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ORIGINAL ARTICLE

Sonography of fetal holoprosencephaly: a guide to recognize the lesser varieties

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ABSTRACT

Background: Alobar holoprosencephaly (HPE) is easily detected during a first-trimester screening examination, conversely, recognizing the lesser varieties may be difficult even in the second trimester.

Objectives: To describe the imaging findings of a cohort of fetuses with holoprosencephaly (HPE) and to elucidate the appearances of the different anatomical varieties.

Materials and methods: We reviewed medical records and stored images of pregnant women referred to our clinic because of a diagnosis or the suspicion of various forms of HPE. We reported the imaging characteristics, the presence of other associated anomalies, magnetic resonance findings, karyotype and autoptic examinations when available.

Results: Alobar forms show great distortion of normal brain anatomy, with a single ventricle detectable during the first trimester of pregnancy. Extracerebral, face and karyotype abnormalities are often associated. In semilobar and lobar forms the septum pellucidum is typically absent in axial planes, with fused frontal horns, while posterior fossa is often normal. At multiplanar neurosonogram, anomalies involving corpus callosum and cortex development can be detected. Face abnormalities are mild in lobar forms: receding forehead, various degrees of hypotelorism and the presence of a single central maxillary incisor are reported.

Conclusions: The alobar forms are detectable since the first trimester, with a peculiar single ventricle and extremely frequent extracerebral and karyotype abnormalities. The semilobar and lobar forms are more challenging and the diagnosis is easily missed in a mid-trimester screening exam unless a careful evaluation of both *cavum septi pellucidi* and frontal horns as well is conducted.

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Holoprosencephaly; central nervous system; ultrasound

Introduction

Holoprosencephaly (HPE) is a complex brain malformation characterized by variable degrees of incomplete cleavage of the two hemispheres and the development of midline structures [1–3]. Prognosis is variable but is most frequently dismal. The most severe forms are frequently associated with aneuploidies, trisomy 13 and triploidy in particular, and result in miscarriage or perinatal death; the less severe forms are compatible with postnatal survival but in most cases are associated with delayed neurocognitive and motor development, epilepsy and endocrine disorders due to pituitary deficiency [4–6].

HPE encompasses a continuum of brain malformations. Classically, three forms with progressive severity have been described: lobar, semi-lobar and alobar. However, there is a broad spectrum of presentation with overlapping findings [7,8]. Thus far, prenatal studies have insisted on the alobar form, the most severe one, which is characterized by typical and very extreme findings [9]. The experience with less severe forms is more limited and the findings that have been described are variable and much more subtle [10–14].

The purpose of this study is to present our experience with the sonographic diagnosis of the different types of HPE, with emphasis on the findings that are documented in the views that are employed in screening examinations [15–17].

Materials and methods

We reviewed medical records of women referred to our center for a suspected cerebral anomaly from

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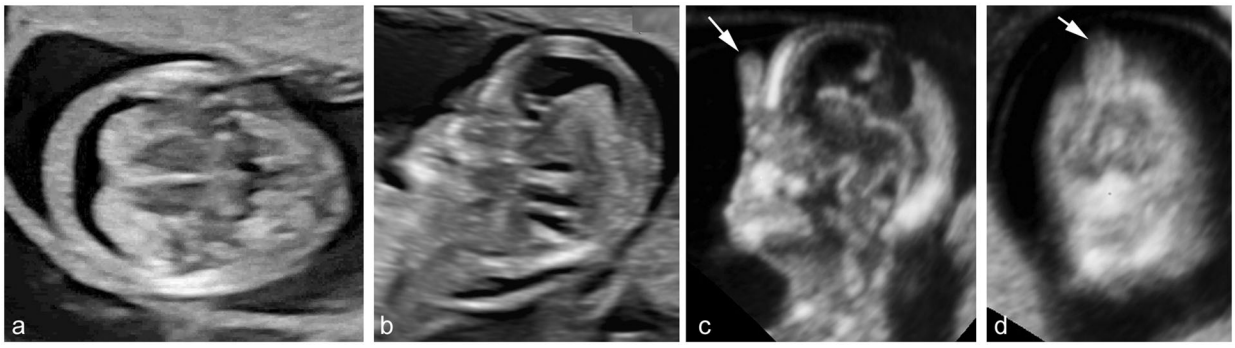

Figure 1. Alobar holoprosencephaly in fetuses at 11–13 weeks' gestation: (a) transverse view of the cephalic pole demonstrating an absence of the midline and single choroid plexus; (b) flat profile; (c)proboscis (arrowhead); (d) proboscis (arrowhead) and cyclopia.

