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**CASE PRESENTATION**

# Case report of alobar holoprosencephaly and review of the literature

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## ABSTRACT

**Introduction:** holoprosencephaly is a congenital malformation of the forebrain characterized by incomplete division of the cerebral hemispheres and midline structures, with high mortality and frequent association with facial anomalies.
**Objective:** to present a clinical case of alobar holoprosencephaly diagnosed prenatally by ultrasound and to discuss its clinical and prognostic implications in light of the scientific literature.
**Case presentation:** a 16-year-old primigravida, with no relevant medical history, presented for ultrasound screening for chromosomal abnormalities. Obstetric ultrasound revealed a single, live, and active fetus with an estimated gestational age of 12,4 weeks. Findings were consistent with alobar holoprosencephaly (absence of choroid plexuses, thalamic and cerebral fusion, persistence of a single ventricle, and absence of the interhemispheric fissure). Cranial morphology appeared normal; however, it was recommended to rule out midline facial abnormalities, such as cleft palate and hypertelorism, through a detailed second-trimester morphological ultrasound. In addition, invasive genetic studies—such as amniocentesis or chorionic villus sampling—were advised to exclude trisomy 13 or other associated chromosomal anomalies. The prognosis was considered poor, given its incompatibility with extrauterine life in most cases.
**Conclusions:** alobar holoprosencephaly represents the most severe form of this cerebral malformation. Early prenatal diagnosis by ultrasound is essential to classify severity, guide complementary studies, and provide genetic counseling. Accurate identification enables informing parents about the prognosis and planning an appropriate multidisciplinary management strategy.

**Keywords: Keywords:** Prenatal Diagnosis; Holoprosencephaly; Central Nervous System Vascular Malformations; Ultrasonography, Prenatal.

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## INTRODUCTION

Holoprosencephaly (HPE) is a developmental defect of the primitive brain that involves an alteration in the midline division of the embryonic prosencephalon. The prosencephalon fails to divide sagittally into the right and left cerebral hemispheres, transversely into the telencephalon and diencephalon, and horizontally into the olfactory tracts and bulbs. It occurs between days 18 and 28 of embryonic life and affects both the brain and face. It is a rare fetal pathology with highly heterogeneous etiologies, affecting approximately 1 in 15,000 to 16,000 births.[1,2]

To understand this disease, it is important to consider that the brain begins to develop in the third week, when the neural plate and tube are developing from the neuroectoderm. The neural tube cranial to the fourth pair of somites becomes the brain. The fusion of the neural folds in the cranial region and the closure of the rostral neuropore form the three primary brain vesicles from which the brain develops. The three primary brain vesicles form the prosencephalon, mesencephalon, and rhombencephalon.[3]

During the fifth week of embryonic development, the prosencephalon partially divides into two secondary brain vesicles: the telencephalon and the diencephalon, while the mesencephalon remains undivided, and the rhombencephalon partially segments into the metencephalon and the myelencephalon, resulting in a total of five secondary brain vesicles. The cavity of the telencephalon contributes to the formation of the rostral part of the third ventricle, while the majority of this ventricle is derived from the cavity of the diencephalon.[4]

In the developed brain, the left and right hemispheres remain separate but communicate via the corpus callosum, a bundle of nerve fibers, and each hemisphere is subdivided into frontal, parietal, occipital, and temporal lobes. This organization allows for the simultaneous processing of multiple pieces of information and the execution of various cognitive and motor functions. Disruptions in the proper division of the hemispheres, as occurs in HPE, cause multiple physical and neurological abnormalities, highlighting the critical importance of these processes during embryonic development.[5,6]

Although the classic definition of holoprosencephaly has many ambiguities, definitional problems are found at the less severe end of the phenotypic spectrum, which includes absence of olfactory bulbs and tracts (arhinencephaly), agenesis of the corpus callosum, hypopituitarism, and a single maxillary central incisor. Holoprosencephaly has traditionally been divided from most to least severe into:[1,6,7]

