

# Prenatal diagnosis of lobar holoprosencephaly

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## ABSTRACT

*Lobar holoprosencephaly was identified with sonography in 12 fetuses between 21 and 35 weeks' gestation. A confident diagnosis was made in each case by a mid-coronal view of the brain demonstrating absence of the cavum septum pellucidum with fusion and squaring of the frontal horns. The only associated anomaly was Dandy–Walker malformation that occurred in three cases. All fetuses had mild to severe ventriculomegaly. Five pregnancies were terminated; there was one spontaneous abortion and six fetuses were delivered at term. A ventriculo–peritoneal shunt was implanted in four. Follow-up was available for five and revealed severe mental retardation in each case. Lobar holoprosencephaly is amenable to prenatal ultrasound diagnosis, although a differentiation with other cerebral malformations may be difficult at times. The outcome of affected infants remains uncertain, but neurological impairment occurs frequently.*

## INTRODUCTION

Holoprosencephaly is a complex developmental anomaly of the forebrain frequently associated with facial dysmorphism. It is rarely found at birth, the incidence varying in different series between 1 : 2500 and 1 : 16 000<sup>1</sup>. However, holoprosencephaly is probably associated with a high intrauterine fatality rate, and it is likely that obstetric sonographers will encounter this condition more frequently than expected from epidemiological surveys at birth. This concept is supported by one study on voluntary terminations of pregnancy in the first and second trimester, in which holoprosencephaly was found in 1 of 250 conceptuses<sup>2</sup>, and by the considerable number of reports on cases, diagnosed antenatally with ultrasound, published in the past few years<sup>3–7</sup>.

The holoprosencephalic sequence is commonly regarded as the consequence of a failed diverticulation of the embryonic prosencephalon. It has been postulated that the primary disorder resides in the precordial mesenchyma, which is responsible for the induction of

both forebrain and median facial structures. Although a continuum of cerebral and facial anomalies is found with this condition, a widely accepted classification recognizes three major varieties: the alobar, semilobar and lobar types<sup>1</sup>.

The criteria for the sonographic diagnosis of fetal alobar<sup>3–6</sup> and semilobar holoprosencephaly<sup>7</sup> are well established. Conversely, experience with prenatal diagnosis of the lobar type is limited. This is not surprising, as in these cases the anatomical derangement is much more subtle. In pathological studies, lobar holoprosencephaly is described as a brain almost completely divided into two distinct hemispheres but for a variable degree of fusion at the level of the cingulate gyrus and frontal horns of lateral ventricles. The cavum septum pellucidum is always absent. The olfactory bulbs and tracts and the corpus callosum may be absent, hypoplastic or normal<sup>1</sup>. The most relevant findings for a neuroradiological diagnosis in infants include absence of the cavum septum pellucidum with incomplete segregation of the frontal horns and third ventricle, squaring of the roof of the frontal horns, incomplete interhemispheric fissure and falx cerebri<sup>8,9</sup>. A previous report has indicated that these findings may be demonstrated with antenatal sonography<sup>10</sup>. We herein describe our experience with 12 cases of lobar holoprosencephaly recognized *in utero* with ultrasound.

## METHODS

This report is based upon 12 cases in which a prenatal sonographic diagnosis of lobar holoprosencephaly was made at the authors' institution between 1983 and 1991. The antenatal diagnosis was always confirmed, either at autopsy or by postnatal neuroradiological evaluation. All cases were referred from level 1 ultrasound facilities, with a suspicion of fetal ventriculomegaly between 21 and 35 weeks' gestation. Sonographic examinations were performed with a Platinum system (Philips Ultrasound,

Santa Ana, California), and Ansaldo 450 and 590 equipment (Ansaldo, Genoa, Italy). In all cases, a detailed examination of the intracranial anatomy was performed. Axial, coronal and sagittal views of the cerebral structures were always obtained. In fetuses presenting by the vertex, vaginal scans were also obtained when necessary for better elucidation of the fetal brain. A thorough examination of the fetal face was performed as well, including measurement of the interorbital distance<sup>11</sup>. The degree of ventriculomegaly was assessed by measurement of the atrial width. In normal fetuses, this measurement is constant between 15 and 40 weeks, and we have previously reported a normal value of  $6.9 \pm 1.3$  mm<sup>12</sup>. A measurement of 9 mm, which corresponds to 4 standard deviations above the mean, has been suggested as the upper limit of normal<sup>13,14</sup>. It has also been suggested that ventriculomegaly should be divided into two different clinical entities: borderline enlargement (atrial width 10–15 mm) and overt hydrocephalus (atrial width more than 15 mm)<sup>15</sup>. This categorization will be used in the following discussion.

