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First-trimester ultrasound diagnosis of holoprosencephaly: three case reports

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ABSTRACT

We present three cases of fetal holoprosencephaly diagnosed by transabdominal and transvaginal ultrasound examinations at 10 and 13 weeks' gestation. The diagnosis was based on two sonographic criteria: first, the intracranial finding of a single ventricle with a cerebral mantle and no visible midline structures but fusion of the thalami and corpus striatum; and, second, facial abnormalities, including hypotelorism. The ultrasound findings were confirmed by embryoscopy before abortion in one case and by pathological examination after abortion in two cases. Chromosome study of the three fetuses showed trisomy 18, triploidy and mosaic 18p deletion and duplication.

INTRODUCTION

The earliest diagnosis of holoprosencephaly has been reported at 10.5 weeks' gestation[1]. We present three cases of early diagnosis of the condition at 10 and 13 weeks' gestation.

CASE REPORTS

Case 1

A 38-year-old Chinese woman was referred for prenatal diagnosis at 13 weeks' gestation because of advanced maternal age in her fourth pregnancy. She had three normal children. Abdominal ultrasound examination (ATL Ultramark 9, 3.5-MHz probe, USA) showed a live fetus with crown–rump length of 73 mm. Hypotelorism and a single ventricle were present, suggestive of holoprosencephaly (Figure 1). Amniocentesis was performed at 14 weeks' gestation, when a fetal proboscis was also noted. Chromosomal study of the cultured amniotic fluid cells showed a 47,XX,+18 chromosomal constitution. The couple requested termination of pregnancy. This was performed at 16 weeks' gestation by vaginal administration of prostaglandin. Examination of the abortus showed cyclops, proboscis, bilateral low-set ears, left facial skin nodule, overlapping fingers of the left hand and single umbilical artery (Figure 2).

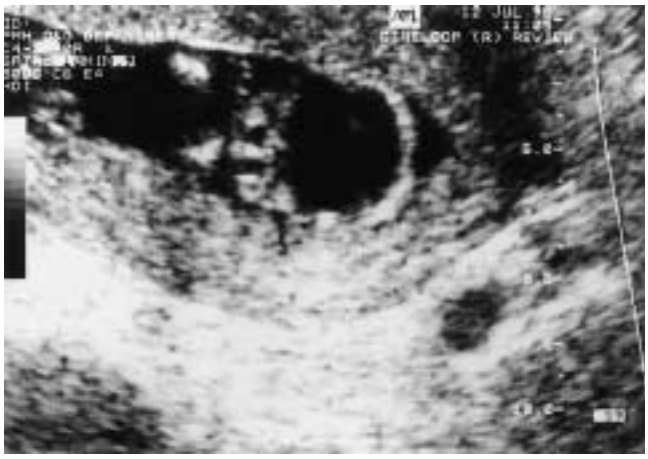

Figure 1 Case 1: transabdominal ultrasound finding at 13 weeks of hypotelorism and a single cerebral ventricle suggestive of holoprosencephaly

Case 2

A 31-year-old Chinese woman underwent an abdominal ultrasound examination (ATL Ultramark 9, 3.5 MHz) for dating at 10 weeks' gestation. This showed a single live fetus of crown–rump length 36 mm, corresponding to 10 weeks' gestation. Holoprosencephaly was suspected. The findings of holoprosencephaly (Figure 3), proboscis (Figure 3) and hypotelorism (Figure 4) were confirmed with transvaginal ultrasound examination (ATL Ultramark 9, 5 MHz). Amniocentesis was performed 3 days later. The couple requested termination of pregnancy because of the poor fetal prognosis. This was performed by administration of vaginal prostaglandin. Postmortem examination confirmed the presence of a proboscis, hypotelorism and

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holoprosencephaly. Chromosome study of the cultured amniotic fluid cells showed triploidy.

