

Sonography of fetal agenesis of the corpus callosum: a survey of 35 cases

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ABSTRACT

Agenesis of the corpus callosum was identified by ultrasound examination in 35 fetuses between 19 and 37 weeks' gestation. The ultrasound findings included absence of the corpus callosum and cavum septum pellucidum (hypoplasia in one case of partial agenesis of the corpus callosum), a typical 'teardrop' configuration of the lateral ventricles, distension of the interhemispheric fissure, upward displacement of the third ventricle, radiate arrangement of the medial cerebral gyri, and abnormal branching of the anterior cerebral artery. Associated anomalies were identified in 20 fetuses, including heterogeneous malformations and chromosomal aberrations (mosaic-trisomy 8 in three, trisomy 18 in two and partial duplication 8p in one). Five cases of agenesis of the corpus callosum were identified in a population of pregnant patients prospectively investigated because of genetic risk for agenesis of the corpus callosum or related syndromes. In this group, no diagnostic errors were made. Long-term neurological follow-up (6 months to 11 years) was available in 11 infants with antenatal diagnosis of isolated agenesis of the corpus callosum. Normal intellectual development was present in nine, and a low intellect (developmental quotient between 70 and 85) was found in two. It is concluded that fetal agenesis of the corpus callosum is associated with elusive sonographic findings that can, however, be accurately identified by targeted examinations. In routine sonograms, an increased atrial width and/or failure to visualize the cavum septum pellucidum should raise the suspicion of fetal agenesis of the corpus callosum. Given the high frequency of associated anomalies, prenatal diagnosis of agenesis of the corpus callosum dictates the need for a careful survey of fetal anatomy and karyotyping. The prognosis of isolated agenesis of the corpus callosum remains uncertain, although it is expected that a normal or borderline intellectual development will occur in many cases.

INTRODUCTION

Agenesis of the corpus callosum is an anomaly of uncertain prevalence and clinical significance. The incidence varies in different studies, depending upon the population investigated and the method of ascertainment. Estimates of 0.3–0.7%¹ in the general population and 2–3% in the developmentally disabled^{2,3} are usually quoted. Agenesis of the corpus callosum is considered a risk factor for neurological impairment and is frequently associated with other malformations⁴, and genetic syndromes⁵, including chromosomal aberrations⁶ and in-born errors of metabolism⁷, but it is also found in asymptomatic individuals with normal intelligence⁸.

By using the diagnostic criteria established by radiological^{3,4,9} and sonographic studies of infants^{10–13}, agenesis of the corpus callosum has been recognized *in utero* with ultrasound during the mid-trimester^{13–19}. We herein report our experience with 35 consecutive cases.

Ontogenesis and antenatal sonography of normal and absent corpus callosum

The corpus callosum is the largest commissure connecting the cerebral hemispheres. It is a broad plate of dense myelinated fibers, located deep in the longitudinal fissure, that reciprocally interconnect regions of the cortex in all lobes with corresponding regions of the opposite hemisphere. It derives from the *massa commissuralis*, an embryological structure formed by the fusion of the lateral margins of the groove that separates the primitive telencephalic vesicles. Development of the corpus callosum is a late event in cerebral ontogenesis, that takes place between 12 and 18 weeks' gestation²⁰. The corpus callosum is in close anatomical and embryological relationship with the underlying septum pellucidum. Although there is no *a priori* evidence to suggest that the development of the septum pellucidum cannot proceed

independently of the corpus callosum, most observers claim that there can be no septum pellucidum without a corpus callosum²⁰.

The corpus callosum is a thin band of white matter, and its sonographic demonstration requires adequate angles of insonation. Only mid-sagittal and mid-coronal scans of the fetal brain usually allow clear visualization.

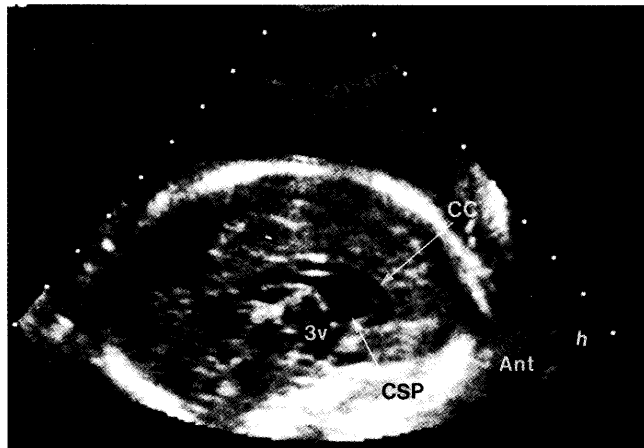
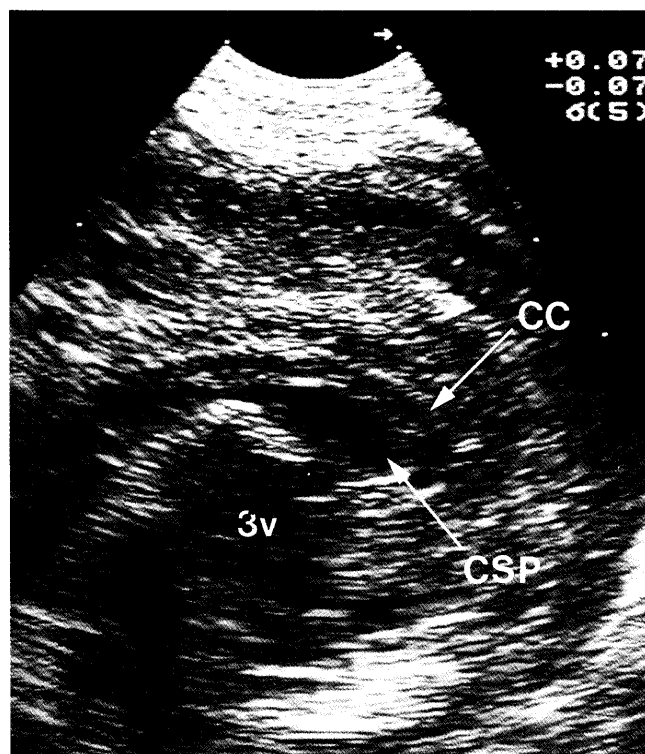


Figure 1 This mid-sagittal view of the brain of a 21-week-old fetus in breech presentation was obtained with abdominal sonography using a 5 MHz transducer. The corpus callosum (CC) is clearly visualized as a sonolucent band demarcated superiorly and inferiorly by two echogenic lines, and appears to be fully developed. The cavum septum pellucidum (CSP) is normally patent at this gestational age and is seen as a triangular sonolucent structure pointing posteriorly, interposed between the corpus callosum superiorly and the third ventricle inferiorly (3v). Note that development of the corpus callosum appears complete at this gestational age, with well-formed body and splenium. Ant, anterior



Such views require a meticulous scanning technique, but can be obtained with standard transabdominal ultrasound in most fetuses in breech position or transverse lie²¹. In fetuses in the vertex presentation, transvaginal sonography is the technique of choice²². Figure 1 shows a mid-sagittal view of the brain of a normal fetus at 21 weeks' gestation. The corpus callosum appears as a sonolucent band demarcated superiorly and inferiorly by two echogenic lines. The superior line presumably arises from the pericallosal cistern; the inferior line derives probably from both the fornix and the roof of the cavum septum pellucidum. By using color Doppler sonography in this scanning plane, we have been able to demonstrate the pericallosal artery, a branch of the anterior cerebral artery, sweeping circularly over the corpus callosum (Figure 2). In a coronal scan, the corpus callosum appears to form the roof of the cavum septum pellucidum and frontal horns (Figure 3).