January 2007 to December 2020, then selected the fetuses diagnosed with holoprosencephaly. Among women referred to our Center for suspected fetal anomalies (excluding congenital heart diseases), central nervous system anomalies are almost 25%. Among those, holoprosencephalies are about 6% (1.4% overall). These numbers, of course, don't reflect the real prevalence among the general population, as in our center we don't perform screening examinations.

We researched the results of the sonographic examinations as well as the genetics studies, magnetic resonance imaging and postnatal studies when performed. The cerebral findings visible on the axial views recommended for a fetal screening examination [15–17] were noted. Neurosonographic examinations were performed in each case, transvaginally whenever possible [18].

Ethics

The study conforms to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008, and was approved by the ethical committee of our hospital (653/2021/Oss/AOUBo). A consent form signed at recruitment was obtained from eligible patients.

Results

During the study period fetal HPE was diagnosed in 15 cases; of these 10 (67%) were of the alobar type and 5 of less severe varieties. One case has been previously reported [19].

Alobar HPE

Most cases were diagnosed in the late first trimester (median 12 weeks, range 11–16 weeks) and were always referred from screening facilities with a presumptive diagnosis of alobar HPE. The findings were very homogeneous: in all cases, a standard axial view of the head the midline revealed an absence of the midline echo and one single undivided choroid plexus, in association with severe cranio-facial anomalies or a very flat fetal profile (Figure 1) The median week for a referral at our center was 12 weeks (11–16). Nine patients underwent termination of pregnancy with dilatation and curatteage; one patient with discordant twins decided to continue the gestation. The karyotype was obtained in 8/10 cases, and was normal in 2 cases without detectable microarray anomalies; there were 5 cases of trisomy 13, and 1 case of 68, XX. Associated extracerebral anomalies were present in 9 fetuses (Table 1).

Less severe varieties of HPE

These patients were referred to our center for abnormal cerebral findings detected during the second-trimester screening at a median gestational age of 21 weeks (range 19–26) with the tentative diagnoses of an absence of the *cavum septi pellucidi* in 3 cases, ventriculomegaly and agenesis of the corpus callosum in one case each (Table 2). In the axial views commonly employed for screening the most remarkable finding was either the complete absence or the difficult visualization of the frontal complex (Figure 2). In one case multiplanar sonography revealed fusion of the anterior hemispheres and a single crescent-shaped ventricular cavity, that were not easily seen in axial planes. This fetus was eventually diagnosed with semilobar holoprosencephaly after the termination of pregnancy (Figure 3). In the remaining four cases a

Table 1. Characteristic of alobar holoprosencephaly.

Case	Gestational age at referral (weeks)	Screening examination	Facial anomalies	Other anomalies	Karyotype
1	12	Alobar HPE	Face not examined	Omphalocele	Normal
2	11	Alobar HPE	Face not examined	None detected	68XX
3	12	Alobar HPE	Flat profile	None detected	Not available
4	11	Alobar HPE	Cleft lip and palate	Great artery transposition	Not available
5	12	Alobar HPE	Face not examined	Omphalocele, single umbilical artery, univentricular heart, scoliosis	46XY + 13der
6	13	Alobar HPE	Flat profile	atrioventricular canal	Trisomy 13
7	11	Alobar HPE	Flat profile, hypotelorism	truncus arteriosus, syndactyly	Normal
8	16	Alobar HPE	Flat profile, microphthalmia, cleft lip and palate,	Ventricular septal defect, cardiac disproportion, renal dysplasia	Trisomy 13
9	14	Alobar HPE	Hypertelorism	Atrioventricular canal	Trisomy 13
10	13	Alobar HPE	Cyclopia and proboscis	Omphalocele, univentricular heart	Trisomy 13

HPE, holoprosencephaly.

Table 2. Characteristic of lobar and semilobar HPE.