Cases of fetal cerebral malformations, which were recognized with ultrasound during the same period and which presented problems of differential diagnosis with lobar holoprosencephaly, were also reviewed and will be discussed later.

## RESULTS

Prenatal diagnosis of lobar holoprosencephaly was made in six cases prior to viability. Five couples opted for pregnancy termination and a spontaneous abortion occurred in the remaining case. Autopsy was performed in all fetuses and confirmed the prenatal diagnosis. A typical cerebral specimen is shown in Figure 1. In six cases referred after viability, the infants were delivered at term, and the diagnosis was confirmed by neuroradiological studies.

The most informative antenatal sonographic view was a mid-coronal scan of the fetal brain. This view reproduces the mid-coronal computed tomographic scan that was found most helpful in recognizing lobar holoprosencephaly postnatally<sup>8,9</sup>. A comparison between an intra-uterine sonogram and the corresponding specimen after autopsy is shown in Figure 2 and demonstrates an excellent correlation. The cavum septum pellucidum is absent and the fused frontal horns communicate centrally with the slightly enlarged third ventricle. The thalami are slightly rounded, closely resembling the bulb-shaped appearance typically described in the alobar and semilobar varieties of holoprosencephaly. The roof of the frontal horns is typically squared. In all fetuses, the coronal and sagittal scans demonstrated the presence of the corpus callosum, although in some instances there was the impression that it was smaller than usual and had an abnormal configuration (Figure 3). In Figures 4 and 5 the antenatal scans in one case are compared with postnatal ultrasound and nuclear magnetic resonance. The amount of information derived from the prenatal

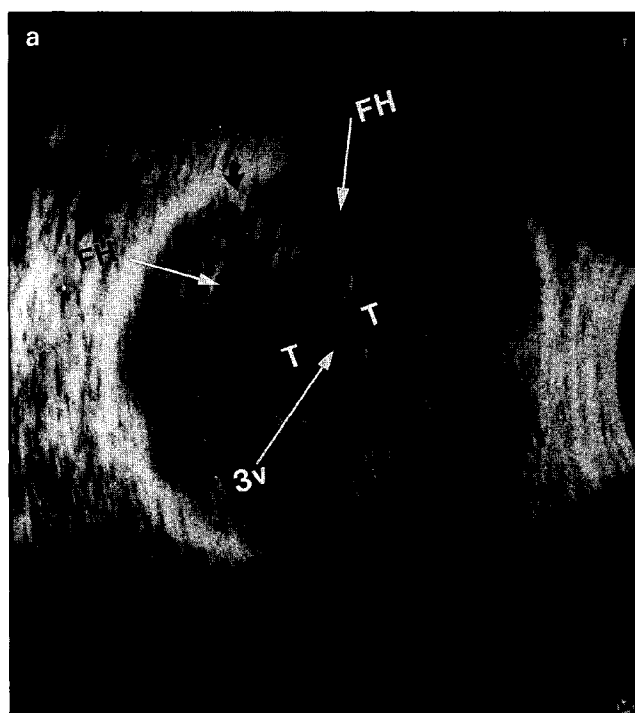


**Figure 1** The brain of a 24 weeks' fetus with lobar holoprosencephaly. There is fusion of the frontal cortex in the inferior aspect of the brain (\*), and the olfactory tracts are typically absent. The convolitional pattern is compatible with the gestational age

