

Alobar holoprosencephaly at 9 weeks gestational age visualized by two- and three-dimensional ultrasound

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ABSTRACT

We present the ultrasound detection of alobar holoprosencephaly (HPE) with cyclopia in an embryo of 9 weeks 2 days last menstrual period (LMP)-based gestational age; the crown–rump length (CRL) was 22 mm. The use of three-dimensional (3-D) ultrasound made additional diagnostic ultrasound tomograms possible, and the volume reconstructions improved the imaging and the understanding of the condition.

INTRODUCTION

Cyclopia has been known since antiquity, as described by Homer in the figure of Polyphemos, the giant cyclopic shepherd from Sicily who was blinded by Odysseus and his men (Homer, *Odysseus journeys*, 9th song, approximately 800 years BC). Cyclopia is associated with holoprosencephaly (HPE) which is a severe central nervous system (CNS) anomaly.

The prenatal recognition of HPE by ultrasound has been described in many papers since the first description by Kurtz *et al.*¹ in 1980, and with increasing quality of ultrasound equipment detection is now possible at an increasingly earlier gestational age. During the 1980s, the transabdominal route allowed diagnosis mainly in the second and third trimester^{1–10}. Detection of HPE was made as early as 14 weeks of gestation in a case with semilobar HPE⁹, and as early as 16 weeks in a case associated with cyclopia¹¹. The transvaginal approach made post-embryonic sonographic diagnoses of holoprosencephaly possible^{12–21}. Detection of anomalies during the embryonic period, which extends until approximately 10 weeks 0–1 days last menstrual period (LMP)-based gestational age, is unusual.

We describe a HPE embryo with cyclopia and proboscis identified at the beginning of the 9th week of gestation by two- (2-D) and three-dimensional (3-D) ultrasound. We

used a specially designed 3-D transvaginal transducer with a 7.5-MHz annular array probe (System V, GE Vingmed Ultrasound).

The statements of gestational age are based on the LMP.

CASE REPORT

The 31-year-old gravida 6 para 1 was referred to our department because of habitual abortion. Her husband had a balanced chromosomal translocation (46,XY,t(8;14)(p21.1; q24.1). At the first examination the gestational age was 9 weeks 2 days according to the LMP. The biometric ultrasound data were: crown–rump length (CRL) 22 mm, biparietal diameter (BPD) 10 mm, occipito-frontal diameter (OFD) 11 mm, mean abdominal diameter (MAD) 9 mm, and heart rate 175 b.p.m. The evaluation of the embryonic anatomy showed abnormal development of the brain with a small monoventricular endbrain behind the forehead (Figure 1a). In addition, a proboscis was found (Figure 1b). The physiological anterior flexure of the head to the body made the evaluation of the lower face difficult. Seven days later, the ultrasound measurements were: CRL 33 mm, BPD 13.5 mm, OFD 14 mm, MAD 12.5 mm. The extension of

Table 1 The volume (mm³) of the brain cavities of the holoprosencephalic embryo compared with mean volumes found in normal embryos/fetuses (in parentheses)^{22,23} of corresponding sizes

	Crown–rump length	
	22 mm (vol.)	33 mm (vol.)
Telencephalic cavity	5ÿ.6(41.5)	11ÿ.6(191.5)
Diencephalic cavity	11ÿ.5(7.3)	10ÿ.3(5.6)
Mesencephalic cavity	12ÿ.4(7.9)	21ÿ.2(12.1)
Rhombencephalic cavity	66ÿ.7(21.0)	46ÿ.7(23.5)

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Figure 1(a) Horizontal section through the head of the 9-week-2-day (LMP-based) embryo, CRL 22 mm, showing the non-division of the forebrain. (b) Tilted section through the head; the mesencephalon and holosphere are visible; in addition, a proboscis can be seen to the left anteriorly to the forehead. (c) Three-dimensional reconstruction of the embryo with volume presentation of body and brain cavities. The lines indicate the sections in (a) and (b). * = holosphere (yellow), D = diencephalon (green), M = mesencephalon (red), Rh = rhombencephalon (blue).