- Alobar holoprosencephaly: This type of pathology indicates that the fetal brain has not divided into two hemispheres at all. It results in the loss of midline structures of the brain and face, as well as the fusion of brain cavities.
- Semilobar holoprosencephaly: This indicates that the fetal brain has partially divided into two hemispheres. It occurs when the left side of the brain fuses with the right side in the areas known as the frontal and parietal lobes. Furthermore, the dividing line between the right and left hemispheres is only present at the back of the brain.
- Lobar holoprosencephaly: most of the brain has separated into two hemispheres, but the division of the two halves is incomplete. There are two ventricles (right and left), but the cerebral hemispheres are fused at the frontal cortex. This is the least severe form of HPE.

Early prenatal diagnosis of this malformation is essential for appropriate and timely obstetric management. Approximately two-thirds of fetuses diagnosed with HPE are of the alobar type, the most severe form.[2] Nearly 80 % of affected embryos or fetuses present with craniofacial anomalies. The most severe of the associated craniofacial anomalies are cyclopia,

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synophthalmos, and proboscis. Other less severe anomalies include microcephaly, hypotelorism, depressed nasal bridge, upper central interincisal diastema, and midline cleft lip and palate.[8] With this in mind, the present research was conducted, with the objective of presenting a clinical case of alobar HPE diagnosed prenatally by ultrasound and discussing its clinical and prognostic implications in light of the scientific literature.

## CLINICAL CASE REPORT

A 16-year-old female patient, primigravida, with a gestational age of 12.4 weeks (according to ultrasound) at the time of diagnosis. Her family and personal medical history, as well as any history of drug abuse or other chronic illnesses, is unknown. She presented for a screening ultrasound for aneuploidies, which revealed (Fig. 1) a single, breech, back-facing fetus, live, active, reactive, with preserved tone and motility, and a heartbeat of 145 bpm. Fetometry: CRL: 6.24 cm (12 weeks 4 days - Hadlock). Estimated gestational age by ultrasound: 12 weeks 4 days, extrapolated LMP: October 7, 2023, estimated due date: July 13, 2024.

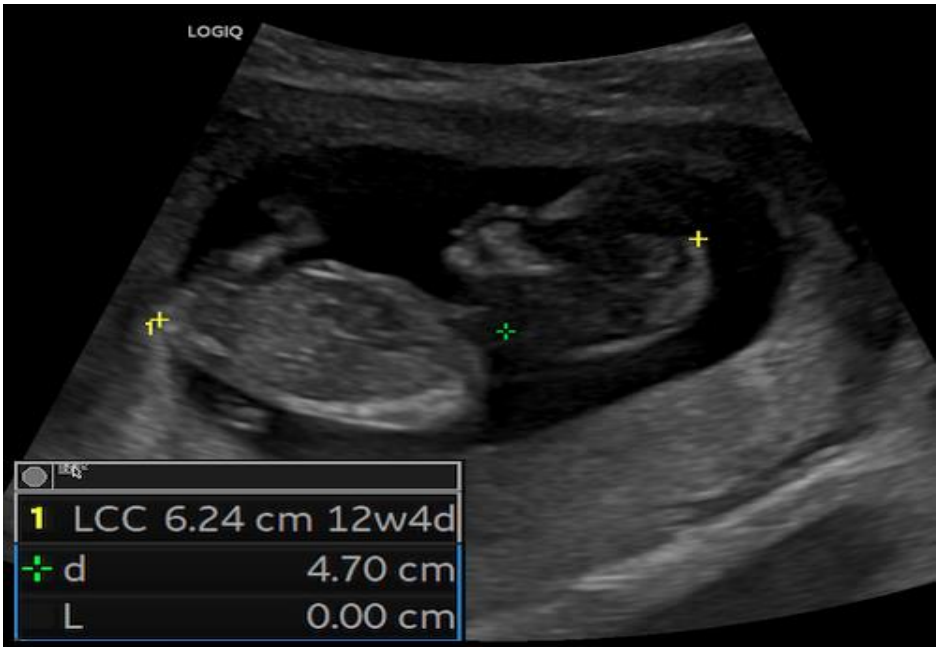


**Fig. 1** Fetus in neutral position for crown-rump length measurement.

In the ultrasound (Fig. 2), the axial slice shows absence of choroid plexuses, no choroid butterfly sign is observed, thalamic and cerebral fusion, ultrasound findings in relation to alobar holoprosencephaly.