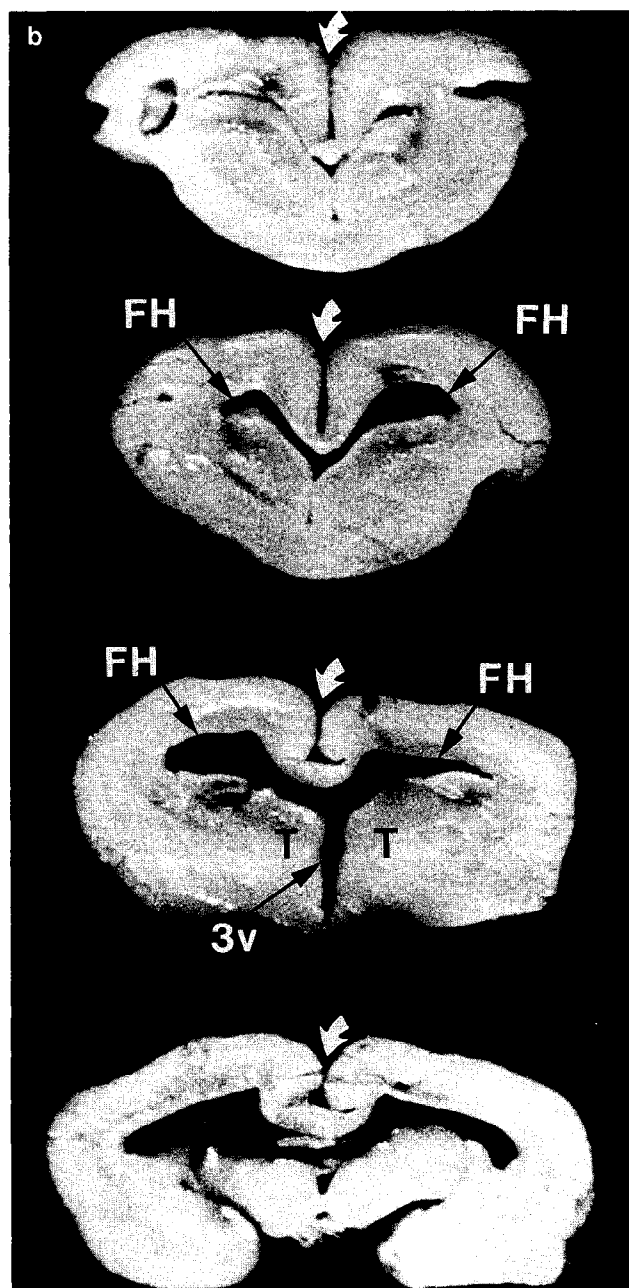
sonograms is remarkable, and can be compared favorably with that obtained from the neonatal studies.

Upon referral, five fetuses had borderline enlargement of the lateral ventricles (atrial width 10–15 mm) and seven had overt hydrocephalus (atrial width 16–23 mm). In one case, the enlargement of the lateral ventricles was markedly asymmetrical. Three fetuses had concomitant Dandy-Walker malformation (Figure 5). This was always diagnosed antenatally by using criteria previously described<sup>16</sup>. No other associated anomalies were found. In particular, the facial structures were always normal, with interocular distances within normal range. This was confirmed by careful clinical inspection of abortion specimens and surviving infants. Karyotype was obtained antenatally in ten cases and postnatally in one, and was always normal (46, XX in six cases; 46, XY in five). No evidence of either maternal diabetes or congenital infections could be found. The familial history was negative for congenital malformations in each case.

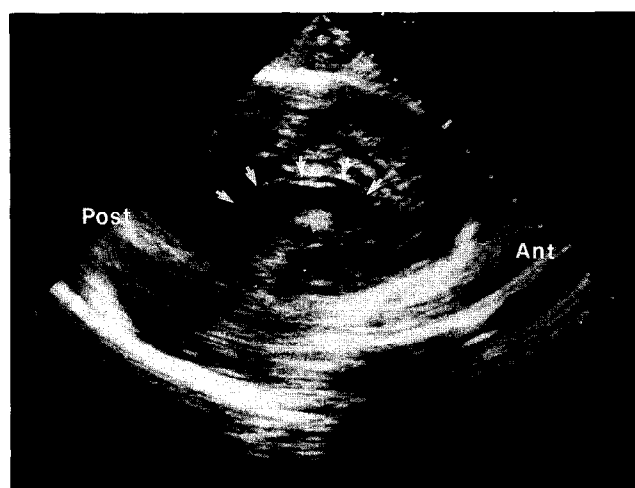
Of the six fetuses continuing to term, two were delivered vaginally and four by Cesarean section (three because of macrocephaly, one because of a previous Cesarean section). All infants survived and are presently alive. Four underwent ventriculo-peritoneal shunting. In one case with associated Dandy-Walker malformation, borderline ventriculomegaly was present at the first examination at 26 weeks and worsened during the following weeks. The fetus developed overt macrocephaly and was eventually delivered by Cesarean section. Severe hydrocephalus with increased cerebrospinal fluid pressure was documented at birth and a ventriculo-peritoneal shunt was inserted in the neonatal period. The other fetus with lobar holoprosencephaly and Dandy-



**Figure 2** The same case as in Figure 1. (a) Antenatal mid-coronal scan of the fetal brain demonstrating mild ventriculomegaly, fusion and squaring of the roof of the frontal horns (FH), which communicate widely and centrally with the inferior third ventricle (3v). Note the rounded appearance of the thalami (T). A seemingly normal mid-line echo is seen in the superior frontal cortex (black arrowhead); (b) coronal sections of the fetal brain after termination of pregnancy. The appearance of the ventricular system correlates well with the antenatal scan. The interhemispheric fissure is well developed superiorly (white arrowhead), while it is entirely absent in the inferior portion of the frontal cortex. The falx cerebri was present but was hypoplastic