Case	Gestational age at referral (weeks)	Screening examination	Neurosonography	Facial anomalies	Other anomalies	Karyotype	Termination of pregnancy
1	22	Ventriculomegaly	Semilobar HPE	Hypotelorism, microphthalmia, cleft palate	Double outlet right ventricle, duodenal atresia	Not performed	No
2	20	Agenesis of corpus callosum	Lobar HPE	Single median incisor, flat profile, hypotelorism	None	46, XX	No
3	19	Absence of septum pellucidum	Semilobar HPE	Single median incisor at autopsy	None	not performed	Yes
4	26	Absence of septum pellucidum	Lobar HPE	Flat profile	None	46, XY	No
5	21	Absence of septum pellucidum	Lobar HPE	None	None	46, XY	Yes

HPE, holoprosencephaly.

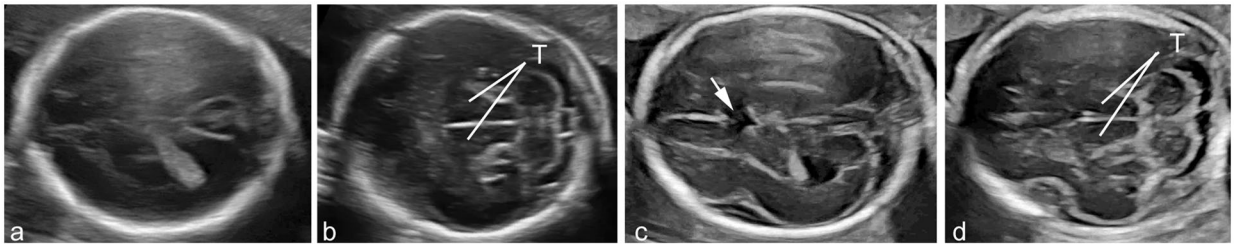

Figure 2. (a,b) Transventricular and transcerebellar view in a fetus with semilobar holoprosencephaly at 22 weeks; the *cavum septi pellucidi* and frontal horns are not seen; (c,d) transventricular and transcerebellar view in a fetus with lobar holoprosencephaly at 22 weeks; a box-like structure resembling a *cavum septi pellucidi* (arrowhead) is present, but the frontal horns normally found on both sides of it are not seen (T, thalami).

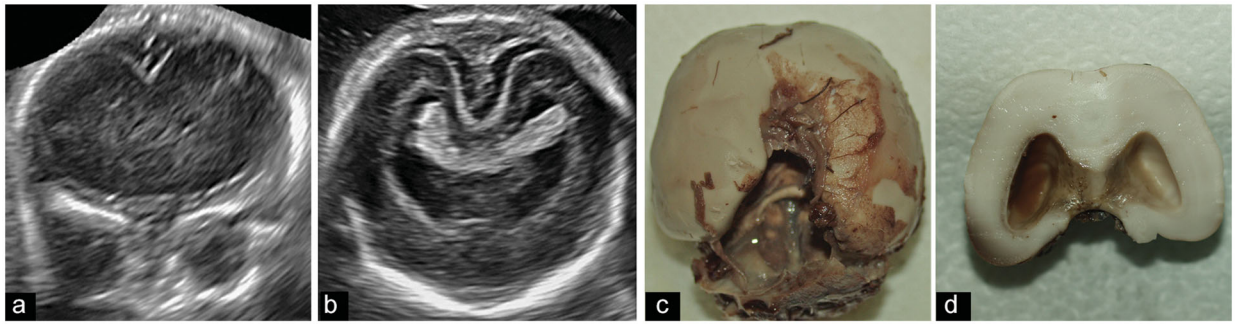

Figure 3. Semilobar holoprosencephaly: (a) there is no evidence of the midline in the anterior brain; (b) a single crescent-shaped ventricular cavity with well developed posterior horns is seen; (b,c) autoptic specimen demonstrating the fusion of the anterior brain and the well-developed cavities of the posterior horns.