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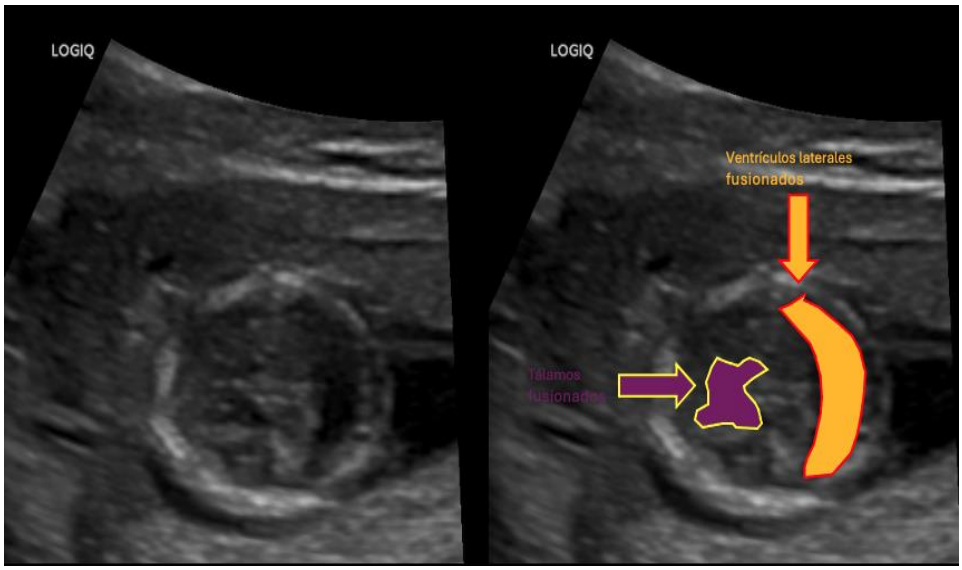
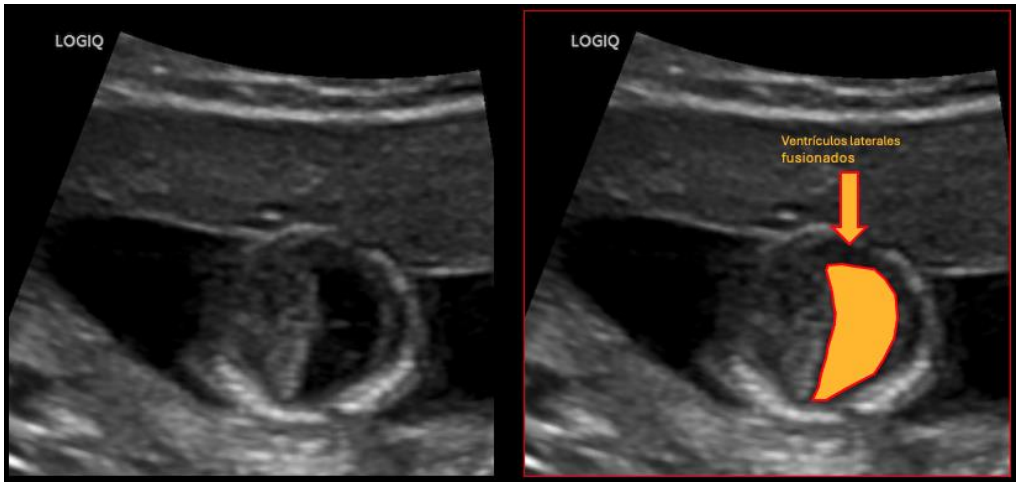