Agenesis of the corpus callosum may be either complete or partial. In the latter case, also referred to as dysgenesis of the corpus callosum, the caudad portion (splenium and body) is missing to varying degrees. Figures 4 and 5 summarize the criteria that have been established for the sonographic diagnosis of agenesis of the corpus callosum in neonates¹⁰⁻¹³ and fetuses¹³⁻¹⁹. They include the direct demonstration of the absence of the corpus callosum and a variety of associated cerebral findings. Among such indirect findings, the most striking one on antenatal ultrasound is probably a typical alteration in the architecture of the lateral ventricles. In complete agenesis of the corpus callosum, the frontal horns and bodies are of normal or near to normal size but are more separated than normal, and there are

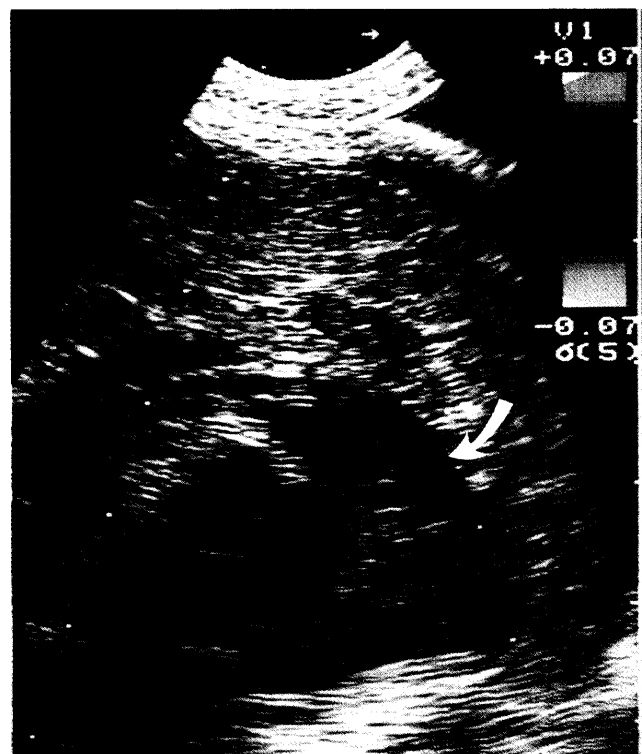


Figure 2 This mid-sagittal view of the brain of a 23-week-old fetus in the vertex presentation could be obtained by transvaginal sonography using a 6.5 MHz transducer. Color Doppler ultrasound reveals the pericallosal artery (curved arrow) sweeping over the corpus callosum. CC, corpus callosum; CSP, cavum septum pellucidum; 3v, the third ventricle

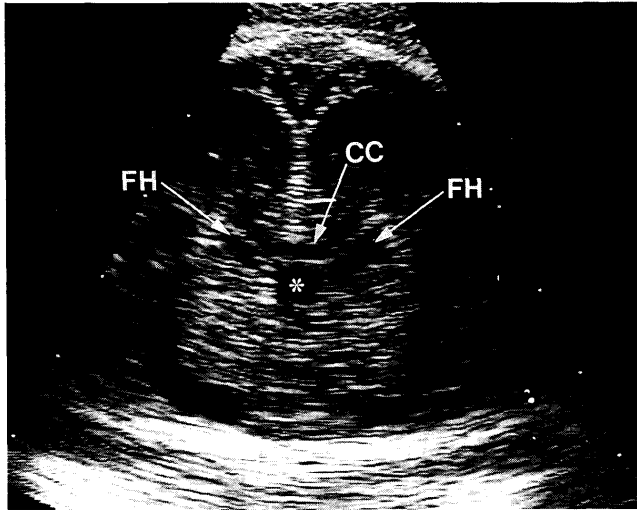


Figure 3 This coronal view of the brain of a 23-week-old fetus in the vertex position was obtained with vaginal sonography. The high frequency, 6.5 MHz transducer demonstrates subtle details of intracranial anatomy. The corpus callosum (CC) is seen interrupting the mid-line echo and forming the roof of the cavum septum pellucidum (*) and the frontal horns of lateral ventricles (FH). As under normal conditions the leaves of the septum pellucidum form the medial walls of the frontal horns, the cavum septum pellucidum and lateral ventricles are closely apposed in this view

varying degrees of enlargement of the atria and occipital horns. An axial scan directed as in Figure 4 results in a peculiar image in which the lateral ventricles have a tear-drop configuration (Figures 4 and 6)^{13,16}. Coronal and sagittal scans are, however, of utmost importance,

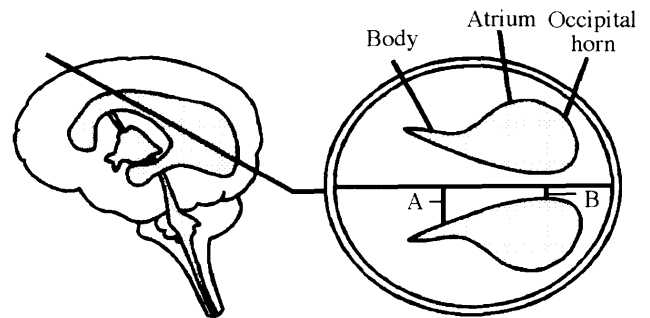


Figure 4 The 'tear-drop' configuration of lateral ventricles typical of agenesis of corpus callosum is demonstrated by an axial plane oriented as in this diagram. This sign results from simultaneous expansion of atria and occipital horns and lateral separation of bodies and frontal horns of lateral cerebral ventricles. In contrast to the normal situation, the medial wall of the bodies is obviously more distant from the mid-line than the medial wall of the atria (A is greater than B)