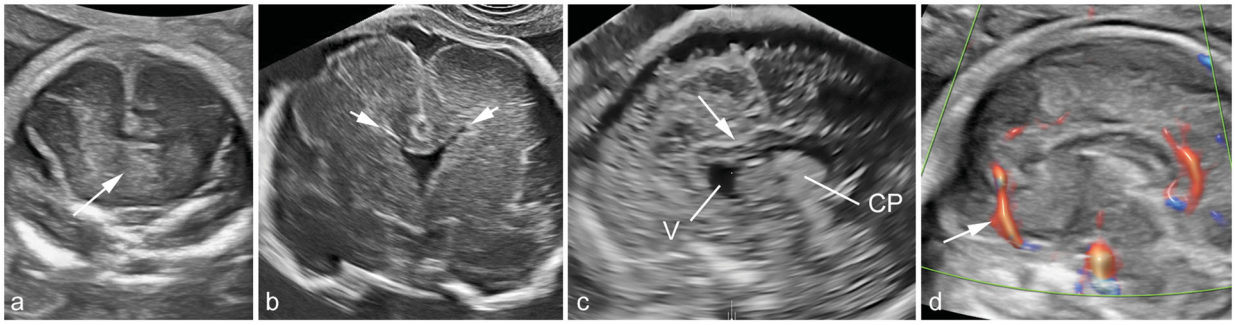

Figure 4. lobar holoprosencephaly: (a) incomplete separation of the frontal lobes (arrowhead); (b) absence of the septum pellucidum with diminutive frontal horns; (c) in a sagittal view an incomplete severely dysmorphic corpus callosum-like structure (arrowhead) is seen bridging over the single ventricular cavity (V) (CP: choroid plexus); (d) color Doppler revelas an abnormal anteriorly displaced course of the anterior cerebral artery (arrowhead).

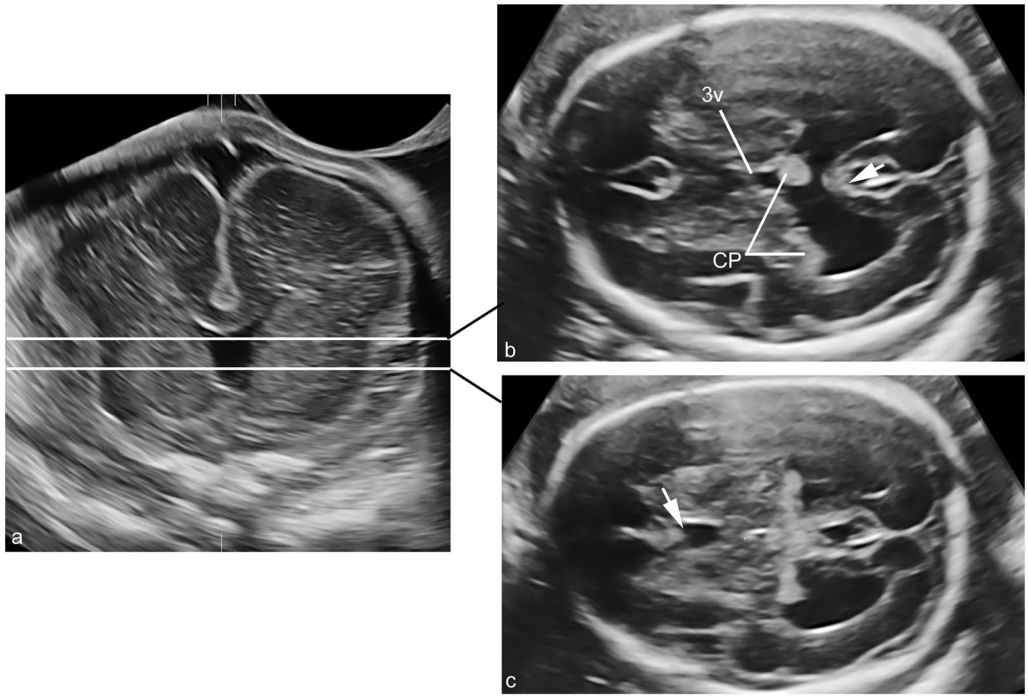

Figure 5. Axial planes demonstrating typical findings of lobar holoprosencephaly (a) a coronal scan is provided for orientation; (b) scan obtained at a slightly superior level than the transventricular plane demonstrates the fusion of the third ventricle (3v) and bodies of lateral ventricles; a parenchymal bridge connects the parietal lobes (arrowhead); (c) in the transventricular plane a cavum septum pellucidum like structure is seen (arrow).

box-like structure interrupting the anterior midline resembling the *cavum septi pellucidi* was seen in the axial views, but the frontal horns could not be clearly identified (Figure 2). Multiplanar sonography demonstrated the typical findings of lobar holoprosencephaly: incomplete separation of frontal lobes, diminutive frontal horns without evidence of the septum pellucidum, fusion of the midbodies of the lateral ventricles that communicated amply with the inferior third ventricles, an irregular corpus callosum-like structure, anterior displacement of the loop formed by the anterior cerebral arteries [2,12–14,19–21] (Figure 4). The most consistent finding was however the presence of a large communication between the bodies of the lateral ventricles and a parenchymal bridge connecting the parietal lobes, which could be easily demonstrated in an axial view slightly superior to the standard transventricular plane [16] (Figure 5).

