



TEXAS

Department of State Health Services
Birth Defects Epidemiology and Surveillance

BIRTH DEFECT RISK FACTOR SERIES: HOLOPROSENCEPHALY

DEFINITION

Holoprosencephaly is a brain malformation that is caused by a primary defect in patterning and induction of the basal forebrain during embryogenesis, causing the brain to develop improperly and resulting in incomplete division of the cerebral hemispheres (Stashinko 2004). The level of non-separation of the cerebral hemispheres indicates the severity of this defect. From most severe to least, the types of holoprosencephaly include alobar, semilobar, and lobar. In alobar holoprosencephaly, there is a single, small ventricular cerebrum without division into hemispheres, a single ventricle, and absent olfactory bulbs and optic tracts. In semilobar holoprosencephaly, there are rudimentary cerebral lobes with partially separated hemispheres. In lobar holoprosencephaly, the central lobes are well developed and the fissure between the hemispheres is distinct, but there is still some fusion of brain structures. Facial anomalies are frequently present, ranging in severity from a flattened nose and closely spaced eyes through a cleft or split lip and a single nostril to cyclopia, where a nose-like proboscis is present over a single eye in the middle of the face. Hydrocephaly or microcephaly is sometimes present. Recently, a fourth type of holoprosencephaly has been described. Middle interhemispheric variant of holoprosencephaly occurs when the rear portion of the brain (posterior frontal and parietal areas) do not separate but the frontal portion of the brain is preserved (Stashinko 2004).

Infants with this defect have a variable survival rate depending upon the severity of the defect. However, it is common for surviving children with this defect to manifest a variety of neurological disorders, including cognitive and developmental delays, seizures, motor impairment, and endocrinologic dysfunction (Stashinko 2004).

GENETIC BASIS

Recent literature has suggested that holoprosencephaly can be caused by either a single gene mutation or as part of a syndrome with multiple genetic anomalies (Wallis 2000). This defect can occur spontaneously or it can be inherited from the parents. Individuals with very mild manifestations of this defect will often have facial changes including hypotelerism, hypertelerism, flat nose, or cleft lip (Wallis 2000). More severe facial defects associated with holoprosencephaly include cyclopia, ethmocephaly, or cebocephaly (Kinsman 2000). While it is often true that the "face reflects the brain", it should be noted that severity of facial defects does not always reflect the severity of the defect in holoprosencephaly.

Approximately half of all infants or fetuses with holoprosencephaly also have chromosomal abnormalities, most often trisomy 13 (Blaas 2002, Bullen 2001, Ming 1998, Peebles 1998, Olsen 1997, Croen 1996, Rasmussen 1996, Cohen 1989). Certain genes or chromosomal regions have been linked to holoprosencephaly; among the genes is Sonic Hedgehog (Shh) found in the 7q36 region (Ming 1998, Peebles 1998), SIX3 (Wallis 1999), and ZIC2 (Brown 2001, Brown 1998). The incidence is much higher among fetal deaths than among live births (Odent 1998).

Genetically normal infants may also present with holoprosencephaly. When the defect presents in children without genetic defects, it is often assumed that the infant was exposed to a teratogenic agent in utero (Croen 2000).

Prenatal ultrasound can detect the more severe forms of holoprosencephaly, and associated defects such as hydrocephaly (Peebles 1998, Vintzileos 1987, Chervenak 1985, Chervenak 1984). Studies from various birth defects surveillance systems have found that, in regions where elective termination is allowed, prenatal diagnosis and elective termination reduce the birth prevalence of holoprosencephaly (Blaas 2002, Bullen 2001, Forrester 2000, Croen 1996, Rasmussen 1996).

EMBRYOLOGY

Holoprosencephaly occurs as a result of failure of the forebrain (prosencephalon) of the embryo to divide into the two cerebral hemispheres, which normally occurs by the 5th-6th week gestation. There is some indication that inhibition of cholesterol synthesis may cause holoprosencephaly. Cholesterol is necessary for Sonic Hedgehog (Shh) to function as it should; any metabolic disruptions that prevent the processing of cholesterol will inhibit Shh functions (Kinsman 2000).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

V Studies have reported differences in risk between racial/ethnic groups, but the differences have not been consistent among the studies (Forrester 2000, Olsen 1997, Croen 1996, Rasmussen 1996). One study indicated that foreign-born women (outside of the U.S. and Mexico) have a higher risk for having a child with holoprosencephaly (Croen 2000). Additionally, women with early menarche are more likely to have a child with holoprosencephaly (Croen 2000).

Several studies have reported an increase in holoprosencephaly prevalence over time. However, these secular trends may reflect improvements in the diagnosis and ascertainment of cases (Rasmussen 1996). Additionally, selective termination of severe cases may change the prevalence of live-birth holoprosencephaly.

One investigation that evaluated geography failed to find differences in risk between urban and rural areas (Forrester 2000).

Maternal age has been associated with holoprosencephaly risk. Women younger than age 25 and older than age 35 are more likely to have an infant with holoprosencephaly. The increased risk among older women is associated with the fact that older women are more likely to have an infant with a chromosomal abnormality (Forrester 2000, Olsen 1997, Croen 1996, Rasmussen 1996).