**Figure 2(b)**

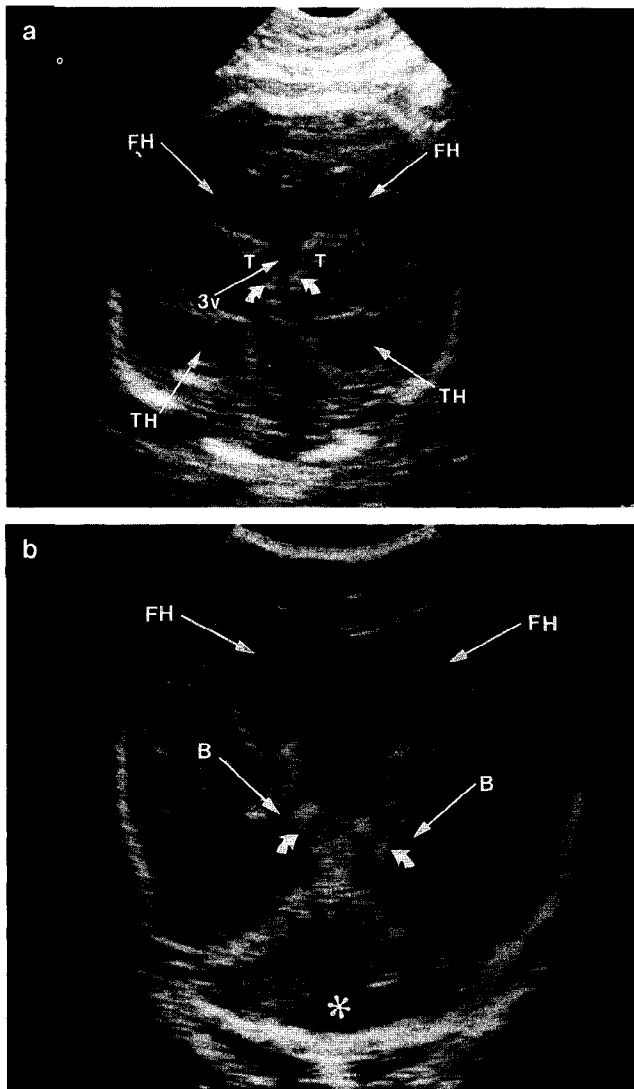


**Figure 3** Mid-sagittal view in a 32 weeks' fetus with lobar holoprosencephaly. The corpus callosum (white arrowheads) is clearly seen bridging over the fused lateral ventricles. It appears, however, thin and poorly developed posteriorly. The bright choroid plexus is seen within the ventricular cavity (black curved arrowhead) (Ant denotes anterior; Post, posterior)

Walker malformation had ventriculomegaly up to birth but developed a severe cerebral hemorrhage in the first days of life. The pathogenesis of hemorrhage in this case

was probably related to maternal alloimmune thrombocytopenia. The infant at birth had circulating antiplatelet antibodies and a platelet count of 12 000 per  $\text{mm}^3$ . It is worth noting that this infant had been delivered by Cesarean section. It remains unclear if the underlying cerebral malformation contributed to the development of the hemorrhage. Severe hydrocephalus developed in the days following and a shunt was implanted. Two fetuses were born with moderate non-hypertensive ventriculomegaly but required implantation of a shunt within 1 year of life due to the progressive worsening of the hydrocephalic condition. A shunt was not deemed necessary in only two cases. The infants are now 6 months and 2 years of age, respectively.

A detailed follow-up was available for five infants. Psychomotor development and intellectual development were progressively evaluated with the Brunet-Lezine