One fetus had a cleft lip and palate. In the remaining cases, there were no overt cranio-facial anomalies malformations although meticulous scanning revealed subtle findings in most: the profile was slightly flat in three cases, and a single median incisor tooth [22,23] was found in two fetuses (Figure 6). Magnetic resonance imaging was performed in 3 cases and confirmed the sonographic findings. Among those women, two

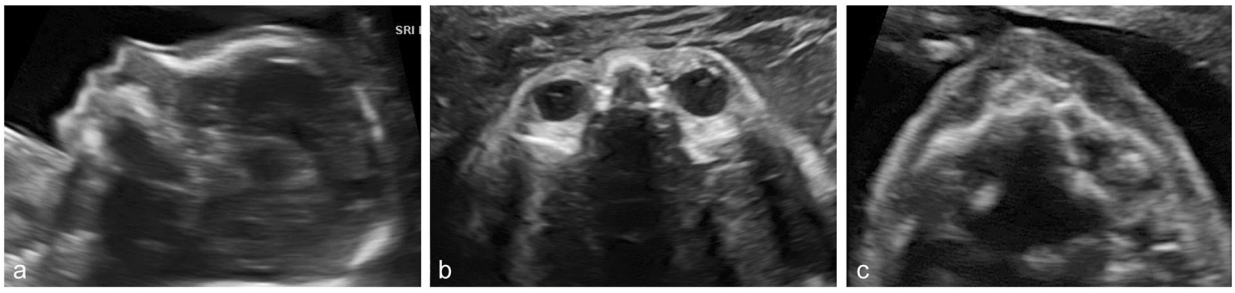

Figure 6. Subtle dysmorphism in fetuses with semilobar and lobar holoprosencephaly: (a) slightly flattened profile (semilobar); (b) narrow spaced orbits and small corpus vitreum (lobar); (c) single median incisor tooth.

underwent termination of pregnancy with the autoptic examination confirming the diagnosis. Among the non-interrupted fetuses, one was lost at the follow up deciding to deliver elsewhere, one died after a few days and the third is now six-month-old, suffering from epileptic seizures not responsive to drugs, needing deep brain stimulation.

Discussion

Principal finding

HPE is a continuum of cerebral anomalies but from the point of view of fetal sonography, it can be subdivided into two rather different entities. Alobar HPE is consistently associated with obvious and specific findings that are easily identified since the late first trimester. The other varieties of HPE are far more difficult to identify and are usually recognized only in the second or third trimester of pregnancy. Lobar holoprosencephaly, a condition usually associated with severe neurologic sequelae [21], and the second most common type encountered in our series, is particularly elusive. The general view is that the most important indicator of this condition in screening exams is the failure to visualize the *cavum septi pellucidi* or anyhow the membranes of *septum pellucidum* [16] In our experience however a box-like structure closely resembling the *cavum septi pellucidi* is present. As expected, most of these fetuses had no obvious cranio-facial malformations [6]. We confirm that the sonographic diagnosis of a single median incisor tooth, a finding typically associated with HPE, is possible since early gestation [22]. A schematic representation of the characteristics of holoprosencephaly varieties in axial and coronal planes is reported in Figure 7.

Comparison with previous studies

The experience with the prenatal diagnosis of lesser varieties of HPE is sparse, and in most of the cases described thus far, ventriculomegaly was present [14,24]. Our experience suggests that recognizing the lobar type, in particular, is challenging when the ventricles are of normal size. Indeed, the abnormal findings in the views commonly used for screening are scanty and may be easily overlooked by a sonographer without a specific competence in neurosonography. Our results are in line with the observation that a *cavum septi pellucidi*-like structure may be observed with different prosencephalic malformations [25,26]. Conversely, we remark that the neurosonographic examination allowed an accurate diagnosis in all cases, using criteria previously described [2,5,9,11–14,19,27]. We have also found that a simple axial plane obtained at a slightly superior level than the standard transventricular view [16] demonstrates very specific findings of lobar holoprosencephaly: central fusion of the bodies of lateral ventricles and a parenchymal bridge between the parietal lobes (Figure 5).

