Case Report

Prenatal Diagnosis and Termination of Pregnancy for Alobar Holoprosencephaly with Cyclopia at 18 Weeks: A Case Report

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Abstract
Introduction: Holoprosencephaly is a rare brain malformation caused by the failure of the prosencephalon to divide into separate cerebral hemispheres. Alobar holoprosencephaly, the most severe form, presents with a monoventricle, lack of interhemispheric fissures, and craniofacial abnormalities such as hypotelorism and cyclopia. Early diagnosis and counseling are crucial for informed decision-making. This case highlights the ethical and diagnostic challenges involved in managing lethal fetal malformation.
Case Report: A 32-year-old pregnant woman at 18 weeks' gestation was referred to the fetomaternal clinic with a diagnosis of alobar holoprosencephaly, confirmed by ultrasound. The imaging revealed significant fetal malformations. After counseling, the patient chose to proceed with pregnancy termination. The patient underwent induction of labor without immediate complications. Psychological support and post-procedure counseling regarding the possibility of future pregnancies were provided in this case. Written informed consent was obtained from the patient for publication.
Conclusion: This case report describes a 32-year-old female, 18 weeks pregnant, diagnosed with alobar holoprosencephaly via ultrasound, who chose to terminate her pregnancy after being counseled on the prognosis. Alobar holoprosencephaly has poor outcomes. Early ultrasound diagnosis and counseling provided the family with the information needed to make an informed decision about pregnancy termination. Multidisciplinary support, including psychological and counseling, is essential for patients and their families when facing complex clinical decisions.

Keywords: Alobar holoprosencephaly; cyclopia; fetal malformation; prenatal diagnosis; pregnancy termination.

Prenatal Diagnosis dan Pengakhiran Kehamilan pada Alobar Holoprosensefali dengan Siklopia pada Usia 18 Minggu: Laporan Kasus

Abstrak
Pendahuluan: Holoprosensefali adalah malformasi otak yang langka, disebabkan oleh kegagalan prosensefalon untuk membelah menjadi dua hemisfer otak yang terpisah. Alobar holoprosensefali merupakan bentuk paling berat, ditandai dengan adanya satu ventrikel, tidak adanya fisura interhemisferik, serta kelainan kraniofasial seperti hipotelorisme dan siklopia. Diagnosis dan konseling dini sangat penting untuk pengambilan keputusan yang tepat. Kasus ini menyoroti tantangan etis dan diagnostik dalam menangani malformasi janin yang mematikan.
Laporan Kasus: Seorang wanita hamil berusia 32 tahun pada usia kehamilan 18 minggu yang dirujuk ke klinik fetomaternal dengan diagnosis alobar holoprosencephaly, yang dikonfirmasi melalui ultrasonografi. Pemeriksaan pencitraan menunjukkan kelainan janin yang signifikan. Setelah konseling, pasien memutuskan untuk melanjutkan dengan pengakhiran kehamilan. Pasien menjalani induksi persalinan tanpa komplikasi. Dukungan psikologis dan konseling pasca tindakan untuk kemungkinan kehamilan berikutnya diberikan pada kasus ini. Persetujuan tertulis untuk publikasi diperoleh dari pasien.
Kesimpulan: Laporan kasus ini mempresentasikan kasus wanita 32 tahun hamil 18 minggu, didiagnosis dengan alobar holoprosencephaly melalui pemeriksaan ultrasonografi, dan memutuskan untuk menghentikan kehamilan setelah mendapatkan konseling mengenai prognosis kondisi tersebut. Alobar holoprosencephaly memiliki prognosis yang buruk. Diagnosis dini melalui ultrasound dan konseling memungkinkan keluarga untuk membuat keputusan yang tepat terkait terminasi kehamilan. Dukungan multidisiplin ilmu termasuk dukungan psikologis dan konseling, sangat penting bagi pasien dan keluarga dalam menghadapi keputusan klinis yang kompleks.