The recurrence risk for a woman who has had one child with holoprosencephaly depends on whether a chromosomal abnormality is involved and the type of chromosomal abnormality. Multiple occurrences of isolated holoprosencephaly without chromosomal abnormalities have been reported in the same family, further supporting a genetic or hereditary basis for at least a portion of holoprosencephaly cases (Ming 1998, Odent 1998, Peebles 1998, Rasmussen 1996).

Infant sex influences the risk for holoprosencephaly. The defect is much more common among females than among males (Croen 2000, Forrester 2000, Olsen 1997, Croen 1996, Rasmussen 1996), although one study observed a higher rate of males among prenatally diagnosed cases (Blaas 2002). One investigation reported a higher than anticipated number of holoprosencephaly cases among multiple births (Bullen 2001).

Another investigation reported no statistically significant association between holoprosencephaly and macrosomia (Waller 2001).

FACTORS IN LIFESTYLE OR ENVIRONMENT

One study has reported an association between low socioeconomic status and holoprosencephaly risk (Cohen 1989). However, this observation has not been confirmed.

A case-control study found a suggestion of an association between cytogenetically normal holoprosencephaly and maternal alcohol consumption during early pregnancy (Cohen 2002). Maternal smoking, respiratory illness medications, and salicylate-containing medications have also shown teratogenic effects (Croen 2000). However, some of these associations were not statistically significant. Another study reported no significant link between alcohol, smoking, or x-ray exposure and holoprosencephaly risk (Cohen 1989). An investigation failed to identify any significant association between holoprosencephaly and proximity to various types of industry (Castilla 2000).

Maternal diabetes has been reported by several studies to increase holoprosencephaly risk (Croen 2000, Ming 1998, Peebles 1998, Ramos-Arroyo 1992). However, one investigation reported no relationship between diabetes and holoprosencephaly (Becerra 1990). It should be noted that diabetes causes a series of metabolic disturbances, and these disturbances interfere with fetal development. Other metabolic disturbances, including cholesterol production, can affect the Sonic Hedgehog (Shh) signaling pathway (Cohen 2002).

Other maternal factors that have been tentatively associated with holoprosencephaly, based on anecdotal evidence or studies involving small numbers of cases, include retinoic acid, salicylates, estrogen/progestin, anticonvulsants, weight reduction diets and/or low maternal weight, previous pregnancy loss, and congenital infection with cytomegalovirus, rubella, and toxoplasmosis (Croen 1996). One survey that involved a small number of cases failed to identify any association between holoprosencephaly and retinoic acid (De Wals 1991). A case-control study suggests that risk of holoprosencephaly may be increased with maternal use of misoprostol, a synthetic prostaglandin used for elective termination (Orioli 2000).

There is no information available about the use of multivitamins and folic acid to reduce the incidence of holoprosencephaly (Czeizel 2004). Maternal residence and vicinity to solid waste incinerators or landfills does not increase the incidence of holoprosencephaly (Cordier 2004), nor does maternal exposure to pesticides (Berkowitz 2003), biological solvents (Wennborg 2005), or marijuana (Fried 2000).

PREVALENCE

Birth prevalence in the United States for holoprosencephaly is not currently known. The rate in Texas for 1999-2002 deliveries was 1.21 cases per 10,000 live births (Texas Department of State Health Services 2005). Differences in prevalence may be due to differences in case inclusion criteria.

REFERENCES

- Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics* 1990;85:1-9.
- Berkowitz G, Obel J, Deych E, Lapinski R, Godbold J, Liu Z, Landrigan P, Wolff M. Exposure to indoor pesticides during pregnancy in a multiethnic urban cohort. *Environmental Health Perspectives*, 2003;111:.