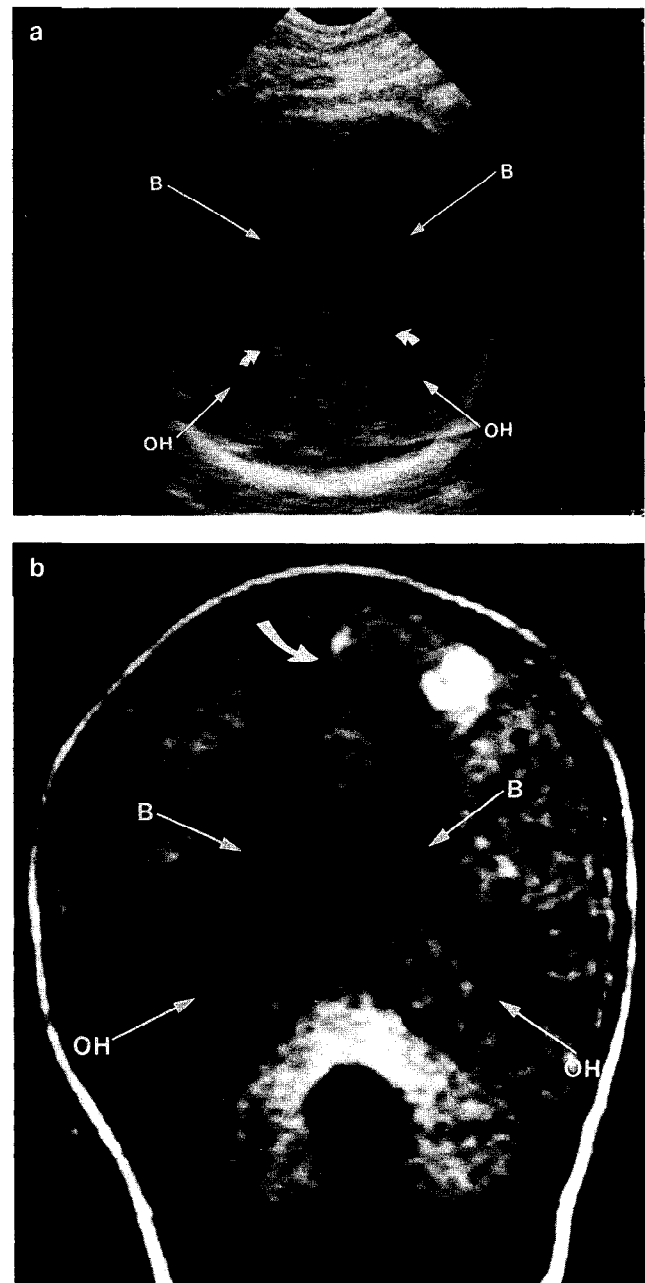


**Figure 4** (a) Antenatal mid-coronal scan in a 29 weeks' fetus with lobar holoprosencephaly. The frontal horns (FH) are fused, have a square roof and communicate centrally with the inferior third ventricle (3v). The choroid plexuses (curved arrowheads) are seen within the latter. The thalami are rounded. The temporal horns (TH) are well formed and appear enlarged. Noise in the proximal field obscures the frontal cortex and does not allow the identification of the mid-line echo; (b) postnatal transfontanellar scan in the same case. The ultrasound findings correlate well with the antenatal sonogram. The scanning plane is slightly more posterior than (a) and does not demonstrate the third ventricle. It reveals the partial fusion of the bodies of lateral ventricles (B), within which the choroid plexuses are seen (arrowheads). A posterior fossa abnormality (\*) suggesting the Dandy-Walker malformation (cystic cisterna magna and defect of the inferior vermis of the cerebellum) can be appreciated

test<sup>17</sup> up to 3 years of age and with the Stanford Binet intelligence scale validated for the Italian language<sup>18</sup> later on. All infants, including those that had not required the implantation of a shunt, had abnormal developmental quotients, ranging between 30 and 60 (Figure 6).

## DISCUSSION

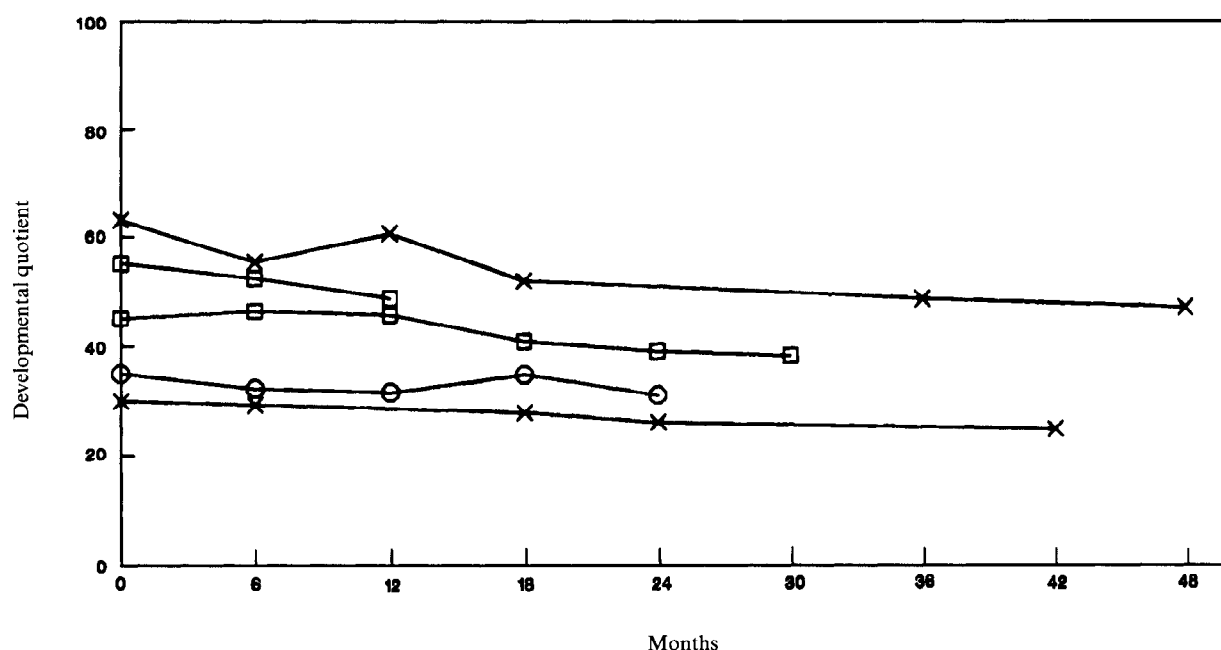
Much attention has been recently dedicated to the problem of prenatal diagnosis of the holoprosencephalic