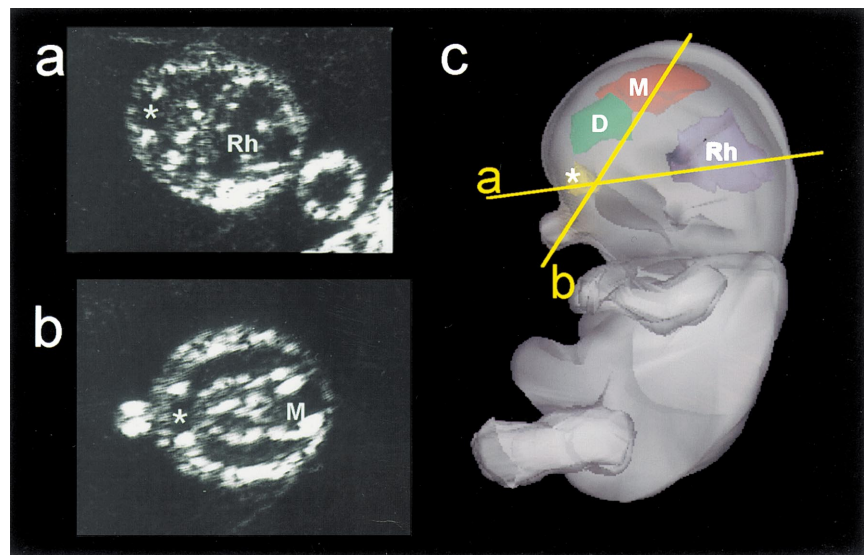


Figure 2 Sagittal anyplane slices from 3-D reconstructions. (a) Normal fetus, CRL 30 mm, the brain cavities are visible. The third ventricle is connected with the mesencephalic cavity by the isthmus prosencephali. The mesencephalic cavity (M) leads to the future fourth ventricle (Rh) through the isthmus rhombencephali. (b) Embryo with holoprosencephaly, CRL 33 mm. In the midline, the abnormal small holosphere and the proboscis in front of the forehead can be seen. The arrow points at the cyclops (compare with Figure 3b-d). * = holosphere, D = diencephalon, M = mesencephalon, Rh = rhombencephalon.