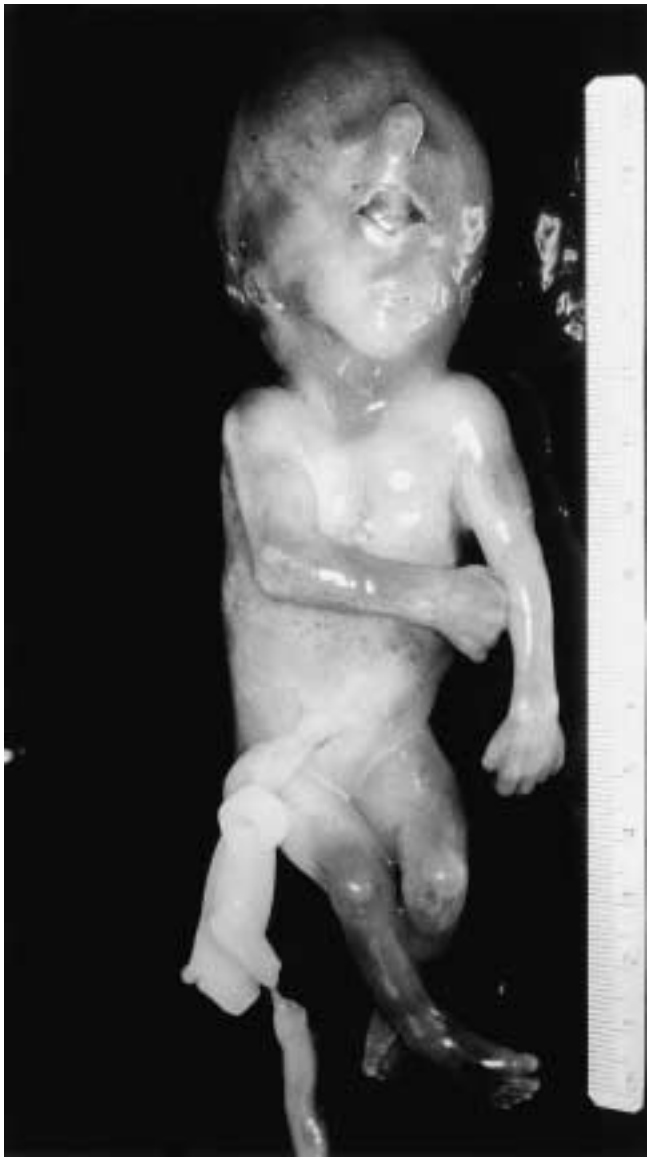

Figure 2 Case 1: postmortem picture of the fetus showing cyclops, proboscis, bilateral low-set ears and left facial nodule

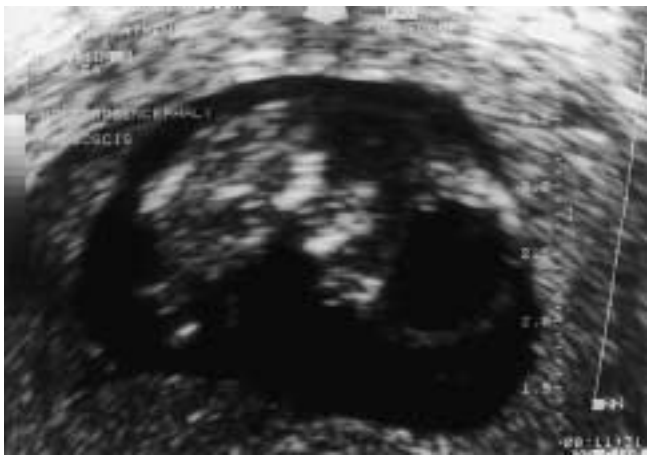

Figure 3 Case 2: transvaginal ultrasound examination showing a proboscis and dilated single cerebral ventricle

Case 3

A 36-year-old Chinese woman underwent an abdominal ultrasound examination (Acuson 128 XP10, 5 and 7 MHz, Mountain View, CA, USA) at 13 weeks' gestation for dating. This showed a live fetus with crown–rump length of 71 mm. Nuchal translucency was increased, and measured 4 mm. A detailed transvaginal ultrasound examination (Acuson 128 XP10, 7 MHz) demonstrated fetal semilobar holoprosencephaly (Figure 5), with a proboscis, single orbit and exomphalos. Chorionic villus biopsy was performed. In view of the poor fetal prognosis, the woman elected for pregnancy termination. She declined medical induction. Transabdominal needle embryoscopy (Karl Storz, Germany, 1-mm endoscope) was performed as described by Reece and co-workers[2]. This confirmed that the fetus had a proboscis, a single eye and no nose. The pregnancy was terminated by suction curettage. Chromosome study of the cultured chorionic villi showed a 46,XX,18p–/46,XX,18p+/46,XX,i(18q)/46,XX chromosome constitution in a ratio of 28 : 23 : 5 : 5. The mosaic cell lines were found in all three subcultures.

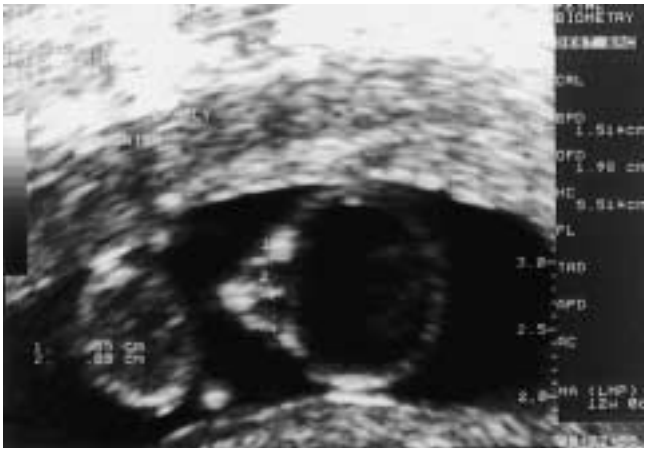

Figure 4 Case 2: transvaginal ultrasound examination showing hypotelorism, single ventricle, fused thalami and a thin layer of cerebral mantle