Kata Kunci: Holoprosensefali alobar; malformasi janin; pengakhiran kehamilan; prenatal diagnosis; siklopia.

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Introduction

The most common malformation of the human forebrain is the developmental disorder holoprosencephaly (HPE). Patients with HPE show a wide range of craniofacial appearances, from nearly normal to the severe and devastating condition of cyclopia.[1] Cyclopia is a congenital malformation characterized by a single eye, often with various degrees of duplication of internal structures, located in the middle of the face where the root of the nose normally is.[2]

While cyclopia itself is a visually striking feature, it is often accompanied by a range of craniofacial abnormalities, including a proboscis (a tubular appendage) above the eye, a single nostril, and a cleft lip and palate. Additionally, affected individuals may show neurological deficits, respiratory distress, and feeding difficulties, reflecting the profound impact of this malformation on both facial and neurodevelopment.[2]

HPE is a heterogeneous disorder characterized by variable penetrance, multiple causes, and a surprisingly broad range of physical features. Fetuses affected by HPE have a high rate of spontaneous abortion of 1 in 250 pregnancies, which shows that, in its most severe form, the condition prevents further fetal development. Among those HPE fetuses that survive to birth, the physical abnormalities are often severe. Along with its high incidence rate (1:10-20,000 live births), HPE is the most common forebrain malformation seen in humans and is an important area of research.[1] This case adds to the limited national literature on prenatal diagnosis and management of lethal fetal anomalies in Indonesia, where access to genetic testing remains limited.

Case Report

The patient is a 32-year-old woman, gravida 2, para 1, with a history of one previous cesarean delivery resulting in a healthy neonate. Identifying details have been removed to protect patient confidentiality. The patient presented for routine prenatal care at 18 weeks' gestation with no complaints. This was her fourth ultrasound during this pregnancy. An ultrasound performed by her obstetrician did not definitively diagnose HPE but raised suspicion of a congenital anomaly. The patient was then referred to a maternal-fetal medicine specialist for further evaluation.

A detailed ultrasound examination by the specialist confirmed the diagnosis of alobar HPE with cyclopia in the fetus. The patient's personal and family history is unremarkable for congenital anomalies or significant medical illnesses. Laboratory results from routine blood tests are within normal limits. Her general condition and vital

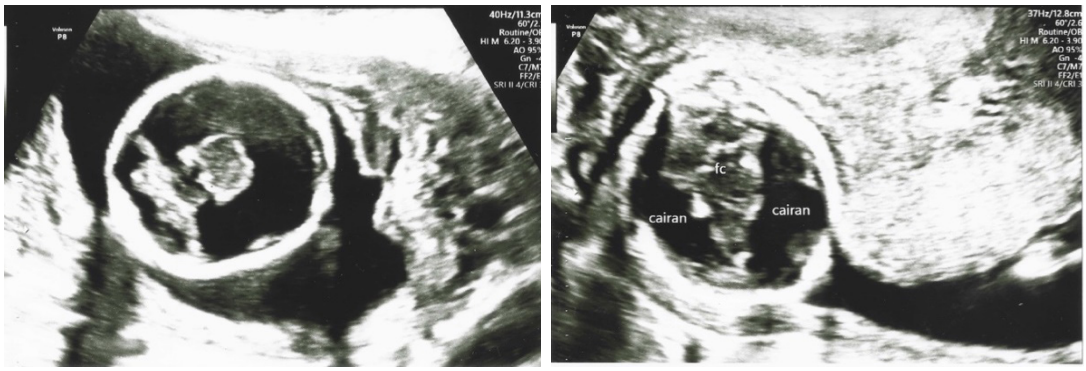

Figure 1 Transverse Cranial Image of The Fetus Showing Fused Thalami, an Abnormal Falx Cerebri, and Encircled by a Monoventricle.