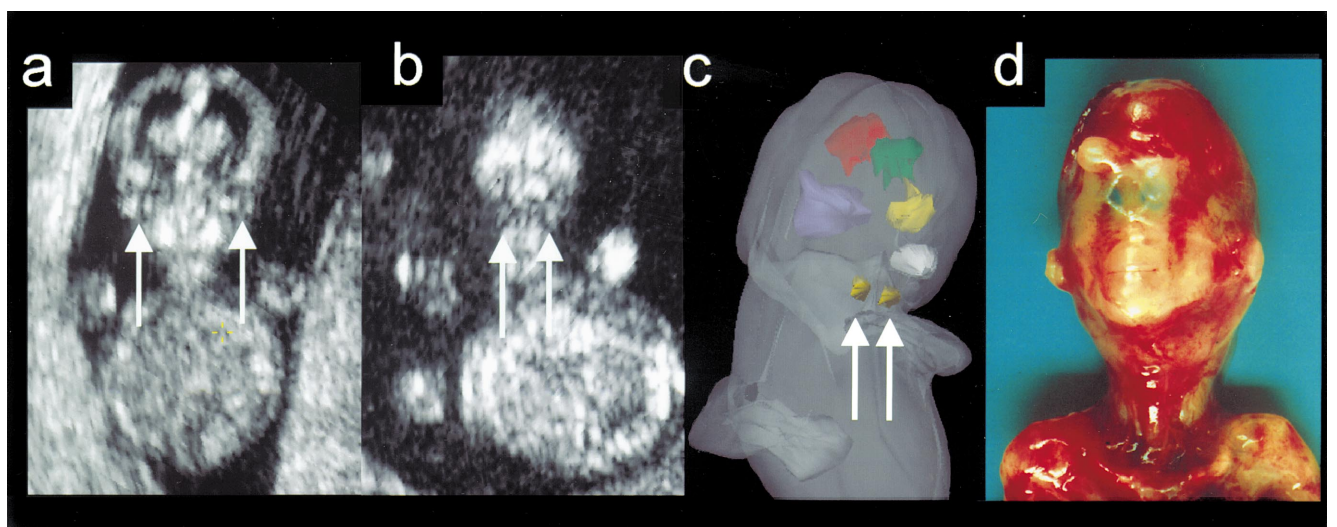
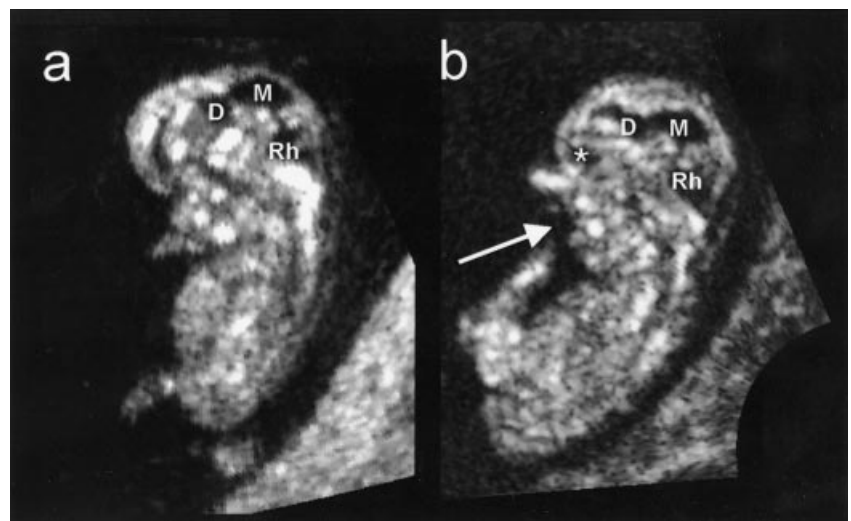


Figure 3(a) Coronal section through the face of a normal fetus, CRL 30 mm, showing the physiological hypertelorism of the eyes (arrows). (b) Fetus with holoprosencephaly, CRL 33 mm, two eye-anlagen are lying close together (arrows). (c) Three-dimensional reconstruction of the same fetus with the holosphere (yellow) and the cavities of the diencephalon (D, green), mesencephalon (M, red) and rhombencephalon (Rh, blue), and the eye-anlagen (yellow, arrows). (d) Post-abortem photograph of the fetus with cyclops, two eye-anlagen, and proboscis.

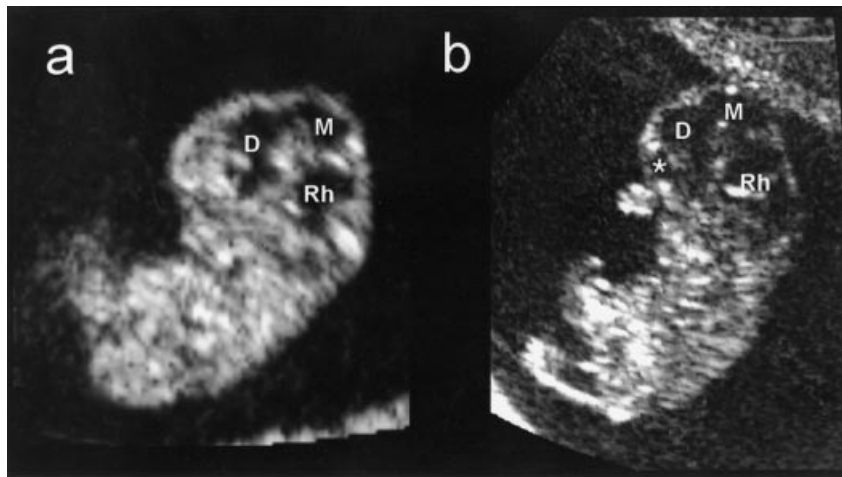


Figure 4 Sagittal anyplane slices from 3-D reconstructions. (a) Normal embryo, CRL 22 mm, the normal brain cavities are visible. (b) Embryo with holoprosencephaly, CRL 22 mm. In the midline, the abnormal small holosphere and the proboscis in front of the forehead can be seen. * = holosphere, D = diencephalon, M = mesencephalon, Rh = rhombencephalon.