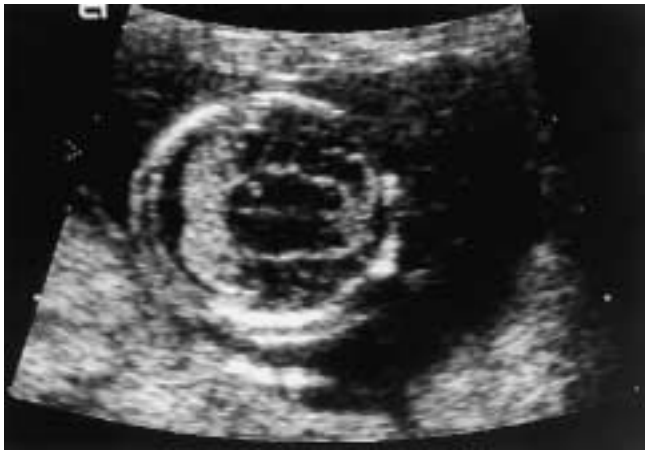

Figure 5 Case 3: transvaginal ultrasound examination showing semilobar holoprosencephaly at 13 weeks

Table 1 Pathological findings in holoprosencephaly

	Alobar	*Semilobar*	*Lobar*
Cerebral hemisphere	interhemispheric fissure and falx cerebri totally absent	cerebral hemispheres partially separated posteriorly; presence of occipital lobes	cerebral hemispheres almost completely divided, with a variable degree of fusion at the cingulate gyrus
Midline structures	absence of the third ventricle, neurohypophysis, olfactory bulbs and tracts	olfactory bulbs and corpus callosum usually absent	olfactory bulbs and tracts and corpus callosum may be absent, hypoplastic or normal

Table 2 Ultrasonographic findings in holoprosencephaly

	Alobar	*Semilobar*	*Lobar*
Ventricles	single	single; rudimentary occipital horns	almost divided except at frontal horns of lateral ventricles; some enlargement of lateral ventricle; flat roof of frontal horns in midcoronal view; wide communication between the frontal horns and the inferior third ventricles
Dorsal sac	present/absent	present/absent	absent
Thalami	fused	fused	divided
Septum cavum pellucidum	absent	absent	absent

DISCUSSION

The frequency of holoprosencephaly has been reported as between one in 5200 and one in 26 730 live births[3–5], but may affect as many as 0.4% of all conceptuses[6].

The diagnosis of holoprosencephaly has been reported as early as 10.5 weeks[1], with other reported diagnoses made at 14 weeks[7,8], 13 weeks[9,10] and 12 weeks[11]. The development of the telencephalon into the two halves of the cerebrum is complete by the beginning of the 10th week of gestation[12]. The diagnosis was made at 10 weeks in the second case presented, at a time close to the theoretical earliest limit for making the diagnosis.

Greene and colleagues[13] proposed the use of two criteria for the prenatal sonographic diagnosis of alobar holoprosencephaly: first, the intracranial criterion of a large central fluid collection in the fetal head, with no visible midline structures but with the presence of a mantle around the fluid collection and fusion of the thalami and corpus striatum; second, sonographic facial abnormalities including hypotelorism, central clefts, facial asymmetry and abnormal orbits. Similarly, Chervenak and associates[14] considered that both hypotelorism and absence of the midline should be observed sonographically to diagnose holoprosencephaly with certainty. The same criteria were used by Parant and colleagues[8]. In the three cases presented here, both of these criteria were satisfied. The better resolution provided by the transvaginal route further increased confidence in the diagnosis.

Although a spectrum of malformations is found in holoprosencephaly, it is generally accepted that the malformation can be divided into three major varieties: alobar, semilobar and lobar types[15,16]. The pathology and ultrasound findings in these types are shown in Tables 1 and 2, respectively.

Because the majority of affected fetuses die shortly after birth[17], and those surviving are severely mentally retarded[5], the benefit of antenatal diagnosis in early pregnancy allowing the option of pregnancy termination is significant. The termination can be performed by prostaglandin induction to preserve an intact fetus for postmortem confirmation. Alternatively, the external morphological fetal abnormalities can be visualized via needle embryoscopy to confirm the ultrasound findings before abortion by suction curettage, as in Case 3.

Chromosomal abnormalities are found in 20–67% of fetuses with holoprosencephaly. The commonest abnormality is trisomy 13[18]. However, associations with trisomy 18[19,20], del(13q), del(18p), dup(3p), del(7)(q36)[21], del(21)(q22.3)[22], –14, + t (13;14)[14] and triploidy[13] have also been reported. Multiple chromosomal defects were noted in 39% of cases[18]. In the three cases presented, trisomy 18, triploidy and mosaic duplication and deletion of chromosome 18 were detected, highlighting the need for karyotyping.

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