**Fig. 2** Fetal ultrasound. Axial section at the level of the cerebral thalami.

Figure 3, corresponding to a suprathalamic axial view of the fetal ultrasound, shows the absence of the usual morphology of the choroid plexuses, a finding that suggests a significant alteration in ventricular organization. Despite this, the skullcap maintains a normal morphology, ruling out associated bone defects at this level. Similarly, the persistence of a single lateral ventricle is noteworthy. The convergence of these findings reinforces the suspicion of a major brain malformation, with unfavorable prognostic implications for fetal neurological development.




**Grades:** The normal morphology of the choroid plexuses is not observed, the cranial vault has a normal morphology, and a single lateral ventricle persists.

**Fig. 3** Fetal ultrasound. Axial slice at the suprathalamic level.

Figure 4 shows the fusion of the cerebral hemispheres, indicating an alteration in the normal separation of brain structures. Despite this anomaly, the orbital basins and eyeballs are identifiable and clearly delineated in the coronal section.

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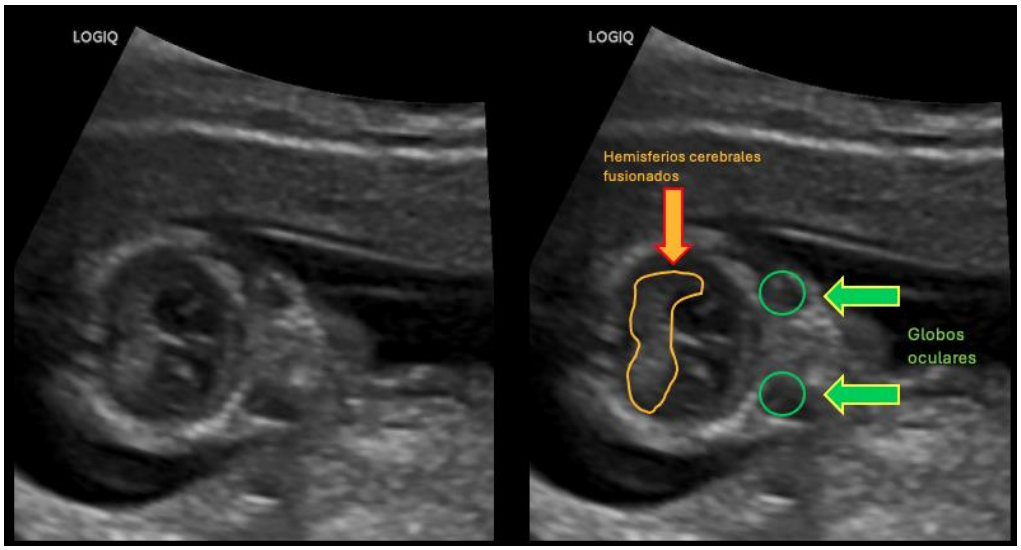


**Fig. 4** Fetal ultrasound. Coronal section at the supraorbital level.

In the transthalamic ultrasound study, axial slices show a morphological pattern characterized by the absence of the interhemispheric falx, indicating a lack of separation of the cerebral hemispheres, a typical finding in hypertrophic epithelial hyperplasia (HEP). At the lowest level (Fig. 5), an increase in the subarachnoid space is also observed, suggesting alterations in cerebrospinal fluid dynamics or brain volume loss. In the highest slice (Fig. 6), the persistent absence of hemispheric division is accompanied by agyria, that is, an absence of cortical gyri, reflecting a severe disruption of cortical organization.