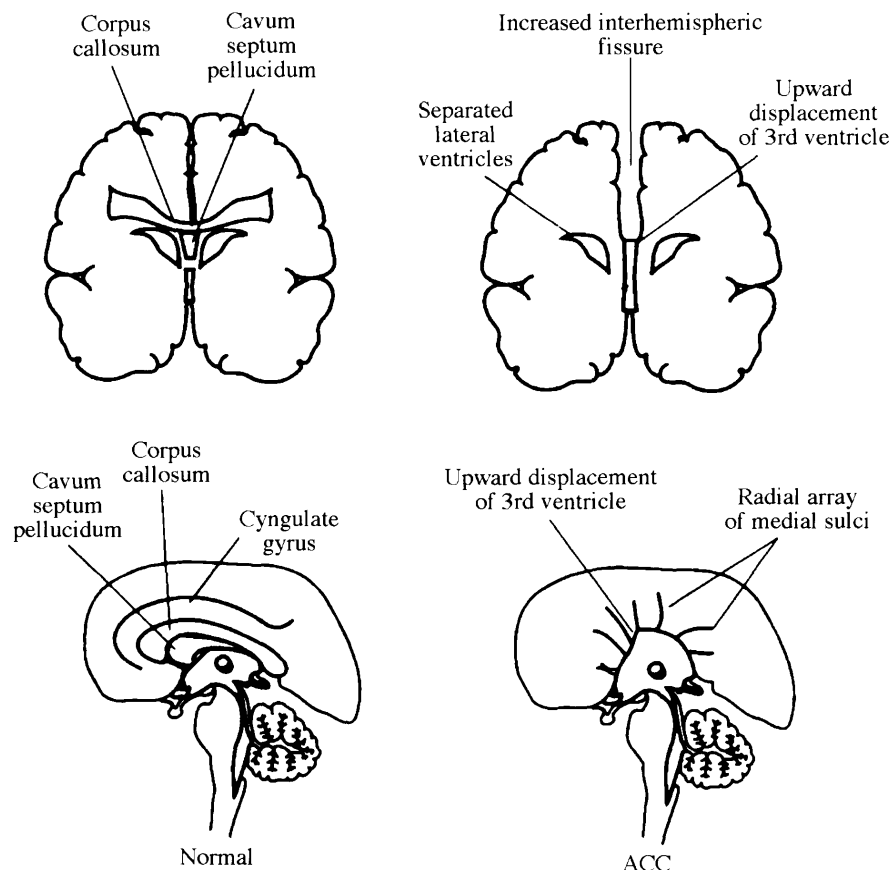


Figure 5 Schematic representation of the findings associated with agenesis of the corpus callosum (ACC) that can be demonstrated with coronal and sagittal views of the brain. Coronal scans (upper drawings) are primarily useful for the direct demonstration of the absence of the corpus callosum–cavum septum pellucidum complex, but may also allow the visualization of a widening of the interhemispheric fissure, of increased separation between the lateral ventricles and of upward displacement of the third ventricle. Sagittal views allow demonstration of the absence of the corpus callosum–cavum septum pellucidum complex and furthermore to appreciate a superiorly elongated third ventricle with a radial array of the medial gyri in the position normally occupied by the cingulate gyrus

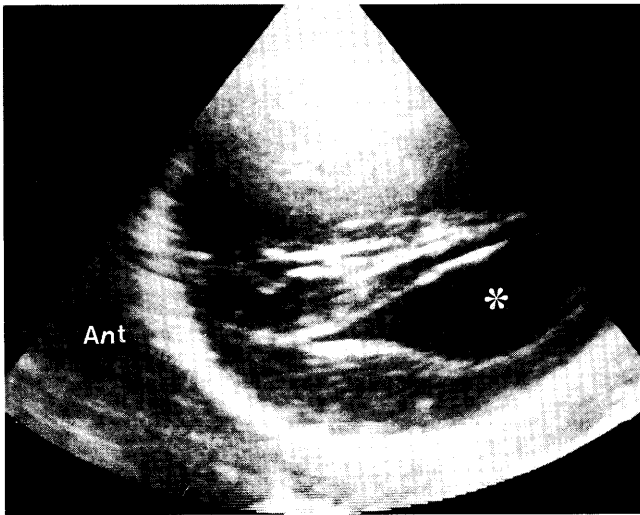


Figure 6 Axial scan of the brain in a third-trimester fetus with agenesis of the corpus callosum demonstrating the 'tear-drop' configuration of lateral ventricles (*) ('Ant' denotes anterior). Compare this image with the diagram reported in Figure 4

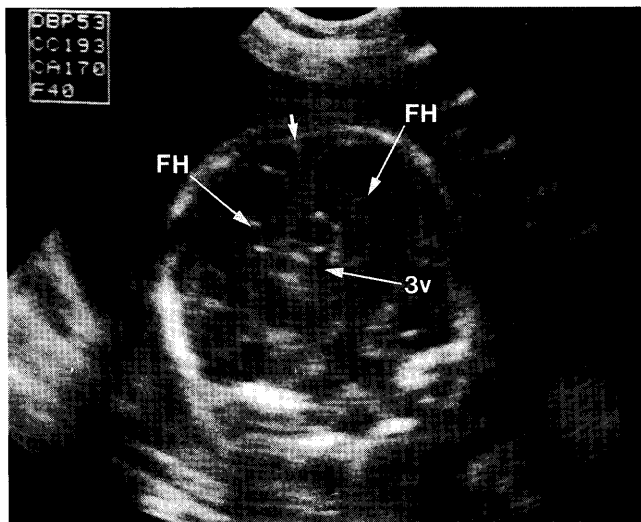


Figure 7 This coronal view of the brain of a 20-week-old fetus with complete agenesis of the corpus callosum in breech presentation could be obtained by transabdominal sonography. The corpus callosum and cavum septum pellucidum are obviously absent. Furthermore, there is obvious widening of the interhemispheric fissure (the arrow head indicates the falx cerebri) that reaches the third ventricle (3v) inferiorly, and the frontal horns are widely separated

in that they allow the direct demonstration of the absence of the corpus callosum^{13,16,18,19} and of other typical findings as well. With complete agenesis of the corpus callosum the septum pellucidum is either absent or grossly distorted²⁰; at any rate no sonographically recognizable cavum is supposed to be present (Figure 7). The absence of the main cerebral commissure frequently results in increased separation of the hemispheres with a prominent interhemispheric fissure. Under such circumstances, sonography will reveal three echogenic lines running parallel in the upper cranium, the middle one representing the falx cerebri, the lateral ones representing the medial borders of the separated hemispheres (Figures 7-9). Upward displacement of the third ventricle, that is also frequently enlarged, can be identified

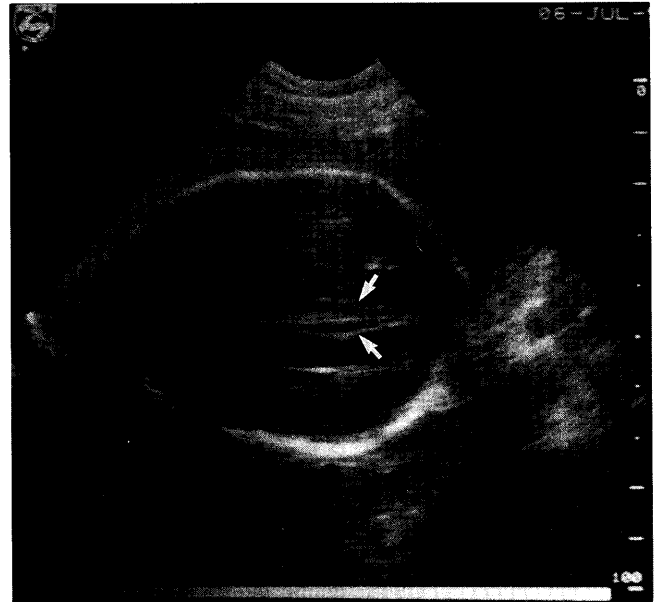


Figure 8 Axial view obtained in the same case as Figure 7. The increased separation of the cerebral hemispheres is inferred by the triplication of the mid-line echo. The lateral lines, indicated by the arrowheads, derive from the medial borders of the hemispheres, the central line derives from the falx cerebri

