Hypotelorism

Society for Maternal-Fetal Medicine; Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction

Hypotelorism is associated most commonly with the fetal holoprosencephaly spectrum and is rarely an isolated finding. Hypotelorism may also be caused by an abnormal skull shape, such as metopic synostosis or other forms of craniosynostosis.

Definition

Hypotelorism is defined as an interocular distance of <5th percentile for gestational age.[1]

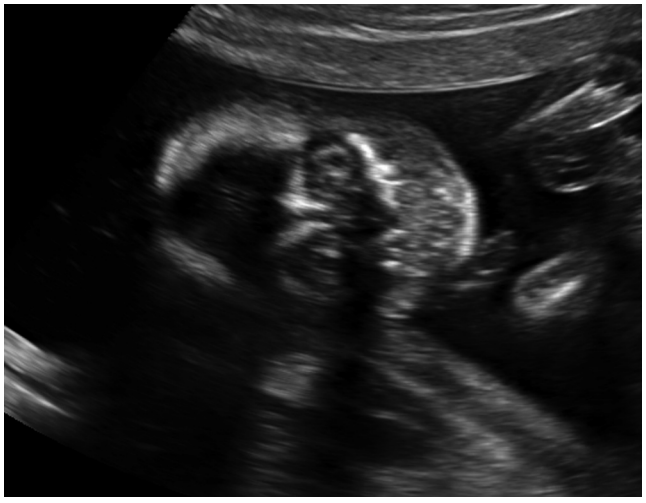
Ultrasound Findings

The coronal view of the fetal face is the best way to evaluate the orbits. The modified coronal view, which shows the upper lip, nose, and lower orbits and is similar to the view used to visualize a facial cleft, is also useful for assessment of the orbits. Charts are available for normative data of the outer-to-outer and inner-to-inner orbital diameters, although most often the hypotelorism is not subtle. Isolated hypotelorism is almost never detected in utero. Other facial, intracranial, or head shape abnormalities are almost always present (Figures 1–3).

Associated Abnormalities

Hypotelorism is most often associated with central facial cleft lip and palate of the type that is seen with holoprosencephaly sequence and midline brain defects, such as septo-optic dysplasia. If the fetus also has heart defects and polydactyly, trisomy 13 is a likely diagnosis.[2,3] Craniosynostosis can also cause abnormal interocular distances; this condition is associated with Crouzon syndrome and other asymmetric forms of craniosynostosis.

FIGURE 1
Coronal view of a fetus with hypotelorism



Coronal view shows a fetus with hypotelorism at 17 weeks of gestation.

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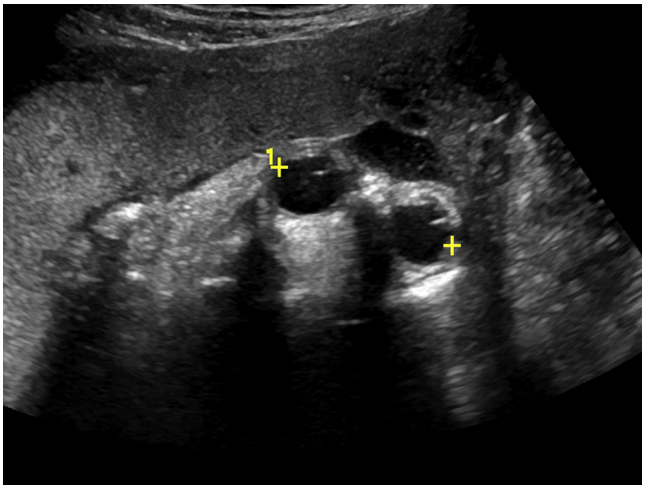
FIGURE 2
Transverse view through the orbits of a fetus with hypotelorism in the third trimester



Note that the orbits are side by side and close together.