Strength and weakness

The main strength of our study is that we report a large series of cases of fetal HPE, a rare malformation [28], and that we have focused upon the findings that can be useful to identify this anomaly in screening examinations. We do acknowledge two weaknesses. First, most cases of alobar HPE underwent a destructive procedure for pregnancy termination and postnatal confirmation was not possible. However, the sonographic findings of this condition are extremely specific and well-established [9] and the pattern of associated anomalies is typical [12]. Second, the other cases of HPE were eventually categorized as semilobar and lobar by prenatal or postnatal MRI and/or autopsy. The fourth type of HPE, the middle interhemispheric variant is also recognized [29,30], that closely resembles the lobar type. The differentiation between the two entities depends upon postnatal MRI, clinical assessment and genetic testing. Prenatal diagnosis has been reported [31] but differentiation from the lobar type is difficult and it is uncertain whether this is possible in all cases with prenatal imaging or even dissection of abortive specimens [32].

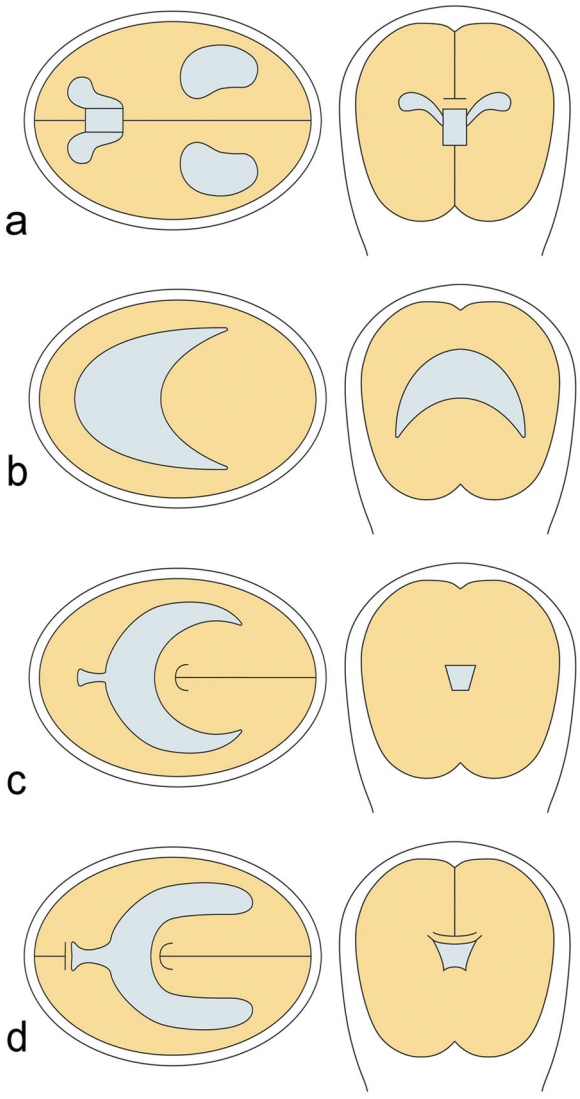

Figure 7. Schematic representation of the characteristics of holoprosencephaly varieties in axial and coronal planes. Normal brain (a): well-developed posterior ventricles, *cavum septi pellucidi* clearly separated from frontal horns. Alobar HPE (b): no interhemispheric fissure, single rudimentary ventricle, fused thalami, associated facial anomalies. Semilobar HPE (c): no midline structures in the anterior part of the brain. Lobar HPE (d): middle line well developed but an absence of the septum pellucidum and wide communication between frontal horns.

We can not exclude therefore that some of our cases of lobar HPE were in reality middle interhemispheric variants. Differentiation would be important because the middle interhemispheric variant is associated with neurologic sequelae that tend to be less severe than the lobar type [6].

Clinical implications

Our results suggest that alobar HPE rarely escapes a first-trimester screening examination performed after 10 weeks [16,33]. Conversely, recognizing the lesser varieties may be difficult even in the second trimester. The ventricular cavity within the frontal area simulates the presence of the *cavum septi pellucidi* and we subscribe to the view of Cagneaux and Guibaud [25] that in screening exams attention should be paid not to the *cavum* only but rather to the entire anatomical complex formed by the cavum and the frontal horns on the sides.

Disclosure statement

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