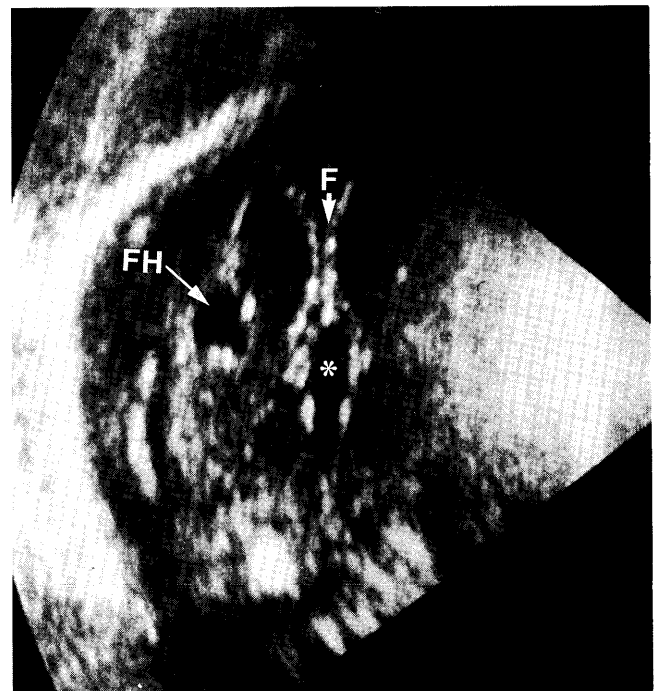


Figure 9 Coronal view of the brain in a third-trimester fetus obtained by transabdominal sonography. Agenesis of the corpus callosum is inferred by many different findings: the third ventricle (*) reaches superiorly to the level of the frontal horns (FH); the frontal horns are obviously separated from the mid-line; the interhemispheric fissure is widened; eventually, the falx cerebri (F) is seen directly the roof of the third ventricle. Notice that the third ventricle appears enlarged

by demonstrating that this structure reaches superiorly to the level of lateral ventricles in either a coronal or axial scan^{13,14,16} (Figure 9). Absence of the corpus callosum also results in abnormal induction of medial cerebral convolutions, determining a radiate arrangement of cerebral sulci around the roof of the third ventricle, extending

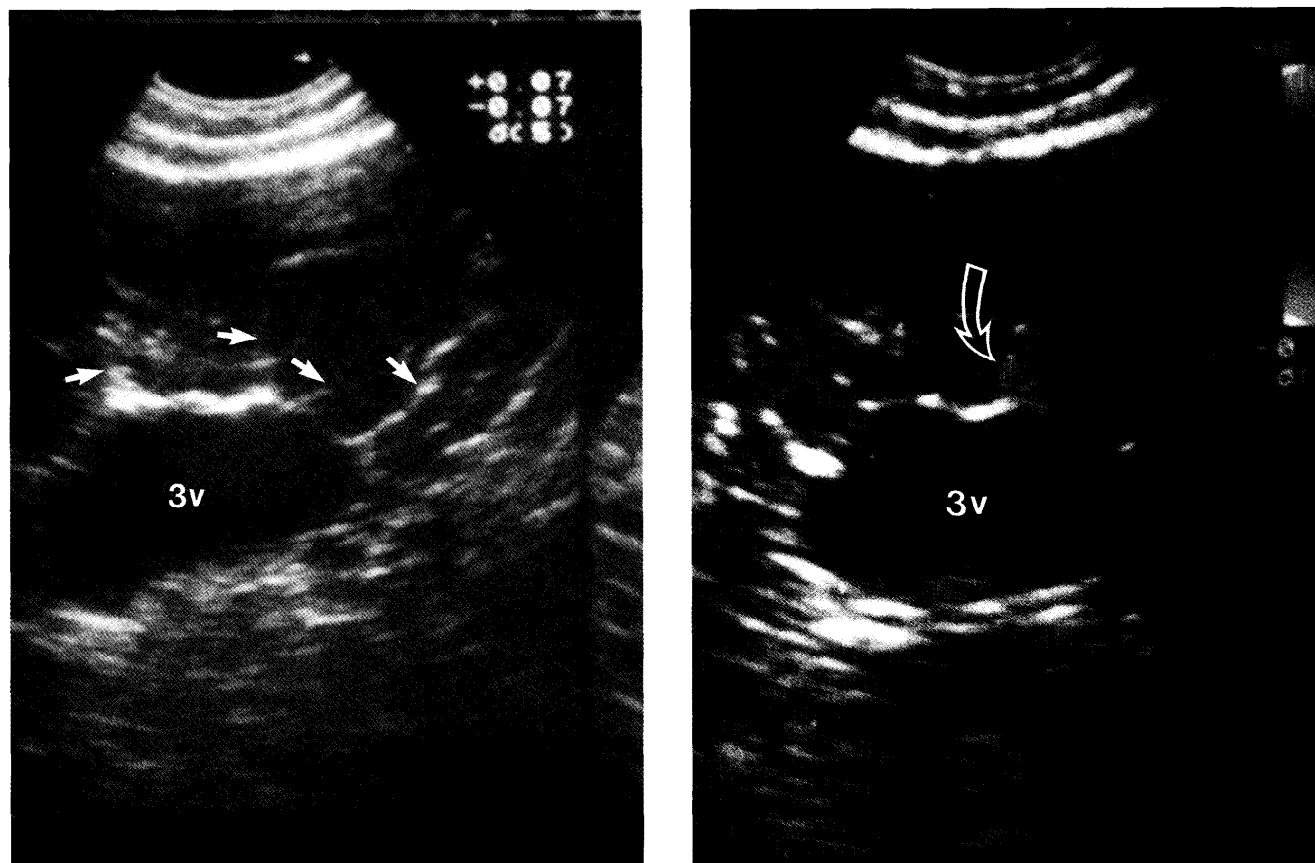


Figure 10 This mid-sagittal view of the brain of a third-trimester fetus with agenesis of the corpus callosum was obtained with vaginal sonography using a 6.5 MHz transducer. The front of the fetus is to the left of the images. The corpus callosum–cavum septum pellucidum complex is obviously absent. The medial sulci have an abnormal radiate array (arrowheads), extending through the area normally occupied by the cingulate gyrus. Color Doppler sonography fails to reveal the semicircular loop of the pericallosal artery, while it demonstrates branches of the anterior cerebral artery that ascend linearly (curved arrow)

through the zone normally occupied by the cingulate gyrus (Figure 10). The modification of the arterial vascular supply in infants with agenesis of the corpus callosum has been investigated in depth with angiography²³ and more recently with transfontanellar sonography¹². With agenesis of the corpus callosum, the semicircular loop of the pericallosal artery is lost and we have been able to demonstrate using color Doppler sonography (Figure 10) branches of the anterior cerebral artery ascending linearly with a radiate arrangement.

The corpus callosum is typically absent in the most severe varieties of the holoprosencephalic sequence²⁴; these, however, will not be considered in this article, as they represent a separate clinical entity whose diagnostic criteria and clinical course are well established.

PATIENTS AND METHODS

Between 1983 and 1992, agenesis of the corpus callosum was recognized in 35 fetuses ranging in gestational age between 19 and 37 weeks. Cases with evidence of holoprosencephaly, albeit lacking a corpus callosum, were excluded from this survey. The diagnostic data of the first nine cases of the present series have been previously reported¹³. A total of 30 pregnant patients were referred

from level one ultrasound facilities because of the suspicion of a fetal anomaly, mostly enlargement of cerebral ventricles. The remaining five cases derived from the prospective examination of 56 patients at risk for fetal agenesis of the corpus callosum because of a positive family history.

