rules out SOD\textsuperscript{2}. Usually, involvement of the visual pathways in SOD carries a much poorer prognosis than endocrine dysfunction\textsuperscript{19}. Moreover, visual deficits are mostly the first presenting sign, whereas endocrine dysfunction may become apparent later on\textsuperscript{20}. Of the eight cases with agenesis of the SP, four had measurements within normal range and long-term follow-up coincided with normal vision. Of the four cases with unusually small OC (cases 5-8), one was a fetus with severe intrauterine growth restriction but normal vision at the 31-month\textsuperscript{'} follow-up. It has been stated that size and volume of intracranial structures are impaired in growth-restricted fetuses and infants\textsuperscript{21,22}. Visual deficit and nystagmus, both signs of SOD\textsuperscript{23}, were diagnosed in three cases of prenatal detection of schizencephaly and small OC. Schizencephaly has frequently been reported associated with SOD\textsuperscript{24-27}. Moreover, in these three cases the OC adopt a different aspect to that described in normal conditions, losing its characteristic dumbbell shape.

Based on our results, fetal OC width measurement is feasible when this structure is seen under direct view on 2D coronal ultrasound. We were unable to get good-quality OC coronal images in only 4.4% of the patients, most commonly due to the impossibility of getting coronal planes due to fetal head position. Limitations in our study include that measurements are made only in vertex presentation. Also the scarcity of cases of agenesis of the SP and the absence of an endocrinological study, a necessary addition to further prospective studies. Despite our abnormal cases included associated brain anomalies that can determine the neurologic outcome, we are aware that the most important contribution of measuring OC is in cases where the septal agenesis is isolated.

In conclusion, this study demonstrates the feasibility of prenatal visualization and assessment of OC development. We provide new reference ranges for OC diameter measured during 2D transvaginal neurosonography which gives evidence that the diameter of the OC increases with GA. Also, we show OC measurements and clinical follow-up in some fetuses with agenesis of SP. Finally, we believe that our study provides a novel parameter that could be useful in assessing and counselling patients with intrauterine signs of septo-optic dysplasia.
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Table 1 Reference ranges for fetal optic chiasm width (mm). GA, gestational age. At 30 weeks gestation, only one fetus was assessed and the optic chiasm width was 10 mm.

<table>
<thead>
<tr>
<th>GA (weeks)</th>
<th>n</th>
<th>3rd</th>
<th>5th</th>
<th>50th</th>
<th>95th</th>
<th>97th</th>
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<tr>
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<td>5.6</td>
<td>6</td>
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<td>15</td>
<td>5.6</td>
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<td>7.5</td>
</tr>
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<td>5.7</td>
<td>5.74</td>
<td>6.5</td>
<td>7.96</td>
<td>8.0</td>
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<tr>
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<td>6.8</td>
<td>9.0</td>
<td>10.0</td>
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<tr>
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<td>7.1</td>
<td>7.85</td>
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</tr>
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<td>3</td>
<td>6.9</td>
<td>6.9</td>
<td>8.2</td>
<td>8.7</td>
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</tr>
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</table>

Table 2 Details of 8 fetuses with agenesis of the septi pellucidi and complete follow-up. * Case with two measurements of the optic chiasm at different gestational age. GA, gestational age; OC, optic chiasm; mm, millimeter; US, ultrasound; ASP, agenesis of the septi pellucidi; b, bilateral; u, unilateral; Schiz, schizencephaly; PMG, polymicrogyria; ante, antenatal; MRI, magnetic resonance imaging; PM, psychomotor.