**Figure 5** Same case as in Figure 4. (a) Antenatal coronal scan more posteriorly inclined than in Figure 4(a). Fusion and enlargement of the bodies of lateral ventricles (B) can be noted. (OH, occipital horns; arrowheads indicate choroid plexuses); (b) postnatal nuclear magnetic resonance image in a scanning plane similar to (a), confirming the antenatal findings. The interhemispheric fissure (curved arrow) is more shallow than normal. A posterior fossa abnormality compatible with Dandy-Walker malformation is clearly demonstrated

sequence. Criteria for identifying the alobar and semi-lobar varieties are well established<sup>3-7</sup>. The lobar variety is associated with a much lesser degree of anatomical derangement and the antenatal diagnosis carries several difficulties.

Lobar holoprosencephaly is invariably associated with absence of the cavum septum pellucidum and central fusion of the frontal horns of the lateral ventricles. Although these features are readily demonstrated with ultrasound, the differential diagnosis includes many



**Figure 6** Developmental quotients in five infants with lobar holoprosencephaly (two with associated Dandy-Walker malformation (—□—); one with progressive hydrocephalus requiring postnatal shunting (—○—); two that underwent no treatment (—×—))

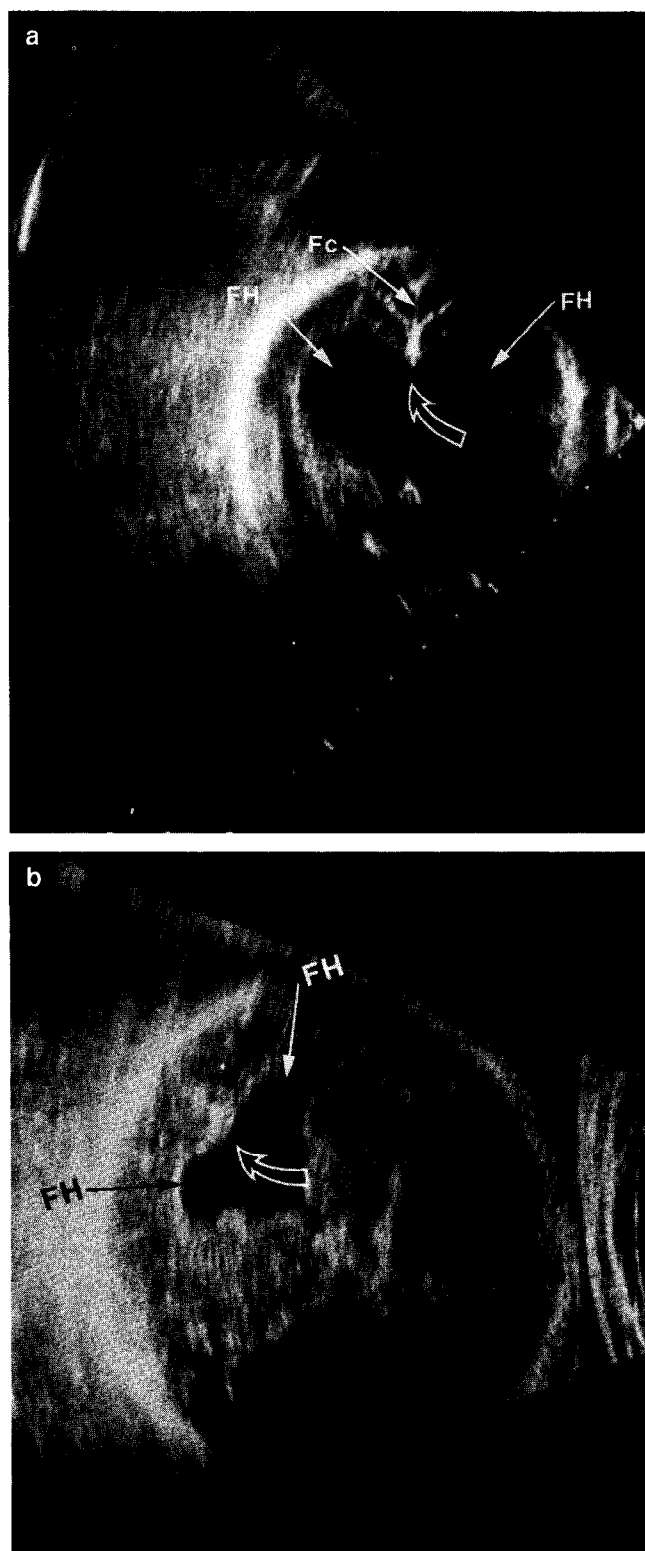
other entities. The distinction from other mid-line abnormalities is usually easy. In the alobar and semilobar variety of holoprosencephaly, there is a single rudimentary ventricle arching above the bulb-shaped thalami, there is no anterior mid-line echo, and typical facial anomalies are frequently seen<sup>3-7</sup>. On the other hand, in complete agenesis of the corpus callosum, the cavum septum pellucidum is absent, the lateral ventricles are not fused and actually are more separated than normal<sup>19</sup>. The distinction from septo-optic dysplasia, also referred to as de Morsier syndrome, is certainly more difficult. This condition features a distortion in cerebral anatomy that is virtually identical to the one encountered in lobar holoprosencephaly (absence of cavum septum pellucidum with fused and squared frontal horns). A definitive diagnosis of septo-optic dysplasia is possible only by demonstrating optic tract hypoplasia, which does not seem possible with antenatal ultrasound at present<sup>20</sup>. Another approach would be to identify signs of hypopituitarism, that are invariably present with this anomaly. This has never been attempted before, but increasing experience with analysis of fetal metabolism from blood samples obtained by cord