Sonographic examinations were performed with a Platinum system (Philips Ultrasound, Santa Ana, California), and Ansaldo 450 and 590 equipment (Ansaldo, Genoa, Italy). Axial, coronal and sagittal views of the cerebral structures were attempted in each case. Since 1987 in fetuses presenting by the vertex, vaginal scans were also obtained when necessary for better elucidation of the fetal brain. Since 1990, color Doppler sonography has been used for the study of fetal cerebral circulation. The degree of ventriculomegaly was assessed by measurement of the atrial width²⁵. It has been suggested that ventriculomegaly should be divided into two different clinical entities: borderline enlargement (atrial width 10–15 mm) and overt hydrocephalus (atrial width > 15 mm)²⁶. This classification will be used in the following discussion. Postnatal follow-up was obtained in each case. The neurological development of surviving infants was evaluated with the Brunet–Lezine test²⁷ up to 3 years of age and with the Stanford Binet intelligence scale validated for the Italian language later on²⁸.

RESULTS

Antenatal sonographic diagnosis

Prenatal diagnosis was made in the second trimester in 20/35 cases. The earliest diagnosis was made at 19 weeks. In all patients presenting after 19 weeks, agenesis of the corpus callosum was always recognized on the first sonogram. The frequency with which the different ultrasound findings indicative of agenesis of the corpus callosum were detected is reported in Table 1. The 'tear-drop' configuration of lateral ventricles was readily demonstrated in all fetuses, with the only exception being a fetus in which severe ventricular enlargement involving the bodies and frontal horns was present. Measurement of the atrial width at the time of initial diagnosis is reported in Figure 11. In all cases but one, including fetuses in which examination was performed due to family history, the measurement was ≥ 10 mm. More precisely, in 22 cases the atrial measurement was 10–15 mm, and in 12 cases was greater than 15 mm. In one case, the measurement was 9 mm at 22 weeks' gestation. In continuing pregnancies, serial examinations were performed. The atrial width was often found to increase slightly with gestation, seemingly in proportion to the increase of the head size. Direct documentation of the absence of the corpus callosum was sometimes difficult in vertex fetuses prior to the introduction of vaginal sonography, but became relatively simple thereafter. Up to 1987, when only standard transabdominal ultrasound was available, the success rate in obtaining satisfying coronal and sagittal scans was only 4/9. Failure was always associated with vertex presentation. With the introduction of vaginal sonography, the success rate increased to 26/26. In one case that was referred at 22 weeks with an atrial width of 13 mm and 'tear-drop' lateral ventricles, meticulous scanning revealed only the most anterior portion of the corpus callosum. The cavum septum pellucidum was present, albeit seemingly foreshortened (Figure 12). A diagnosis of partial agenesis of the corpus callosum was made, and confirmed after birth. With the exception of this case only, the cavum septum pellucidum could never be demonstrated in any of the other 34 cases. A widened interhemispheric fissure was detected in 21 cases and upward displacement of the third ventricle in 18. A radial arrangement of the cerebral sulci overlying the third ventricle was never seen in mid-trimester fetuses. Conversely, it was always documented

Table 1 Sonographic findings in 35 fetuses with callosal agenesis

Findings	Number of cases
'Tear-drop' lateral ventricles	34*
Absent cavum septum pellucidum	34†
Absent corpus callosum	30
Widened interhemispheric fissure	21
Upward displacement of third ventricle	18
Radial arrangement of medial gyri	18
Absent pericallosal artery	3‡

*Not including one case of severe ventriculomegaly; †not including one case with partial callosal agenesis; ‡color Doppler sonography only used in three cases

in the third trimester, with the only exception of one case in which a large interhemispheric cyst was present and caused significant distortion of intracranial anatomy. A bright echogenic mass in the position of the genu of the corpus callosum was noted in two fetuses in the third trimester (Figure 13). Topography and sonographic appearance of the lesions suggested the diagnosis of a lipoma¹⁸, which was confirmed after birth. In both cases, ultrasound examinations had been carefully performed in the second trimester, without revealing the echogenic mass.

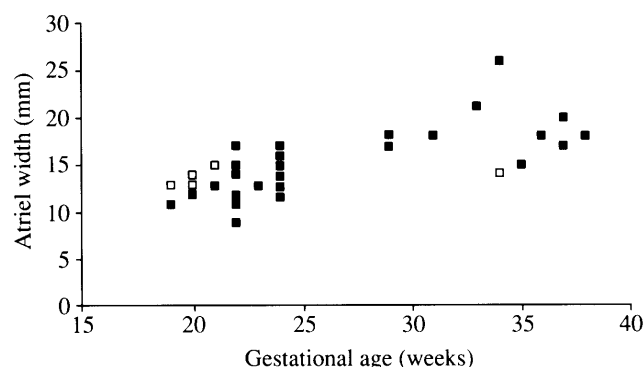


Figure 11 Atrial width in 35 fetuses with agenesis of the corpus callosum. Measurements were taken at the time of diagnosis. Open squares indicate familial cases. Black squares indicate cases referred because of a suspicious first level scan. The measurement was always obtained from the atrium distal to the ultrasound transducer. In many cases there was, however, asymmetrical enlargement of the atria. Although these measurements were obtained from different fetuses, the distribution suggests a slight increase of atrial width in agenesis of the corpus callosum with increasing gestation. This impression was confirmed in those cases in which serial examinations were performed

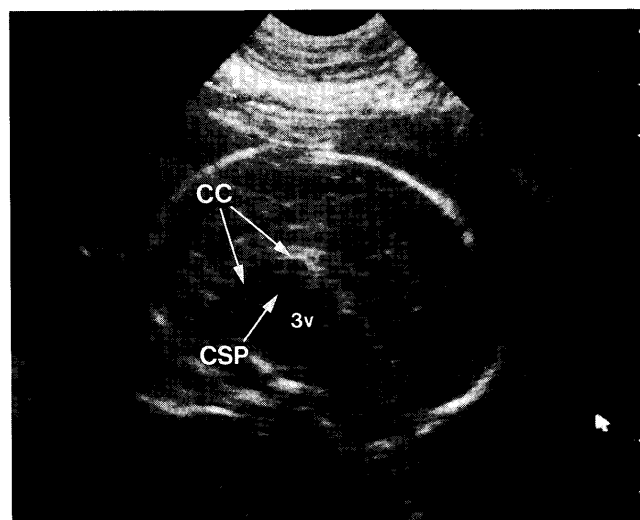


Figure 12 In this mid-trimester fetus with 'tear-drop' lateral cerebral ventricles, meticulous scanning revealed foreshortening of the corpus callosum and cavum septum pellucidum. Notice that the corpus callosum-cavum septum pellucidum complex does not arch over the entire third ventricle (3v) as normally happens (compare with Figure 1), but only over the most anterior portion. This view prompted a diagnosis of partial agenesis of the corpus callosum that was confirmed after birth. It must be noted that mid-coronal scan demonstrated a seemingly normal corpus callosum and only sagittal views revealed the defect