<table>
<thead>
<tr>
<th>Case</th>
<th>GA (weeks)</th>
<th>OC width (mm)</th>
<th>Centile</th>
<th>Fetal sex</th>
<th>US diagnosis</th>
<th>Current age</th>
<th>ante/postnatal MRI</th>
<th>Outcome</th>
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<td>28/31*</td>
<td>7,7/8.2*</td>
<td>normal</td>
<td>Female</td>
<td>ASP</td>
<td>5 years/11 months</td>
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<td>Normal vision</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>8.5</td>
<td>normal</td>
<td>female</td>
<td>ASP</td>
<td>5 years/11 months</td>
<td>-</td>
<td>Normal vision</td>
</tr>
<tr>
<td>3</td>
<td>24/30*</td>
<td>7,8/8.8</td>
<td>normal</td>
<td>Female</td>
<td>ASP</td>
<td>2 years/3 months</td>
<td>-</td>
<td>Normal vision</td>
</tr>
<tr>
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<td>33</td>
<td>10.6</td>
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<td>Female</td>
<td>ASP</td>
<td>4 years/7 months</td>
<td>-</td>
<td>Normal vision</td>
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<td>5.1</td>
<td>&lt; 3rd</td>
<td>Female</td>
<td>ASP</td>
<td>2 years/7 months</td>
<td>yes</td>
<td>Normal vision</td>
</tr>
<tr>
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<td>29</td>
<td>5.1</td>
<td>&lt; 3rd</td>
<td>Female</td>
<td>ASP - b Schiz</td>
<td>2 years</td>
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<td>Nistagmus. Poor vision. Epilepsy. PM delay</td>
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<tr>
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<td>6.5</td>
<td>&lt; 3rd</td>
<td>Male</td>
<td>ASP - u Schiz</td>
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<td>8</td>
<td>29</td>
<td>4.3</td>
<td>&lt; 3rd</td>
<td>Female</td>
<td>ASP-u Schiz-PMG</td>
<td>6 months</td>
<td>yes</td>
<td>Nistagmus. Right deafness. PM delay. Epilepsy</td>
</tr>
</tbody>
</table>
Figure 1 Transvaginal neurosonography in a 29-week normal fetus. (A) Coronal view through the anterior fontanelle showing the optic chiasm (arrows); *, cavum septi pellucidi delimited laterally by the leaves of the septi pellucidi. (B) In the same fetus, the supracavernous segment of the internal carotid artery (large arrowhead) and the anterior cerebral artery (small arrowhead) were identified.
Figure 2 Transvaginal coronal ultrasound measurement of a normal optic chiasm width at normal 26 weeks gestation fetus.
Figure 3 Reference range for fetal optic chiasm width at 21–30 weeks, calculated by linear regression (5th, 50th and 95th centiles) \( (r=0.33) \)
Figure 4 Bland–Altman plot for interobserver variability, showing the difference between pairs of fetal optic chiasm width measurements plotted against their mean. Mean difference (---) and 95% limits of agreement (----) are shown.
Figure 5  Reference range for fetal optic chiasm width at 21–30 weeks, calculated by linear regression (5th, 50th and 95th centiles) (r=0.33), showing the eight cases of agenesis of the septi pellucidi (case 1, ■; case 2, ◆, there are two different measurements at 28 and 31 gestational age; case 3, ◆; case 4, ◆; case 5, ★, there are two different measurements at 24 and 30 gestational age; case 6, ◆; case 7, ■, case 8, ▲) From all the cases of agenesis of the septi pellucidi, the optic chiasm width in the cases 5, 7 and 8 are below the limits of the confidence interval according to the linear regression curve.
Figure 6 Small and abnormal shape optic chiasm (arrows) in a 28 weeks gestation fetus (A and B) with unilateral schizencephaly (*) and agenesis of the septi pellucidi. The small chiasm was confirmed at 30 weeks gestation by coronal T2 fetal magnetic resonance imaging (C).

Figure 7 Optic chiasm (OC) in a 25 weeks gestation fetus with agenesis of the septi pellucidi (*) and severe intrauterine growth restriction (A). OC width (B) was below the 3rd centile. At 55 months of age, she presents normal development and vision.
Figure 8 Normal aspect (A) and size (B) of the optic chiasm in a 30 weeks gestation fetus with agenesis of the septi pellucidi (*). At 51 months of age, he presents normal development and vision.