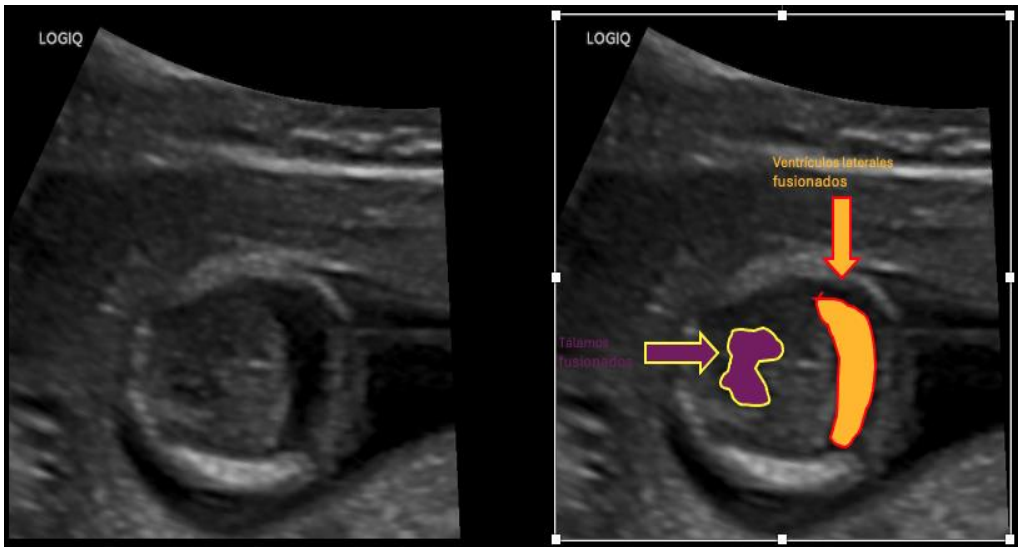


**Fig. 5** Fetal ultrasound. Transthalamic axial view.

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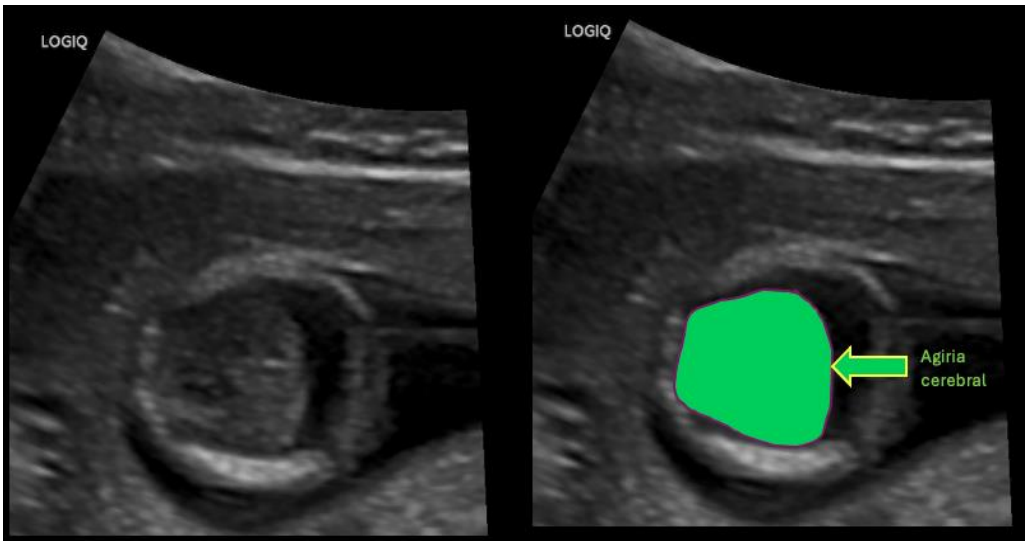


**Fig. 6** Transthalamic axial section (higher in relation to the previous one).



## DISCUSSION

HPE is a congenital malformation of the forebrain characterized by the lack of segmentation and proper division of the cerebral hemispheres during early embryonic development, typically between the third and fourth weeks of gestation. This structural alteration is frequently accompanied by midline facial anomalies, which can range from mild defects such as hypotelorism or a single central incisor to severe manifestations such as cyclopia, proboscis, or absence of the nose—features that are often correlated with the most severe forms of HPE, such as alobar HPE. HPE represents one of the most common and complex forebrain developmental disorders, with high phenotypic variability that depends on the extent of brain involvement and the presence of concomitant genetic and environmental factors.[9,10]