Table 1 Prenatal Care and Clinical Findings of Alobar Holoprosencephaly

Prenatal Care	Age of Gestation	Clinical Finding	Notes
1	6 weeks	Fetal Pole+	Asam Folat, Vitamin D
2	10 weeks	Movement+	Asam Folat, Vitamin D
3	14 weeks	Movement+ Placenta Anterior	Asam Folat, Vitamin D, Calcium
4	18 weeks	USG: Fluid in the head Congenital Anomaly	Refers to Fetal Medicine
5	19 weeks	USG: Alobar HPE Cyclopia	Counseling Termination of Pregnancy Informed consent for Publication

Figure 2 3D ultrasound image and post-mortem photograph of the infant with Cyclopia

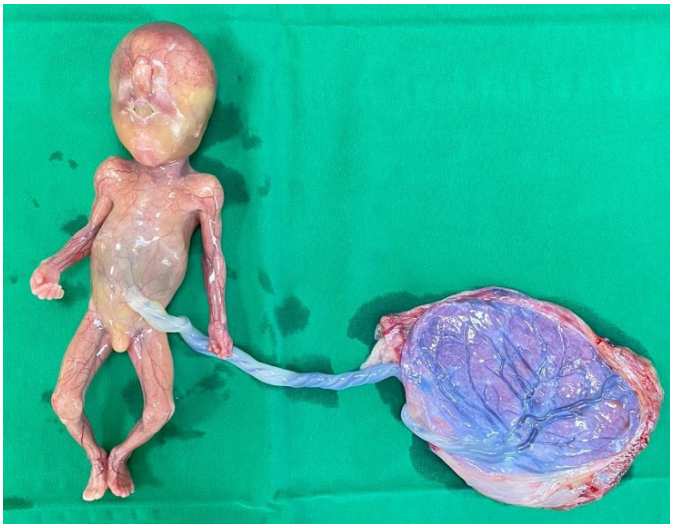

Figure 3 The Post-Mortem Photograph of The Infant with Multiple Severe Congenital Anomalies of Cyclopia. Key Findings Include a Prominent, Centrally Located Proboscis, Hypotelorism, and an Abnormally Shaped Forehead

signs are normal. Following the diagnosis, she demonstrated a good understanding of the condition and accepted the diagnosis without difficulty. She is a well-educated individual who actively engaged in discussions about her options. The patient resides in a rural area.

After extensive counseling on the diagnosis, prognosis, and available management options, the patient decided to terminate the pregnancy with informed consent. Because of the early gestational age and small fetal size, the termination was carried out through labor induction, resulting in vaginal delivery and fetal demise.

Labor induction was performed using misoprostol according to national guidelines for pregnancy termination in cases of lethal fetal anomalies. The patient tolerated the procedure well, and her physical condition was good at the time of discharge. The patient received comprehensive counseling on post-termination care and future family planning, including the recommendation for preconception counseling and folic acid supplementation if she desires future pregnancies.

Discussion

The management of this case showed several strengths, such as early diagnosis, thorough counseling, shared decision-making, suitable intervention, and supportive care. However, there were also limitations, including limited access to advanced fetomaternal services and the absence of genetic testing to identify the cause. It is important to recognize that the findings from this single case might not apply to other patients.

In early normal brain development, the prosencephalon, or forebrain, divides into the telencephalon and diencephalon. With holoprosencephaly, the prosencephalon fails to fully separate into two distinct cerebral hemispheres and the underlying diencephalic structures. The main forms of HPE exist on a spectrum that includes, with decreasing severity, alobar, semilobar, and lobar types. In the most severe form, alobar holoprosencephaly, there is a single monoventricle, with or without a covering mantle of cortex, that surrounds the fused central thalami (Fig. 4). In semilobar holoprosencephaly, the hemispheres are partially separated. Lobar HPE is characterized by varying degrees of fusion of the frontal structures. Lobar HPE should be considered when a normal cavum septum pellucidum cannot be visualized.[3]

