# A Male Fetus with Cyclopia Was Discovered after Miscarriage: A Rare Case Report

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April 15, 2024

**Introduction:**

Cyclopia (synophthalmia) is a fatal uncommon congenital abnormality.[1-3] It is the severest case of holoprosencephaly (HPE).[1,3-7] During the organogenesis, the embryonic prosencephalon is divided partially or never into the right and left cerebral hemispheres,[2,3]which leads to the pilgrims not being divided into double separate caves.[1,4,7-9] This happens between the eighteenth and the twenty-eighth day of pregnancy.[1,4,7,8] The incidence is 1.05 per 100,000 births including stillbirth[1] with a tendency to occur in females[8]. Clinically, there are typical craniofacial features including a single or imperfectly cleft eye in one orbit, nasal agenesis or proboscis, which is a non-functional nose located above the central orbit and that is known as Rhinocephaly.[1-3,6,9,10] Furthermore, the extracranial characteristics along with Cyclopia, for instance, polydactyly, renal dysplasia, Omphalacele[1,2,6] also cardiac malformations such as ventricle septum defect (VSD).[10] Synophthalmia is possible to develop for no specific reason[7] or due to risk factors such as exposure to deformed substances during pregnancy[10], diabetes, infections[6], and genetic mutations[6,10]. This case is incompatible with life[4,5,7] either abortion or stillbirth or dying several hours after birth.[1,3,8,10] Diagnosis began from the 22$^{nd}$ week of pregnancy[6] by ultrasound (US).[4-7] The most common syndrome associated with Cyclopia is Patau (trisomy 13)[3,10]. Herein, we present a unique case of alobar holoprosencephaly with cyclopia which was diagnosed after miscarriage.

**Case presentation:**

A 29-year-old female presented to the Obstetrics and Gynecology Department with a sudden stop in pregnancy symptoms such as pregnancy craving, vomiting and nausea, accompanied by pain in the lower abdomen and mild bloody mottling. There were no other symptoms. The patient had a partus caesarius two years ago. Our patient has smoked 3 packs\year for 6 years. There was no other medical, family, surgical, or allergic history. The pregnancy age depends on the last menstrual cycle was 12 weeks +2 days. The patient had never had a US before. The US demonstrated a dead fetus inside the uterus at age 11 weeks with irregularities in the skull bones and severe cerebral malformation. A single orbital cave is also noted. The US investigation was ineffective. 800 mg of Misoprostol was prescribed to induce medical miscarriage (400 mg oral and 400 mg vaginal). The pathological exam demonstrated a male embryo measuring 7 cm in length (Fig. 1). Gross examination showed a single central orbit located in the middle of the face with a cutaneous horn above it (Fig. 2); and polydactyly in its foot, attached with a normal umbilical cord (Fig. 3). The visceral organs of the embryo were normal except the brain's front, which showed adhesion of its right and left hemispheres. A placenta measures 7 x 2 cm and is composed of normal villi and decidual tissue (Fig. 1).

**Discussion:**

HPE is a rare complex congenital malformation occurring in the human brain during organogenesis due to