The etiology of HPE is multifactorial, including both genetic and environmental causes, often interacting. Among the genetic factors, chromosomal abnormalities are identified in approximately 25–50 % of cases, with trisomy 13 being the most frequent, representing around 75 % of these cases, followed by trisomy 18, triploidies, and other structural abnormalities. In individuals with a normal karyotype, mutations have been described in genes involved in brain signaling and development, mainly SHH (Sonic Hedgehog), ZIC2, SIX3, and TGIF1, which participate in ventral segmentation and the formation of midline structures of the forebrain. These mutations show variable penetrance and heterogeneous clinical expressivity, which explains the wide phenotypic diversity observed even within affected families. [9,11,12,13]

In addition to genetic factors, HPE is associated with several environmental risk factors. Poorly controlled maternal diabetes is one of the most well-documented, significantly increasing the risk of HPE in offspring, estimated at approximately 1 % of live births to mothers with uncontrolled hyperglycemia. Proposed mechanisms include oxidative stress, tissue hypoxia, apoptosis, and epigenetic alterations affecting genes involved in brain development. Other identified teratogenic factors include prenatal exposure to alcohol, retinoic acid, drugs that interfere with the SHH signaling pathway, and low levels of essential nutrients, such as folic acid. While multivitamin supplementation may reduce the risk of certain birth defects, it does not completely eliminate the risk of HPE associated with maternal diabetes. [6,14,15]

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HPE is clinically classified according to the extent of the brain defect. Alobar forms represent the most severe expression, with a complete absence of hemispheric division, while semilobar and lobar forms show partial or almost complete segmentation of the forebrain. Interhemispheric variants also exist, such as syntelencephaly, which manifests with focal midline involvement. This phenotypic classification is often correlated with the severity of facial anomalies and associated neurological and endocrine complications, including developmental delay, feeding disorders, and endocrinopathies.[16]

In prenatal diagnosis, detailed second-trimester ultrasound is the primary tool for identifying brain and facial abnormalities associated with HPE. Complementary chromosomal and molecular studies, such as karyotyping, amniocentesis, or genetic panels, can be performed to rule out trisomy 13 or other genetic mutations. Early identification allows for genetic counseling, appropriate perinatal planning, and multidisciplinary management of the affected newborn. This is especially relevant in cases of alobar HPE, where craniofacial and ventricular anomalies are more pronounced and may include hydrocephalus and dorsal midline cysts communicating with the ventricular system.[17,18]

The clinical management of HPE requires a multidisciplinary approach focused on evaluating brain anatomy, establishing prognosis, and treating associated neurological, endocrine, and respiratory complications. Following diagnosis, genetic and neuroimaging studies are essential to determine the HPE subtype and plan a therapeutic strategy centered on clinical stability and quality of life. In the neonatal period, care is directed toward controlling epileptic seizures, feeding difficulties, hypothalamic disorders, and providing palliative support when appropriate, especially in alobar forms. Family involvement and coordination among pediatrics, neurology, genetics, and palliative care are fundamental for comprehensive management.[19]



## CONCLUSIONS

Hemispheric hyperplasia (HPE) is a rare brain malformation affecting early embryonic and fetal development, characterized by the absence of hemispheric division and the formation of a unified brain. This can lead to a range of conditions, from cognitive impairments to facial malformations. Prenatal diagnosis is crucial for appropriate management, and ultrasound is the preferred imaging modality due to its accessibility. Management requires a multidisciplinary approach involving obstetricians, geneticists, neurosurgeons, and neonatologists, who must inform parents about the poor prognosis and refer newborns for early rehabilitation interventions. In the most severe cases, such as alobar HPE, the condition is incompatible with extrauterine life, necessitating compassionate and respectful support for families to make informed decisions based on their own values.



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