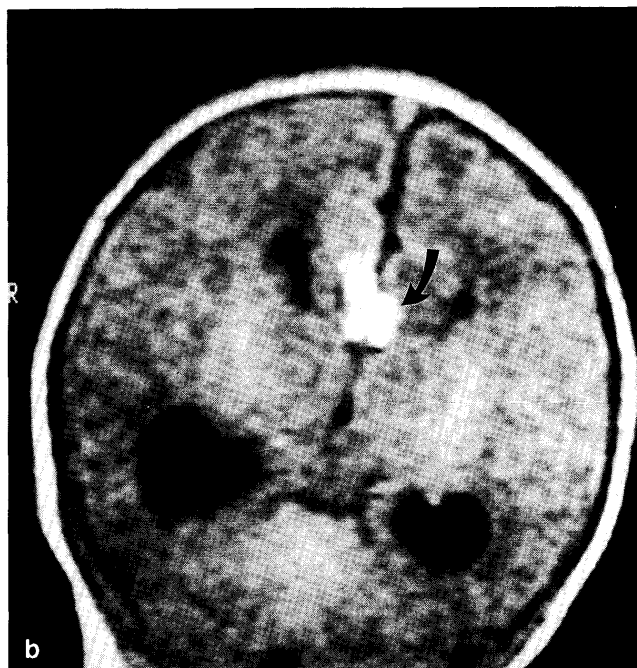
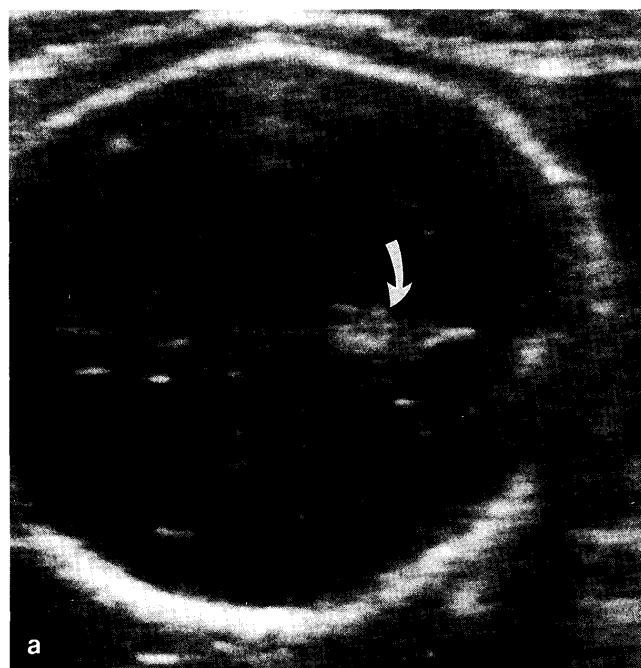


Figure 13 (a) In this fetus diagnosis of agenesis of the corpus callosum was made in the mid-trimester. On a follow-up scan at 35 weeks a bright mass (curved arrow) was first noted in the position normally occupied by the genu of corpus callosum, prompting the diagnosis of intracranial lipoma; (b) postnatal magnetic resonance scan confirming the antenatal diagnosis. It is postulated that the lipoma developed in the last trimester of gestation

Table 2 Anomalies associated with agenesis of the corpus callosum

Anomalies	Number of cases
Dandy-Walker malformation	5*
Dandy-Walker malformation, double outlet of the right ventricle, hypertelorism	2
Mosaic trisomy 8	3 [†]
8p+	1
Clubfoot, clubhand, trisomy 18	1
Omphalocele, choroid plexus cyst, clubfoot, trisomy 18	1
Double outlet of the right ventricle	1
Tetralogy of Fallot	1
Interhemispheric cyst	1
Microcephaly, diaphragmatic hernia	1
Cystic hygroma, hydrops, choroid plexus cyst	1
Hydronephrosis, absent stomach bubble, nuchal cysts	1
Hydrops	1

*One case with severe ventriculomegaly; one case with clubfoot; one case with hypoplastic left heart; [†]one case with hydronephrosis

Associated anomalies

Associated anomalies were found antenatally in 20 cases (Table 2). The anatomical lesions were extremely heterogeneous. The one most frequently encountered was, however, the Dandy-Walker malformation (seven cases). A karyotype was available in 29 cases, and was found to be normal in 23 (46,XY in 14, 46,XX in nine) and abnormal in six (21%). The chromosomal aberrations included three cases of mosaic-trisomy 8, one case of

partial duplication 8p and two cases of trisomy 18. It should be noted that two of three fetuses with mosaic-trisomy 8 and the fetus with partial duplication 8p were not found to have any abnormal sonographic finding apart from agenesis of the corpus callosum. A detailed postnatal follow-up was available in all cases but four, in which a destructive procedure had been employed for pregnancy termination. No major anomalies were missed by the antenatal examination. The fetus with an absent stomach bubble had esophageal atresia with tracheo-esophageal fistula. One fetus was found after birth to have a hemodynamically insignificant ventricular septal defect, one had clubfoot and one inguinal hernia.

Familial cases

Five cases of agenesis of the corpus callosum were diagnosed in a group of 57 pregnancies at increased risk for fetal agenesis of the corpus callosum. The predominant indication for the ultrasound examination in this group was a family history of agenesis of the corpus callosum or related syndromes. Postnatal follow-up was obtained in each case, and transfontanellar sonography could be performed in 49 neonates. No callosal anomalies were missed antenatally. The relevant clinical data of positive cases are reported in Table 3. It should be noted that in case 1 both the proband and the index case were diagnosed antenatally with sonography in the second trimester, and were found to have similar pattern of multiple anomalies, including agenesis of the corpus callosum, Dandy-Walker malformation, double-outlet right ventricle and hypertelorism.

Table 3 Prenatal diagnosis of familial agenesis of the corpus callosum (ACC)

Case number	Indication	Age at diagnosis (weeks)	Associated anomalies
1	previous fetus* with ACC, double-outlet right ventricle, hypertelorism	19	Dandy–Walker malformation, double-outlet right ventricle, hypertelorism
2	previous child with Dandy–Walker malformation	20	Dandy–Walker malformation
3	previous child with ACC and severe mental retardation	34	none
4	previous child with Walker–Warburg syndrome	20	none
5	previous child with microcephaly, lissencephaly	20	none

*Pregnancy terminated following sonographic diagnosis

Postnatal follow-up

A total of 17 pregnancies were terminated at the patient's request. Autopsy was performed and confirmed the antenatal diagnosis in all cases but four in which a destructive procedure for termination of pregnancy had been used. A total of 18 fetuses with agenesis of the corpus callosum were delivered, vaginally in 13 cases, by Cesarean section in five cases (failure to progress in four cases, intrapartum distress in one). Deliveries were reported to be uneventful and Apgar scores were well within the normal range in all but two cases. The infant with intrapartum distress had low Apgar scores but did well otherwise. One infant with multiple anomalies (Dandy–Walker malformation, hypoplastic left heart) died soon after birth. Of the 17 survivors, three had chromosomal aberrations (two trisomy 8 in mosaic, one partial trisomy 8), one had Dandy–Walker malformation, one had an interhemispheric cyst, one was a familial case with a sibling affected by both agenesis of the corpus callosum and severe mental retardation (case 3). In all these cases, severe retardation was found at follow-up, with the exception of the case with an interhemispheric cyst. This infant was delivered and treated at another institution. Due to progressive enlargement of the cyst, a cyst–peritoneal shunt was implanted in the first years of life. Although a formal follow-up could not be obtained, the pediatricians reported that the infant was developing normally at 6 years of age.