the physiological herniation was 5 mm (Figure 2b). Apart from the CNS anomaly no defects were detected.

We made 3-D ultrasound reconstructions from both examinations. The body, including the proboscis and all brain cavities, were outlined by manual segmentation and given different colors (Figures 1c and 3c; Table 1). We evaluated the face by anyplane slicing (Figures 2b, 3b and 4b) and were able to identify two eye-anlagen lying close together below the proboscis at 10 weeks of gestation (Figure 3b). There was a small monoventricular holosphere behind the forehead, connected to the diencephalon by a narrow duct (Figures 1c, 2b, 3c and 4b).

Chorion villus biopsy at 10.5 weeks revealed the same balanced translocation as that of the father.

The patient was informed about the diagnosis of alobar HPE at the first visit. With the informed consent of the patient, the pregnancy continued until 12.5 weeks of gestation before TOP using PGE₁ prostaglandin was performed. This was done to confirm^{22,23} the diagnosis by ultrasound, by karyotyping and by post-abortem autopsy.

The autopsy (Figure 3d) confirmed the diagnosis of alobar holoprosencephaly associated with cyclopia with two eye-anlagen, proboscis, and a small monoventricular holosphere.

DISCUSSION

Knowledge of normal²⁴ and abnormal²⁵ neural development is important in understanding the appearance of HPE. The occurrence of the primitive streak in the epiblast of the two-cellular layer embryonic disc at Carnegie stage 6²⁶ initiates the developmental phase 'gastrulation'. Cells from the organizer tissue²⁷ in the primitive node migrate anteriorly along the midline and establish the notochord and the prechordal plate. Molecular signals from these midline structures induce the overlying ectoderm to differentiate into a plate of neuroepithelium²⁸. The process of neurulation converts the neural plate into the neural tube. The neurulation is completed at Carnegie stage 12²⁶ after approximately 5.5 weeks based on the LMP. The optic primordia develop from the diencephalic part of the forebrain at Carnegie stage 10, at 5 weeks 1 day²⁶. The

future hemispheres arise as small bilateral evaginations from the endbrain at Carnegie stages 14 and 15, which correspond to 6 weeks and 4–5 days. If there are defective signals from the notochord or prechordal plate, holoprosencephaly may develop²⁹.

Aborted human embryos with more or less severe anomalies of the neural tube have been presented by embryologists and pathologists. In 1910, Mall showed a photograph of an embryo of 16 mm CRL with iniencephaly and a ventral wall defect³⁰. In a study from Japan, where 36380 induced first trimester abortions were examined, 150 cases with HPE were identified³¹. Histologically, the diagnosis could be made from Carnegie stage 13 onwards, which corresponds to approximately 6 weeks 0 days. Matsunaga and Shiota calculated the incidence of HPE to be 1 : 250 in early pregnancies. Most of the cases ($n = 63$) were categorized as 7-week-old embryos of Carnegie stages 16 and 17. Using high-frequency 2-D and 3-D ultrasound, the development of the brain can be depicted in detail from 7 weeks 0 days onwards²³. Consistently, the hemispheres become visible during week 7 in embryos of about 10 mm CRL. Therefore, it should be possible to suspect alobar HPE as early as 7 weeks when embryos have a CRL of about 10 mm.