puncture may render this possible in the near future<sup>21</sup>. Simple absence of the cavum septum pellucidum has occasionally been described in radiological studies of infants and it has been suggested that it is not associated with neurological impairment<sup>8,9</sup>. A differentiation from lobar holoprosencephaly by antenatal ultrasound would probably be impossible. However, it is important to stress that both septo-optic dysplasia and isolated absence of the cavum septum pellucidum are exceedingly rare conditions.

From a practical point of view, we believe that the major problem resides in recognizing lobar holoprosencephaly from other types of hydrocephalus with secondary disruption of the cavum septum pellucidum.

Neuroradiological studies in infants and the present sonographic study of fetuses demonstrate that the most important clue in these cases is the shape of the roof of the frontal horns. To better elucidate this concept, coronal sonograms in fetuses with different types of hydrocephalus are demonstrated in Figure 7. In hydrocephalus arising from causes different from lobar holoprosencephaly, the roof of the frontal horns is V-shaped because of a central indentation at the level of the mid-line. In lobar holoprosencephaly, the roof of the frontal horns is typically flat. Additional clues for recognizing this condition include the central communication with the third ventricle and the rounded appearance of the thalami (Figures 2, 3 and 7).

Pathological and radiological studies report that in lobar holoprosencephaly the interhemispheric fissure is shallow in the frontal cortex and that the falx cerebri may be hypoplastic or absent<sup>8,9</sup>. In our experience the ultrasound study of these structures *in utero* was of little diagnostic utility. It is difficult with antenatal sonography to distinguish the falx cerebri from the interhemispheric fissure, as both are normally merged to form the thin mid-line echo. Evaluation of the mid-line echo with mid-coronal scans is usually unsatisfactory because of ultrasound artifacts and/or inadequate angling of the incident ultrasound beams (Figures 2 and 3). Axial views demonstrate clearly the mid-line echo but do not allow the clear identification of how deep it penetrates into the brain. It is, therefore, not surprising that, in our cases, the antenatal ultrasound appearance of the mid-line was found to be rather normal. Demonstrating that a mid-line echo in the frontal area of the brain is present is, however, important in that it excludes with absolute certainty both alobar and semilobar holoprosencephaly.