The remaining 11 infants had isolated non-familial agenesis of the corpus callosum and were enrolled in a long-term neurological follow-up. Serial cranial sonograms were performed until closure of the anterior fontanelle, and the development was assessed twice a year. The follow-up ranged between 6 months and 11 years. All infants had head circumferences above the

Table 4 Intracranial findings and outcome of agenesis of corpus callosum

Findings	Good outcome (n = 11)	Poor outcome (n = 22)	Probability level
Atrial width (mm) (mean $\pm$ SD)	17.4 $\pm$ 4	14 $\pm$ 2.4	$p = 0.008^*$
Atrial width > 15 mm	5	6	NS
Upward displacement of third ventricle	1	15	$p = 0.001^{\dagger}$
Widened interhemispheric fissure	2	17	$p = 0.003^{\dagger}$
Asymmetrical enlargement of lateral ventricles	4	10	NS [†]

NS, non-significant; *Mann–Whitney *U*-test for non-normal data; [†]Fisher's exact probability test

50th centile and four were above the 90th centile. However, signs of intracranial hypertension or progression of ventricular enlargement were never found. Apart from macrocrania in four cases, no dysmorphic signs could be identified. Overall, 9/11 infants had normal developmental quotients, with scores greater than 85. The remaining two infants were found to have borderline scores (75 and 82), and one was affected by seizures.

Sonographic intracranial findings and outcome

While collecting this series of cases, it became clear that a wide variety of different intracranial findings was being documented with fetal agenesis of the corpus callosum. This observation prompted an attempt to correlate the different cerebral appearances with the final outcome. The prenatal sonograms were retrospectively reviewed, and two distinct groups of fetuses were identified and compared. Eleven cases of isolated agenesis of the corpus callosum with normal or borderline postnatal development formed the group with 'good' outcome, while 22 cases with poor developmental scores, other associated anomalies or both formed the group with 'poor' outcome. Table 4 demonstrates the variables considered. The group with 'poor' outcome had a lesser degree of ventricular enlargement, a significantly higher frequency of upward displacement of the third ventricle and widening of the interhemispheric fissure. Cases with an atrial width greater than 15 mm and cases with asymmetrical enlargement of ventricles were evenly distributed in both groups. A 'poor' outcome, according to the previous definition, was present in 7/17 cases without displacement of the third ventricle and in 5/13 cases without widening of the interhemispheric fissure. Conversely, the relative risks when these two findings were present were 2.2 (95% confidence interval 1.4–3) and 2.5 (95% confidence interval 1.6–3.4), respectively.

DISCUSSION

Agenesis of the corpus callosum is amenable to early prenatal diagnosis by sonography^{13–19}. The most striking finding is probably the enlargement of the occipital horns and atria. It has been postulated that the absence of the

posterior portion of the corpus callosum results in distortion of the array of white matter tracts in the occipital lobes, leading to caudad expansion of the lateral ventricles²⁹. Such ventricular enlargement tends *per se* to be stable and is not usually associated with intracranial hypertension. The observation that the ventricular atrium and occipital horn are abnormally large in agenesis of the corpus callosum has a practical value for the obstetric sonologist. Routine sonography of the fetal brain is usually performed with axial scans³⁰, that do not allow the demonstration of the corpus callosum. However, enlargement of the atria of the lateral ventricles is readily appreciated with these views. In this regard, it is worth noting that agenesis of the corpus callosum has been found in 3% of all fetuses with ventriculomegaly³⁰ and in almost 10% of those with mild ventriculomegaly²⁶.

Unfortunately, it remains uncertain what proportion of fetuses with agenesis of the corpus callosum have an abnormal atrial width. Although in our series, 34/35 fetuses had measurements greater than 10 mm, a bias is expected, as most cases had been primarily referred because of a suspicion of ventriculomegaly. However, it is worth noting that the atrial width had been abnormal since the mid-trimester in all four cases in which the diagnosis was made prospectively because of a positive family history. It would also seem that the majority of cases described in the postnatal series have some degree of ventricular enlargement. Although the exact sensitivity remains unclear, we believe it reasonable to assume that measurement of the atrial width can identify many cases of fetal agenesis of the corpus callosum.

Once atrial enlargement has been observed, other ultrasound findings can be researched to identify possible agenesis of the corpus callosum. In our preliminary experience¹³ and in the present series as well, the most consistent and easy to identify finding was the 'tear-drop' configuration of lateral ventricles. In a readily obtained axial plane, enlargement of the atria and occipital horns and separation of the bodies combine to generate a pattern that is readily recognizable. In our experience with a large number of heterogeneous anomalies of the fetal brain, 'tear-drop' ventricles were never documented in conditions other than for agenesis of the corpus callosum, and we believe, therefore, that this is a very specific sign, the diagnosis of callosal agenesis. It seems reasonable, however, that mid-coronal and mid-sagittal scans are obtained in these cases, to document directly the callosal lesion. It has been pointed out that these views are difficult to obtain, in particular in vertex fetuses^{13,16}. However, the previously described use of vaginal sonography¹⁹ proved to be of great advantage. In our preliminary series, satisfactory coronal and sagittal scans of the fetal brain were possible only in 4/9 fetuses¹³ versus 26/26 of the subsequent cases, examined at a time in which vaginal sonography was available. A distinction should be made between complete and partial agenesis of the corpus callosum. Complete agenesis of the corpus callosum is commonly regarded as a malformation, deriving from faulty embryogenesis, while partial agenesis of the corpus callosum may represent both a

true malformation and a disruptive event occurring at any time during pregnancy. It is of note that one case of partial agenesis of the corpus callosum has been identified previously in the third trimester¹⁷ and another one recognized at 20 weeks is reported in the present series. Both fetuses had an unequivocal 'tear-drop' configuration of lateral ventricles. The natural history of partial agenesis of the corpus callosum is, nevertheless, uncertain, and the cerebral findings associated with it are probably more subtle than with the complete form. It is, therefore, expected that antenatal diagnosis will not be possible in all cases.

With the exception of the case with partial agenesis of the corpus callosum, the cavum septum pellucidum could never be identified. This observation supports the view that sonographic evaluation of this structure is potentially helpful in routine screening, alerting the sonologist of the possible presence of elusive anomalies such as agenesis of the corpus callosum³⁰.

Other findings of agenesis of the corpus callosum described in the pediatric literature were found to be less consistent than the previous ones. Widening of the interhemispheric fissure and upward displacement of the third ventricle were documented only in about half of our cases. Radial arrangement of the medial cerebral sulci was seen only in the third trimester. This is in agreement with pathological and sonographic studies on preterm infants indicating that the surface of the hemispheres is smooth in the second trimester, with secondary sulci appearing only at the onset of the third trimester³¹. The use of Doppler sonography for revealing the abnormal arterial tree of the anterior cerebral artery is promising, but our experience is limited. Intracranial lipomas are rare lesions that are associated in about 50% of cases with abnormalities of the corpus callosum³². Their clinical significance is poorly understood. Prenatal diagnosis has been previously reported and on that occasion the authors formulated the hypothesis that these lesions developed throughout pregnancy¹⁸. This view is supported by our experience. In two consecutive cases that underwent serial examinations, sonographic demonstration was not possible until the third trimester.