Differentiation into two cerebral

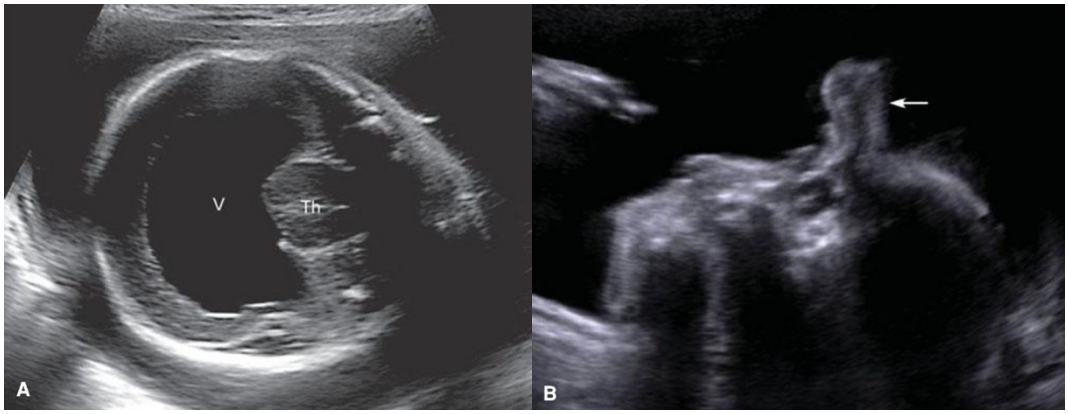

Figure 4 Alobar Holoprosencephaly. A. Transverse Cranial Image of a 26-Week Fetus Displaying Alobar Holoprosencephaly, Showing Fused Thalami (Th) Surrounded by a Monoventricle (V). The Midline Falx is Absent. B. In This Profile View of The Face and Head, A Soft Tissue Mass-A Proboscis (Arrow)—Protrudes from The Region of The Forehead.[3]

hemispheres is induced by prechordal mesenchyme, which is also responsible for the formation of the midline face. Thus, HPE may be associated with anomalies of the orbits and eyes, such as hypotelorism, cyclopia, or microphthalmia; lips-median cleft; or nose conditions like ethmocephaly, cebocephaly, or arhinia with a proboscis (Fig. 1).[3] Therefore, differential diagnosis with hydrocephalus was not included. The use of Magnetic Resonance Imaging (MRI) in Alobar HPE is crucial for diagnosis, evaluation, and treatment planning, but it is not performed in some cases due to cost limitations.

The prevalence of HPE is only 1 in 10,000 to 15,000. However, the abnormality has been identified in nearly 1 in 250 early abortuses, which attests to the extremely high in-utero lethality of this condition. The alobar form accounts for 40 to 75 percent of cases, and approximately 30 to 40 percent have a numerical chromosomal abnormality, particularly trisomy 13. Conversely, two-thirds of trisomy 13 cases are found to have holoprosencephaly. Fetal karyotyping should be offered when this anomaly is identified.[3]

The case we have presented involves early diagnosis of Alobar HPE Cyclopia in the first trimester, based on ultrasound findings. This diagnosis of HPE relies solely on sonographic features; there are no obstetric signs of the condition. Like most anomalies, the diagnosis is typically made during routine ultrasound screening or following a scan performed for other reasons.

It is important to distinguish HPE from simple hydrocephalus because they differ in both management and prognosis. Once alobar or semilobar HPE is definitively diagnosed, therapeutic termination should be offered due to the uniformly poor outcome.[4]

Like most cerebral structural congenital abnormalities, alobar HPE is visible across all imaging modalities, but it is generally detected through antenatal ultrasound (if conducted) and is best described by MRI.[4]

The key findings on ultrasound: In a fetus with alobar HPE, ultrasound can reveal characteristic features resulting from the failure of the forebrain (prosencephalon) to divide into two hemispheres. These findings include several cranial and brain abnormalities, such as a monoventricle, fused thalami, absent corpus callosum, absent interhemispheric fissure, absent cavum septi pellucidi, absence of the third ventricle, and, in some cases, middle and anterior cerebral arteries may be replaced by tangled branches of the internal carotid and basilar arteries. Severe facial malformations may also be present. These abnormalities are usually detectable during the second trimester ultrasound (after 18 weeks of gestation), although more severe cases may be suspected earlier with advanced imaging techniques like transvaginal ultrasound or 3D/4D imaging.[5]

Figure 2 displays a post-mortem photograph of the infant. The infant exhibits multiple severe congenital anomalies consistent with the prenatal diagnosis of alobar holoprosencephaly.