Three-dimensional ultrasound has been used to evaluate the shape and the volume of embryonic brain cavities²². Though the primary diagnosis was made by 2-D ultrasound, the presented case illustrates the possibilities opened by the 3-D imaging modality: The anyplane slicing helped to reconstruct 2-D sections of the face not available from the 2-D original scan plane. Thus, the two eye-anlagen could be identified. The segmentation of the brain cavities gave information about the volumes and about the shape (Figures 1c, 3c; Table 1). At 9 weeks 2 days the rhombencephalic cavity was large. In alobar HPE, usually varying degrees of fusion of the basal ganglia and/or thalami are found³². In the presented case, the third ventricle was still a considerably large cavity in the first trimester. The monoventricular cavity of the endbrain was, as expected, very small, in fact $< 1/10$ of the normal volume of the lateral ventricles.

The time and the number of targeted ultrasound examinations in high risk pregnancies for embryonic or

early fetal maldevelopment depend on the type of anomaly one is looking for, and on the geographical distance between the patient's home and the diagnostic centre. Though the diagnosis of certain anomalies can be suspected very early in gestation, efforts should be made to confirm the diagnosis by post-abortem examination. The importance of post-abortem confirmation of an ultrasound diagnosis is grounded in legal, ethical and genetic considerations. Since an abortion at 9 weeks will usually mutilate the embryo to such an extent that the examination by the pathologist/embryologist is impossible, a policy is recommended that implies the delay of termination of a pregnancy until 12–13 weeks with the informed consent of the patient.

The presented case illustrates that ultrasound diagnosis of embryonic anomalies, i.e. younger than 10 weeks LMP-based gestational age, has become possible. Two-dimensional ultrasound imaging was the basis for the detection of the anomaly. High-quality 2-D ultrasound tomograms, as achieved by annular array transducers, are important for good 3-D reconstructions. Three-dimensional ultrasound represents a supplement which may enhance the imaging of the condition and give further information.