No false positives occurred in our experience. In the group of pregnancies at high risk for fetal agenesis of the corpus callosum, no false negatives occurred either. It is therefore concluded that targeted ultrasound examinations are extremely accurate in the prediction of agenesis of the corpus callosum after the mid-trimester. This observation has a practical relevance. Although usually of sporadic occurrence, familial cases of agenesis of the corpus callosum have been occasionally reported. The available literature suggests a marked genetic heterogeneity with autosomal dominant, autosomal recessive and sex-linked transmission^{5,33}. Agenesis of the corpus callosum is also a member of the Mendelian syndromes, including Walker-Warburg syndrome³⁴, Andermann's syndrome³⁵, acrocallosal syndrome³⁶, F. G. syndrome³⁷, and Fryn's syndrome³⁸. Callosal agenesis is also found in two conditions with sex-linked dominant etiology and lethality in males: the orofaciocaudal type I

syndrome³⁹ and Aicardi syndrome⁴⁰. Frontonasal dysplasia or median cleft face syndrome is also frequently associated with agenesis of the corpus callosum. This condition is usually a sporadic disease, but a few family cases consistent with an autosomal dominant transmission have been described⁴¹. The recurrence in two male siblings described in this series of a very specific pattern of anomalies (agenesis of the corpus callosum, Dandy-Walker malformation, double-outlet right ventricle, hypertelorism) may suggest a new syndrome with either autosomal recessive or X-linked recessive transmission. A high frequency of agenesis of the corpus callosum, both partial and complete, has been documented in infants with inborn errors of metabolism⁷. Various teratogens have also been implicated as a possible cause of agenesis of the corpus callosum, including alcohol⁴², valproate⁴³, cocaine⁴⁴, rubella⁴⁵ and influenza virus⁴⁶. Our experience indicates that couples at risk for fetal syndromes consistently associated with agenesis of the corpus callosum can be offered antenatal sonography as a possible means of prenatal diagnosis.

Postnatal series report a high incidence of heterogeneous malformations and chromosomal aberrations in infants with agenesis of the corpus callosum^{4,6,29}. In our series, anatomic anomalies were present in 50% of cases, and an abnormal karyotype in 20%. Furthermore, family history suggests that genetic conditions, namely Walker-Warburg syndrome and lissencephaly, were present in two other fetuses, although direct evidence could not be found at postabortion examination. The anomaly most frequently encountered was Dandy-Walker malformation, a mid-line defect of the cerebellum that is probably embryologically related to agenesis of the corpus callosum. This association is well known and it has been postulated to represent a poor prognostic factor for neurological development, although this is controversial⁴⁷. The association between agenesis of the corpus callosum and chromosomal anomalies has been recently addressed by Serur and co-workers⁶, who reviewed a total of 100 cases. Overall, trisomy 18 was found in 29 cases, a form of trisomy 8 in 21 cases, trisomy 13 in 20, and a variety of different conditions in the remaining cases. It is, therefore, postulated that chromosomes 8, 13 and 18 have a direct influence on the development of the corpus callosum. This correlates well with our experience, even though we did not find any cases of trisomy 13. This may be due to our limited numbers, but we believe that there is reason to wonder if the association with trisomy 13 that is commonly quoted refers to the entity of agenesis of the corpus callosum in itself, or rather to absence of corpus callosum in severe manifestations of the holoprosencephalic sequence. Three fetuses with abnormalities of chromosome 8 had agenesis of the corpus callosum as the only sonographic finding. It would seem, therefore, that agenesis of the corpus callosum is an indication for fetal karyotyping *per se*, independently of the presence of other sonographically detectable anomalies.

In our experience, antenatal sonography was very accurate in predicting gross anomalies associated with

agenesis of the corpus callosum. It should be stressed, however, that a careful postmortem survey of individuals with agenesis of the corpus callosum demonstrated subtle lesions such as abnormalities of the cerebral gyri and medullary tracts in a significant proportion of cases⁴. Such anomalies are presently unpredictable *in utero*, and yet may have clinical significance.

Some intracranial findings were found in excess in fetuses with a poor outcome, and, therefore, may have prognostic value. Upward displacement of the third ventricle and a widened interhemispheric fissure were most frequently associated with neurological impairment, associated anomalies or both. This is perhaps not surprising when one considers that these findings probably indicate a more severe derangement of cerebral development. Surprisingly enough, fetuses with a good outcome tended to have larger cerebral ventricles than the ones with poor outcome. This may, however, be the consequence of a selection bias. The group with poor outcome included several cases of multiple anomalies that were seen early in gestation and subsequently underwent termination, while the cases with good outcome were more frequently recognized late in gestation. The difference in gestational age at the time of diagnosis between the two groups may account for the discrepancy in atrial size, as we have experienced that, in contrast to normal fetuses^{25,48}, those with agenesis of the corpus callosum tend to have a mild increase in atrial size throughout pregnancy. Most cases of agenesis of the corpus callosum in this series had an atrial width between 10 and 15 mm. This observation further stresses the need for a thorough examination of brain anatomy in fetuses with borderline ventriculomegaly²⁶.

Counselling couples in which isolated agenesis of the corpus callosum is serendipitously encountered at antenatal sonography in the absence of associated anomalies remains a difficult task. Pediatric series are mainly based upon investigation of symptomatic individuals and are, therefore, presumably biased. Many authorities believe that agenesis of the corpus callosum in itself has little consequence for neurological development, that will be revealed only by specific tests⁸. However, no specific risk figures are available at present. Prenatal sonographic diagnosis represents a unique opportunity in this regard, in that it allows the evaluation of a population of individuals identified independently from neurological manifestations. Vergani and co-workers¹⁵ reported that three infants with prenatal diagnosis of agenesis of the corpus callosum had normal or borderline developmental quotients at a 3-year follow-up examination. In our series, a normal developmental quotient was found in nine of 11 non-familial cases with a follow-up ranging between 6 months and 11 years, and a borderline development was found in the remaining two. Although we realize that the number of cases and the duration of follow-up are limited, we believe that these results are worthy of note. The diagnosis of isolated agenesis of the corpus callosum in the fetus leads to concern about the possibility of an association with either genetic syndromes, inborn errors of metabolism or anatomic

anomalies which cannot be predicted by antenatal testing. However, the available experience suggests that callosal agenesis is compatible with a normal or borderline postnatal development in most cases. It should be remembered that agenesis of the corpus callosum is a unique condition that, even in the presence of a normal intelligence, is associated with peculiar neurological findings and subtle cognitive deficits. The interested reader is referred to specific works on this subject^{8,49-53}. A possible relationship between agenesis of the corpus callosum and psychotic disorders has also been hypothesized⁵⁴.

In continuing pregnancies, the diagnosis of fetal isolated agenesis of the corpus callosum does not require any modification of standard obstetric management. In the present series, labor requiring Cesarean delivery occurred on several occasions, and this may be somehow related to the high frequency of macrocrania in infants with callosal agenesis⁸.

In routine sonograms, the demonstration in an axial view of the complex formed by the cavum septum pellucidum in close proximity to the frontal horns is postulated to rule out complete agenesis of the corpus callosum, although it does not exclude partial agenesis of the corpus callosum. Measurement of the atrial width is also helpful, as many cases of agenesis of the corpus callosum are associated with some degree of enlargement. However, in fetuses at specific risk for agenesis of the corpus callosum, a detailed examination of the brain, including the demonstration of the corpus callosum in sagittal and coronal views of the brain, is required.

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