- Proboscis: A prominent, centrally located proboscis is observed above the expected position of the upper lip. This fleshy, tubular appendage replaces the nose and is a characteristic feature of severe holoprosencephaly, as indicated by prenatal ultrasound.
- Hypotelorism: The eyes are unusually close together, indicating hypotelorism. This finding aligns with the failure of normal midline brain development observed in holoprosencephaly.
- Midface Hypoplasia: Significant underdevelopment of the midfacial structures leads to an overall dysmorphic facial appearance.
- Abnormal Forehead: The forehead has an unusual slope and shape.

In cyclopia, a single orbital cavity develops due to the absence of the ethmoid complex, which normally separates the two orbits. The midline facial features, such as the nose, are significantly altered, with the nose often replaced by a proboscis located above the orbital cavity. This malformation indicates severe disruption in midline brain development, especially in the forebrain, which impacts nearby craniofacial structures. These changes stem from defects in the Sonic Hedgehog (SHH) protein signaling pathway, essential for early brain and facial development.[6]

In most cases, but not all, craniofacial manifestations tend to follow DeMyer's 1964 maxim, "the face predicts the brain." In other words, the severity of the craniofacial phenotype usually reflects the severity of brain malformations and correlates inversely with survival. The most severe facial phenotypes include pronounced microcephaly, cyclopia (a single, centrally placed eye), synophthalmic (partial union of the two eyes in the center of the face), and a proboscis (a tube-like nasal appendage with a single nostril located above the ocular region). Less severe facial phenotypes can include microcephaly (except in cases of hydrocephalus, which can cause macrocephaly), hypotelorism, midface hypoplasia with a flat nasal bridge, cleft lip and/or palate, ocular colobomas, and a single maxillary central incisor.

Individuals with microforms of holoprosencephaly, usually identified as relatives of probands with frank holoprosencephaly, have isolated craniofacial findings without the classic clinical issues and neurologic impairment seen in holoprosencephaly. Conversely, individuals with mutations in ZIC2, one of the genes implicated in select cases of holoprosencephaly, present an exception to the "face predicts the brain" maxim, as these patients have severe holoprosencephaly, neurologic impairment, and characteristic clinical sequelae, but have a much milder facial phenotype than that of other patients.[7]

In this case, further investigations to identify the underlying cause of alobar HPE, such as genetic testing or fetal MRI, were not pursued due to the patient's financial constraints. This highlights a major limitation in our understanding of the case. Identifying the specific cause of HPE, whether genetic or environmental, could have provided valuable information for counseling the patient about recurrence risks in future pregnancies and potential implications for other family members.

Genetic testing is vital for diagnosing and understanding HPE. Usually, a combination of gene-targeted testing and comprehensive genomic analysis is used to find the underlying cause. Gene-targeted methods, like single-gene testing or multigene panels, are employed when specific genes are suspected based on clinical signs, while broader approaches like chromosomal microarray analysis (CMA), genome sequencing, or exome sequencing are used without prior hypotheses about the genes involved. CMA, which detects genome-wide large deletions or duplications, has found pathogenic variants in up to 14% of individuals with HPE who have normal karyotypes and negative results on multigene panels. Karyotyping remains a key test when trisomy 13 is suspected clinically, as it is one of the most common chromosomal abnormalities linked to HPE.[8]