REFERENCES

- Kurtz AB, Wapner RJ, Rubin CS, Cole-Beuglet C, Ross D, Goldberg BB. Ultrasound criteria for *in utero* diagnosis of microcephaly. *J Clin Ultrasound* 1980; 8: 11–16
- Hidalgo H, Bowie J, Rosenberg ER, Ram PC, Ford K, Lipsit E. *In utero* sonographic diagnosis of fetal cerebral anomalies. *Am J Roentgenol* 1982; 139: 143–8
- Blackwell D, Spinnato J, Hirsch G, Giles H, Sackler J. Prenatal diagnosis of cyclopia. *Am J Obstet Gynecol* 1982; 143: 848–9
- Hill LM, Breckle R, Bonebrake CR. Ultrasonic findings with holoprosencephaly. *J Reprod Med* 1982; 27: 172–5
- Mok P, Douglas-Jones A. Prenatal diagnosis of holoprosencephaly by sonography. *Aust Radiol* 1983; 27: 5–7
- Filly RA, Chinn DH, Callen PW. Alobar holoprosencephaly: ultrasonographic prenatal diagnosis. *Radiology* 1983; 151: 455–9
- Cayea PD, Balcar I, Alberti O, Jones TB. Prenatal diagnosis of semilobar holoprosencephaly. *Am J Roentgenol* 1984; 142: 401–2
- Chervenak FA, Isaacson G, Hobbins JC, Chitkara U, Tortora M, Berkowitz RL. Diagnosis and management of fetal holoprosencephaly. *Obstet Gynecol* 1985; 66: 322–6
- Nyberg DA, Mack LA, Bronstein A, Hirsch J, Pagon RA. Holoprosencephaly: prenatal sonographic diagnosis. *Am J Roentgenol* 1987; 149: 1051–8
- Pilu G, Romero R, Rizzo N, Jeanty P, Bovicelli L, Hobbins J. Criteria for the prenatal diagnosis of holoprosencephaly. *Am J Perinatal* 1987; 4: 41–9.
- Tóth Z, Csécséi K, Szeifert G, Török O, Papp Z. Early prenatal diagnosis of cyclopia associated with holoprosencephaly. *J Clin Ultrasound* 1986; 14: 550–3
- Bronshtein M, Wiener Z. Early transvaginal sonographic diagnosis of alobar holoprosencephaly. *Prenat Diagn* 1991; 11: 459–62
- Gonzales-Gomez F, Salamanca A, Padilla M, Camara M, Sabatel R. Alobar holoprosencephalic embryo detected via transvaginal sonography. *Eur J Obstet Gynecol Reprod Biol* 1992; 47: 266–70
- Nelson LH, King M. Early diagnosis of holoprosencephaly. *J Ultrasound Med* 1992; 1: 57–9
- Achiron R, Achiron A, Lipitz S, Mashiach S, Goldman B. Holoprosencephaly: alobar. *Fetus* 1994; 4: 7422: 19–12
- Bonilla-Musoles FM, Raga F, Ballester MJ, Serra V. Early detection of embryonic malformations by transvaginal and color Doppler sonography. *J Ultrasound Med* 1994; 13: 347–55
- Gembruch U, Baschat AA, Reusche E, Wallner SJ, Greiwe M. First trimester diagnosis of holoprosencephaly with a Dandy-Walker malformation by transvaginal ultrasound. *J Ultrasound Med* 1995; 14: 619–22
- van Zalen-Sprock R, van Vugt JM, van der Harten HJ, Nieuwint AW, van Geijn HP. First trimester diagnosis of cyclopia and holoprosencephaly. *J Ultrasound Med* 1995; 14: 631–3
- Pilu G, Perolo A, David C. Midline anomalies of the brain. In Timor-Tritsch I, Monteagudo A, Cohen HL, eds. *Ultrasonography of the Prenatal and Neonatal Brain*. Stamford: Appleton and Lange, 1996: 241–58
- Turner C, Silva S, Jeanty P. Prenatal diagnosis of alobar holoprosencephaly at 10 weeks of gestation. *Ultrasound Obstet Gynecol* 1999; 13: 360–2
- Wong HS, Lam YH, Tang MHY, Cheung LWK, Ng LKL, Yan KW. First-trimester ultrasound diagnosis of holoprosencephaly: three case reports. *Ultrasound Obstet Gynecol* 1999; 13: 356–9
- Blaas H-G, Eik-Nes SH, Berg S, Torp H. *In-vivo* three-dimensional ultrasound reconstructions of embryos and early fetuses. *Lancet* 1998; 352: 1182–6
- Blaas H-G. The embryonic examination. Ultrasound studies on the development of the human embryo [Thesis]: Norwegian University of Science and Technology, Trondheim, 1999: 1–178
- O'Rahilly R, Müller F. The embryonic human brain. In *An Atlas of Developmental Stages*. New York: Wiley-Liss, 1994
- Siebert JR, Cohen MM, Sulik KK, Shaw C-M, Lemire RJ, eds. *Holoprosencephaly: An Overview and Atlas of Cases*. New York: Wiley-Liss, 1990
- O'Rahilly R, Müller F. *Developmental Stages in Human Embryos*. Washington DC: Caneg Instn Publications, 1987
- Spemann H, Mangold H. Über Induktion von Embryonenanlagen durch Implantation artfremder Organisatoren. *Arch mikr Anat Entw Mech* 1924; 100: 599–638
- Rubenstein JLR, Shimamura K, Martinez S, Pelles L. Regionalization of the prosencephalic neural plate. *Annu Rev Neurosci* 1998; 21: 445–77
- Golden JA. Holoprosencephaly: a defect in brain patterning. *J Neuropathol Exp Neurol* 1998; 57: 991–9
- Keibel F, Mall FP, eds. *Handbuch der Entwicklungsgeschichte des Menschen*. Leipzig: Hirzel, 1910
- Matsunaga E, Shiota K. Holoprosencephaly in human embryos: epidemiologic studies of 150 cases. *Teratology* 1977; 16: 261–72
- Lemire RJ. Deep cerebral nuclei. In Lemire RJ, ed. *Normal and Abnormal Development of the Human Nervous System*. Hagerstown, MA: Harper & Row, 1975: 169–95