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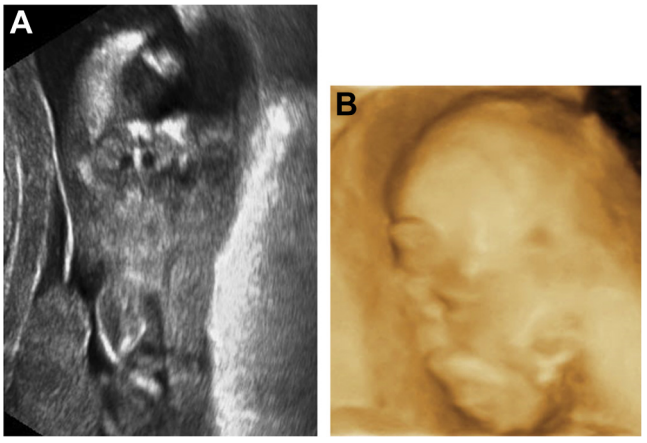
FIGURE 3
Two- and three-dimensional surface rendering



A, Two-dimensional and **B,** three-dimensional surface rendering of the face of a fetus with trisomy 13 and cyclopia with a proboscis above the single orbit.

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Differential Diagnosis

Although the diagnosis of hypotelorism is usually subjective without a true differential diagnosis, the orbits may be distorted or impinged on by masses such as intracranial teratomas (associated with an intracranial component) that can displace an orbit medially. As mentioned earlier, hypotelorism can also result from craniosynostosis and other syndromes. Severe hypotelorism is usually syndromic and rarely is isolated.

Genetic Evaluation

Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when hypotelorism is detected. Given the association with trisomy 13, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization with reflex to CMA if these test results are normal, particularly if other suggestive findings (polydactyly or heart defects) are present. If there are additional anomalies, consanguinity, or a family history suggestive of a genetic condition, gene panel testing or exome sequencing is sometimes useful because CMA does not detect single-gene (Mendelian) disorders. Gene panel testing should be tailored to associated sonographic findings, and appropriate panels may include genes that are associated with holoprosencephaly sequence. If exome sequencing is pursued, appropriate pretest and posttest counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[4] After appropriate counseling, cell-free DNA screening is an option for patients who decline diagnostic evaluation when a common aneuploidy is suspected. In isolated cases, a parental examination occasionally can reveal mild familial hypotelorism.

Pregnancy and Delivery Management

In addition to a detailed ultrasound examination, careful evaluation of the fetal cardiac anatomy is important, and a fetal echocardiogram should be considered. Fetal magnetic resonance imaging can be useful to assess any intracranial findings or for detection of subtle anomalies not detected by ultrasound imaging. Referral to pediatric ophthalmology and craniofacial specialists may be considered. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected, although with truly isolated, mild hypotelorism, the prognosis should be excellent. No change in route of delivery is necessary for isolated hypotelorism, although delivery at a tertiary care center with pediatric genetic, craniofacial, and ophthalmology services should be considered.

Prognosis

Prognosis is dependent on the associated findings and underlying diagnosis. Isolated hypotelorism has a favorable prognosis.

Summary

Hypotelorism is a rare abnormality and is almost always associated with a syndrome, most commonly holoprosencephaly. Associated anomalies are usually present and depend on the underlying syndrome. Detection of such anomalies should help to direct the genetic evaluation.

REFERENCES

1. Burns NS, Iyer RS, Robinson AJ, Chapman T. Diagnostic imaging of fetal and pediatric orbital abnormalities. AJR Am J Roentgenol 2013;201:W797–808.
2. Pineda-Alvarez DE, Solomon BD, Roessler E, et al. A broad range of ophthalmologic anomalies is part of the holoprosencephaly spectrum. Am J Med Genet A 2011;155A:2713–20.
3. Guion-Almeida ML, Richieri-Costa A, Zechi-Ceide RM. Holoprosencephaly spectrum, ano/microphthalmia, and first branchial arch defects: evidence for a new disorder. Clin Dysmorphol 2008;17:41–6.
4. International Society for Prenatal Diagnosis, Society for Maternal Fetal Medicine, Perinatal Quality Foundation. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. Prenat Diagn 2018;38:6–9.