Single-gene testing is prioritized when a specific syndromic cause is suspected, focusing on sequence analysis to detect point mutations or small deletions/duplications in key genes like SHH, ZIC2, or SIX3. If no variants are found, gene-targeted deletion or duplication analysis is recommended. Multigene panels, designed to include HPE-associated genes, are highly effective in identifying causative mutations while reducing the risk of uncertain findings. Comprehensive genomic testing,

including exome or genome sequencing, is valuable when gene-targeted methods are inconclusive. These techniques are especially effective at identifying multiexon deletions or duplications, particularly in cases showing evidence of Mendelian inheritance. Together, these genetic testing strategies offer a strong foundation for determining the molecular cause of HPE and guiding clinical management.[8]

The absence of etiological details in this case creates difficulties in counseling the patient about future pregnancies. While the recurrence risk for alobar HPE is generally considered low, it may be significantly higher depending on the underlying cause. Without additional investigation, providing an accurate and personalized risk assessment remains challenging. Despite this limitation, the patient was given comprehensive counseling on the importance of preconception care and folic acid supplementation to lower the risk of neural tube defects in future pregnancies.

This case highlights the importance for healthcare providers to recognize and tackle potential barriers to accessing diagnostic services, such as financial limitations. Identifying options for financial assistance or alternative diagnostic methods may be necessary to ensure patients receive the most thorough care possible. Moreover, it is essential to offer comprehensive counseling and support to patients, even when a clear cause cannot be identified, to help them make informed decisions about their healthcare and future family planning.

Beyond the acknowledged limitations in this case, fetal MRI is an important adjunct to ultrasound for outlining midline brain and craniofacial abnormalities, refining prognostication, and supporting counseling in suspected holoprosencephaly. MRI complements sonographic findings by better defining commissural structures, thalamic fusion, dorsal cysts, and facial anomalies relevant to decision-making. Incorporating MRI when available enhances counseling quality in severe cases such as alobar HPE with cyclopia.[9-11]

Similarly, molecular diagnostics now go beyond karyotype and chromosomal microarray. In fetuses with structural anomalies, prenatal exome sequencing (pES) offers additional diagnostic information that clarifies the cause and helps assess recurrence risk. A large cohort study reported an 8.5% overall yield, while a meta-analysis found a pooled incremental yield of approximately 31% over karyotype/CMA, with higher yields in pre-selected phenotypes. These findings support offering pES (or genome sequencing where available) when initial testing is inconclusive and when results could influence counseling and reproductive decisions planning.[12-14]

Recurrence risk in HPE varies and depends on cause. Reviews show that when a monogenic autosomal-dominant variant with incomplete penetrance is identified (e.g., SHH, ZIC2, SIX3), the recurrence can be much higher than in cases related to aneuploidy; conversely, in aneuploidy such as trisomy 13, the empiric recurrence risk is usually low (~1%). This variability highlights the clinical importance of determining the cause whenever possible and the necessity for customized pre- and post-test genetic counseling.[9,13,14]

Finally, contemporary literature and recent case reviews confirm that in alobar HPE with cyclopia, outcomes are consistently poor; therefore, ethically sensitive, multidisciplinary counseling that discusses options including termination of pregnancy when legal and culturally appropriate remains the standard. Clear counseling that incorporates imaging and genetics best supports shared decision-making and equitable care, especially in resource-limited settings similar to this case.[9-11,15]

This case emphasizes the ethical importance of obtaining written informed consent before publication, especially when

postmortem fetal images are shared. It also highlights the need for better access to genetic diagnostics in resource-limited settings.

Conclusion

This case of alobar holoprosencephaly with cyclopia diagnosed at 18 weeks of gestation highlights the importance of early prenatal diagnosis through ultrasound and the need for comprehensive counseling to support informed decision-making. The poor prognosis linked to this severe fetal anomaly requires a compassionate and supportive approach to patient care, helping families make difficult choices about pregnancy management. While this case demonstrates successful termination and post-termination care, it also exposes limitations in access to advanced genetic testing that could better inform future reproductive choices. Ultimately, this report underscores the need for ongoing advancements in prenatal diagnosis, accessible healthcare services, and empathetic patient counseling to address the challenges related to severe fetal anomalies.

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