Ventricular findings may be sufficient for a positive prediction of fetal lobar holoprosencephaly. The validity



**Figure 7** A comparison of mid-coronal scan in fetuses with different types of ventriculomegaly. (a) This fetus was found at birth to have hypertensive hydrocephalus of the communicating type. The frontal horns (FH) are large and communicate centrally due to the disruption of the cavum septum pellucidum. However, the roof of the frontal horns has an obvious indentation at the level of the mid-line (curved arrow). The mid-line echo is well delineated, and within the enlarged supracortical cistern, a portion of the falx cerebri is clearly seen (Fc); (b) lobar holoprosencephaly. The roof of the fused frontal horns (FH) is typically flat (curved arrow). The roundness of the thalami (T) is also well demonstrated in this scanning plane. A mid-line echo is seen; however it appears blurred because of the unfavorable scanning angle

of this approach is attested to by one previous study, in which at least two cases were correctly identified<sup>10</sup>, and by our study of 12 cases. However, we do expect that in some cases difficulties will arise. Severe ventriculomegaly with considerable distortion of the cerebral architecture probably renders a certain diagnosis impossible. In all cases in this series, the corpus callosum was present. Lobar holoprosencephaly may be found with absence of the corpus callosum. Under this circumstance, the third ventricle may be displaced upward through the inter-hemispheric fissure<sup>1</sup>. The antenatal ultrasound appearance of this anatomical configuration is unknown at present, but we assume that it will be difficult or impossible to differentiate it from alobar or semilobar holoprosencephaly with a dorsal sac. Septo-optic dysplasia and isolated absence of the cavum septum pellucidum have been previously discussed.

The clinical significance of lobar holoprosencephaly is uncertain. The holoprosencephalic sequence has a very heterogeneous etiology. Genetic factors probably play a major role. Chromosomal aberrations such as triploidy, trisomy 13, 18, deletions (18p-) and ring chromosomes (mainly 18) are frequently found<sup>1,22</sup>. A Mendelian transmission has also been described<sup>23</sup>. Albeit most cases are sporadic, the recurrence risk is quite high, and an empirical estimate of 6% is usually suggested<sup>24</sup>. A correlation with maternal diabetes and congenital infection has also been described<sup>1</sup>. Most of these data were, however, collected from infants with either alobar or semilobar varieties, and it is unclear if they apply as well to the lobar type. The experience with lobar holoprosencephaly is scanty. In all our cases, the familial history was negative, the fetal karyotype was normal, and there was no evidence of either maternal diabetes or congenital infection. The only concomitant malformation was Dandy-Walker malformation. This association has been previously described<sup>24</sup>. Although hypotelorism is almost constant in the alobar variety<sup>1</sup>, orbital measurements were always normal in our cases. The sonographic examination *in utero* as well as the clinical evaluation on abortion specimens and infants failed to reveal any dysmorphic facial features.

Lobar holoprosencephaly is very frequently associated with hydrocephalus, although the pathophysiology is unclear<sup>1,8-10,25</sup>. All our cases had some degree of ventriculomegaly. Nevertheless, the sensitivity of ventricular measurement in identifying lobar holoprosencephaly remains uncertain, as our series is entirely based upon cases referred from other ultrasound facilities with a suspicion of hydrocephalus. It is worth noting that most fetuses had only borderline enlargement of the atria in early gestation. Such observation confirms the usefulness of measuring the atrial width in ultrasound screening for fetal malformations<sup>13,14</sup>. It also indicates the need for a very careful assessment of the cerebral anatomy in fetuses with mild ventricular enlargement. In most fetuses, hydrocephalus worsened during gestation and implantation of a shunt was necessary after birth. The presence of Dandy-Walker malformation may have contributed to the progression of hydrocephalus in two cases, but even

several fetuses with isolated lobar holoprosencephaly developed gross ventricular enlargement either *in utero* or after birth.

The prognosis of lobar holoprosencephaly is uncertain. The available clinical data are extremely limited. It has been reported that affected individuals may have a normal life span<sup>1</sup>, but mental retardation and neurological sequelae are very common<sup>25</sup>. The outcome of the survivors in the present series is dismal, albeit we recognize that the association with Dandy-Walker malformation and/or hydrocephalus is a confounding factor.

In conclusion, lobar holoprosencephaly can be recognized *in utero* with ultrasound during the second trimester, although a clear differentiation from other entities may prove difficult at times. The prognosis for this anomaly is still uncertain, but mental retardation does seem frequent.

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