a failure in dividing the prosencephalon into right and left hemispheres completely or partially[3-6,8,10], which causes a group of craniofacial anomalies.[5] There are three levels of HPE depending on the severity of the case: Lobar, characterized by the separation of the left and right ventricles with a degree of frontal cortical continuity, semi-labor where there is an incomplete separation, and alobar where the interhemispheric fissure is absent there is only one cerebral ventricle.[10] The alobar HPE is considered the most severe form due to its manifestation which also includes: undifferentiated cerebral hemispheres, a thalamic fusion[2,4], a missing corpus callosum, no olfactory nerves or optic tracts[4], and cyclopia.[8] The last is the rarest and most severe facial expression of alobar HPE.[1,3,7] Cyclopia is defined by the fusion of two optic grooves[1] as a result of the embryonic prosencephalon's improper division of the eye's orbits into two cavities.[3,6,7] Cyclopia itself is always an outward sign of a profound brain abnormality.[4] The term "cyclopia" refers to anarchist giant shepherds that had a single round eye in their front in Greek mythology.[8] The prevalence of newborns with cyclopia, including stillbirths, is 1.05 per 100,000 live births.[1] This congenital condition occurs during embryonic development, which typically happens between the 18th and 28th day of gestation[1,6,7], and there is a preponderance of female babies.[7,8] In our case, it was a male stillborn. This congenital condition occurs during embryonic development, which typically happens between the 18th and 28th day of gestation[1,6,7], and there is a preponderance of female babies.[7,8] The etiology of this condition is still unknown exactly.[1,2,7,9] Due to the embryonic forebrain and mid-face both deriving from the prechordal mesoderm, several facial malformations are typically linked, along with several other defects.[10] Despite the limitation of evidence, the Sonic Hedgehog (SHH) gene regulator was revealed to be involved in the division of the single eye field into two bilateral fields, so when mutations cause SHH muting, the result will be cyclopia and there is a fusion of the eye in the middle of the face.[3,6,8]Multiple heterogeneous risk factors are related. Both genetic and environmental factors are the possible culprits including teratogenic medication exposure during pregnancy (anticonvulsants, aspirin, retinoic acid, aspirin, lithium), maternal diabetes, alcohol consumption, infections like toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH), and chromosomal defects[1,2,6-9]. However, in this presented case, no risk factors could be observed. Alobar HPE is associated with many syndromes such as Smith-Lemli-Opitz Syndrome (SLOS), Pallister-Hall Syndrome, and Trisomy 13 'Patau Syndrome'[2,3,10], which is the most common cause of HPE.[10] The facial deformities associated with alobar HPE may include cyclopia, a single orbit with a median single eye, or a partly split eye[6,10]. The nose is either absent completely or replaced with a proboscis as a non-functioning nose[1,3,7,10]. Typically, such a proboscis is observed on the back or above the central eye and is a defining feature of a form of cyclopia known as rhinocephaly or rhinencephaly.[1]Missing philtrum, otocephaly, astomia or microstomia also could be found.[6] In our case, we found the typical facial features of cyclopia include: a median single orbit, the absence of a nose, and a proboscis above the eye (Fig. 2). The presence of extra-facial deformities like polydactyly, renal dysplasia, omphalocele[6-8], ventricular septal defects, and myelomeningocele reported in other literatures.[10] Only polydactyly in the left foot could be observed in our dead fetus (Fig. 3). During the first trimester, the US can reveal distinctive images that make it the most helpful investigation for diagnosing cyclopia.[1,2,4,6,7,9] After the third or fourth week of pregnancy, the US can typically detect clear indications of cyclopia or other forms of holoprosencephaly.[1] In most cases that were reported, the anomaly was detected early during the anomaly scan.[2] When HPE is suspected by the US, careful intrauterine scanning of the fetus's face can lead to a more accurate diagnosis.[4] However, the usual US may not detect certain features that are useful in diagnosis[7], thus obtaining more information about the development of brain structures is possible through in-utero magnetic resonance imaging (MRI)[4] or high-resolution MRI scans.[7] However, in our case, the woman never had any prenatal care and the anomaly was only discovered after the fetus was miscarried. The survival rate is extremely low in this condition[10] and the prognosis depends on brain fusion degree, malformation, and complications.[2,4] In cases of lobar HPE, children can survive for several years with neurological and mental challenges. Alobar and semi-labor HPE have been associated with the worst prognosis[2] and are not compatible with life.[2,4,7] Generally, the result will be a miscarriage or a stillborn, and even if a child is born alive, it dies within hours after birth.[2,3,6,7] The fetus in our case, presented with the alobar form of HPE associated with cyclopia (Fig. 1), Without being genetically tested after the medical expulsion. In all cases, termination of the pregnancy should always be offered as an option for management. This procedure follows a comprehensive prenatal examination and relevant genetic counseling, owing to the

severity of the defects. Further aids in the diagnosis of cyclopia include postnatal chromosomal analysis and gross examination of the specimen.[6,10]There is no currently known treatment for this condition, and there is no way to prevent it.[8] This report emphasizes the importance of prenatal check-ups, particularly in developing countries, and the significance of early ultrasound diagnosis for gestation termination and maternal psychological trauma prevention.

**Conclusion:**

Cyclopia is a rare lethal abnormality that occurs in the early stages of pregnancy, and this condition is incompatible with life. Routine check-ups during gestation have an important value in helping identify fetuses with anomalies and lead to pregnancy termination after the parent's approval.

**Abbreviations list:**

HPE: holoprosencephaly

VSD: ventricle septum defect

US: ultrasound

SHH: Sonic Hedgehog

TORCH: toxoplasmosis, rubella, cytomegalovirus, and herpes simplex

SLOS: Smith-Lemli-Opitz Syndrome

MRI: magnetic resonance imaging

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**Figure Legends:**

Fig. 1: Anomalous abortion with normal placenta.

Fig. 2: A single eye with proboscis above the eye.

Fig. 3: A postaxial polydactyly in the left foot.