- Blaas HG, Eriksson AG, Salvesen KA, Isaksen CV, Christensen B, Mollerlokken G, Eik-Nes SH. Brains and faces in holoprosencephaly: pre- and postnatal description of 30 cases. *Ultrasound Obstet Gynecol* 2002;19:24-38.
- Brown LY, Odent S, David V, Blayau M, Dubourg C, Apacik C, Delgado MA, Hall BD, Reynolds JF, Sommer A, Wieczorek D, Brown SA, Muenke M. Holoprosencephaly due to mutations in ZIC2: alanine tract expansion mutations may be caused by parental somatic recombination. *Hum Mol Genet* 2001;10:791-796.
- Brown SA, Warburton D, Brown LY, Yu CY, Roeder ER, Stengel-Rutkowski S, Hennekam RC, Muenke M. Holoprosencephaly due to mutations in ZIC2, a homologue of Drosophila odd-paired. *Nat Genet* 1998;20:180-183.
- Bullen PJ, Rankin JM, Robson SC. Investigation of the epidemiology and prenatal diagnosis of holoprosencephaly in the North of England. *Am J Obstet Gynecol* 2001;184:1256-1262.
- Castilla EE, Campana H, Camelo JS. Economic activity and congenital anomalies: an ecologic study in Argentina. *Environ Health Perspect* 2000;108:193-197.
- Chervenak FA, Isaacson G, Mahoney MJ, Tortora M, Mesologites T, Hobbins JC. The obstetric significance of holoprosencephaly. *Obstet Gynecol* 1984;63:115-121.
- Chervenak FA, Isaacson G, Hobbins JC, Chitkara U, Tortora M, Berkowitz RL. Diagnosis and management of fetal holoprosencephaly. *Obstet Gynecol* 1985;66:322-326.
- Cohen MM. Perspectives on holoprosencephaly: Part 1. Epidemiology, genetics, and syndromology. *Teratology* 1989;40:211-235.
- Cohen, M, Shiota, K. Teratogenesis of Holoprosencephaly. *American Journal of Medical Genetics*, 109: 1-15, 2002.
- Cordier S, Chevrier C, Robert-Gnansia E, Lorente C, Brula P, Hours M. Risk of congenital anomalies in the vicinity of municipal solid waste incinerators. *Occup Environ Med* 2004; 61: 8-15.
- Croen LA, Shaw GM, Lammer EJ. Risk factors for cytogenetically normal holoprosencephaly in California: A population-based case-control study. *Am J Med Genet* 2000;90:320-325.
- Croen LA, Shaw GM, Lammer EJ. Holoprosencephaly: epidemiologic and clinical characteristics of a California population. *Am J Med Gen* 1996;64:465-472.
- Czeizel A. The primary prevention of birth defects: multivitamins or folic acid? *International Journal of Medical Sciences*. 2004;1:1:50-54.
- De Wals P, Bloch D, Calabro A, Calzolari E, Cornel MC, Johnson Z, Ligutic I, Nevin N, Pexieder T, Stoll C, Tenconi R, Tilmont P. Association between holoprosencephaly and exposure to topical retinoids: results of the EUROCAT survey. *Paediatr Perinatal Epidemiol* 1991;5:445-447.
- Forrester MB, Merz RD. Epidemiology of holoprosencephaly in Hawaii, 1986-97. *Ped Perinatal Epidemiol* 2000;14:61-63.
- Fried P. The consequences of marijuana use during pregnancy: a review of the human literature. *Women and Cannabis: Medicine, Science, and Sociology*, Haworth Integrative Healing Press, 2000.
- Kinsman S, Plawner L, Hahn J. Holoprosencephaly: recent advances and new insights. *Current Opinion in Neurology*, 13: 127-132, 2002.
- Ming JE, Muenke M. Holoprosencephaly: from Homer to Hedgehog. *Clin Genet* 1998;53:155-163.

- Odent S, Le Marec B, Munnich A, Le Merrer M, Bonaiti-Pellie C. Segregation analysis in nonsyndromic holoprosencephaly. *Am J Med Genet* 1998;77:139-143.
- Olsen CL, Hughes JP, Youngblood LG, Sharpe-Stimac. Epidemiology of holoprosencephaly and phenotypic characteristics of affected children: New York State, 1984-1989. *Am J Med Gen* 1997;73:217-226.
- Orioli IM, Castilla EE. Epidemiological assessment of misoprostol teratogenicity. *BJOG* 2000;107:519-523.
- Peebles DM. Holoprosencephaly. *Prenat Diagn* 1998;18:477-480.
- Ramos-Arroyo MA, Rodriguez-Pinilla E, Cordero JF. Maternal diabetes: the risk for specific birth defects. *Eur J Epidemiol* 1992;8:503-508.
- Rasmussen SA, Moore CA, Khoury MJ, Cordero JF. Descriptive epidemiology of holoprosencephaly and arhinencephaly in Metropolitan Atlanta, 1968-1992. *Am J Med Gen* 1996;66:320-333.
- Stashinkio, E, Clegg, N, Kammann, H, Sweet, V, Delgado, M, Hahn, J, Levey, E. A retrospective survey of perinatal risk factors of 104 living children with holoprosencephaly. *American Journal of Medical Genetics*, 2004;128A:114-119.
- Vintzileos AM, Campbell WA, Nochimson DJ, Weinbaum PJ. Antenatal evaluation and management of ultrasonically detected fetal anomalies. *Obstet Gynecol* 1987;69:640-660.
- Waller DK, Keddie AM, Canfield MA, Scheuerle AE. Do infants with major congenital anomalies have an excess of macrosomia? *Teratology* 2001;64:311-317.
- Wallis D, Muenke M. Mutations in holoprosencephaly. *Human Mutations*, 2000;16:99-108.
- Wallis DE, Roessler E, Hehr U, Nanni L, Wiltshire T, Richieri-Costa A, Gillessen-Kaesbach G, Zackai EH, Rommens J, Muenke M. Mutations in the homeodomain of the human SIX3 gene cause holoprosencephaly. *Nat Genet* 1999;22:196-198.
- Wennborg H, Magnusson L, Bonde J, Olsen J. Congenital malformations related to maternal exposure to specific agents in biomedical research laboratories. *JOEM*, 2005; 47:1.

Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information. This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*

Document E58-10957

Revised November 2005