Prenatal Sonographic Features of Fetuses in Trisomy 13 Pregnancies (II)

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SUMMARY

Prenatal ultrasound is a powerful tool for detecting structural abnormalities in fetuses in trisomy 13 pregnancies. This article provides a comprehensive review of the prenatal sonographic features of trisomy 13 in the second and third trimesters, including holoprosencephaly, brachycephaly, microcephaly, Dandy-Walker complex and posterior fossa abnormalities, ventriculomegaly, neural tube defects, facial cleft, and micrognathia. [*Taiwan J Obstet Gynecol* 2009;48(3):218–224]

Key Words: congenital malformations, prenatal diagnosis, trisomy 13, ultrasound

Introduction

Prenatal ultrasound is a powerful tool for detecting structural abnormalities in fetuses in trisomy 13 pregnancies [1]. This article provides a comprehensive review of the prenatal sonographic features of trisomy 13 in the second and third trimesters, including holoprosencephaly (HPE), brachycephaly, microcephaly, Dandy-Walker complex (DWC) and posterior fossa abnormalities, ventriculomegaly, neural tube defects (NTDs), facial cleft, and micrognathia. The Table summarizes the frequencies of second- and third-trimester sonographic features of trisomy 13 pregnancies reported in the literature.

Holoprosencephaly

HPE is a developmental abnormality characterized by congenital malformations of the forebrain and midface. There are several types of HPE, ranging from severe alobar HPE with cyclopia, ethmocephaly, cebocephaly or premaxillary agenesis, to microforms with microcephaly, corpus callosum agenesis/dysgenesis, mental retardation, ocular hypotelorism, or a single maxillary central incisor [2]. Chromosomal aberrations, Mendelian mutations, X-linked inheritance and teratogens are all well-known causes of HPE [3–7]. Cytogenetic abnormalities have been reported in 24–25% of infants born with HPE, with trisomy 13 being the most common [8]. Reported chromosomal abnormalities associated with HPE include trisomy 13, trisomy 18, triploidy, del(2p), dup(3p), del(7q), del(13q), del(18p), del(21q), and interstitial deletion of 14q13 [2,9–21].

The prevalence of HPE is about 1.2 per 10,000 registered births [22,23], and its prevalence in the second trimester is about 1 per 8,000 [23]. Berry et al [24] found chromosomal abnormalities in 28.9% (11/38) of fetuses with HPE, including trisomy 13 ($n=8$), trisomy 18 ($n=1$), i(18q) ($n=1$) and del(21q) ($n=1$). They also found that the karyotype was normal in all 12 cases with isolated HPE and in all five cases with HPE and only facial defects, while the karyotype was abnormal in 52.4% (11/21) of fetuses with extrafacial malformations. Croen et al [22] found chromosomal abnormalities in 41.3% (50/121) of registered births

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Table. Frequency of prenatal ultrasound features in six studies of fetuses with trisomy 13

	Authors/Year of publication					
	Nicolaides et al [33]/1992	Lehman et al [34]/1995	De Vigan et al [32]/2001	Tongsong et al [35]/2002	Papp et al [30]/2006	Watson et al [31]/2007
Fetuses, *n*	31	33	58	15	28	54
Gestational age (wk)	15–39	12–32	20–30	16–22	19.5 (average)	14–21
Features, *n* (%)						
Brachycephaly	5 (16.1)	–	–	–	–	–
Microcephaly	3 (9.7)	4 (12.1)	–	–	–	–
Holoprosencephaly	11 (35.5)	13 (39.4)	15 (25.9)	7 (46.7)	5 (17.9)	10 (18.5)
Posterior fossa cyst	6 (19.4)	–	–	1 (6.7)	2 (7.1)	4 (7.4)
Enlarged cisterna magna	–	5 (15.2)	–	–	–	–
Dandy-Walker malformation	–	–	–	–	–	4 (7.4)
Ventriculomegaly	3 (9.7)	3 (9.1)	3 (5.2)	3 (20.0)	11 (39.3)	9 (16.7)
Spina bifida	–	–	–	–	–	2 (3.7)
Congenital heart defects	14 (45.2)	16 (48.5)	17 (29.3)	5 (33.3)	15 (53.6)	31 (57.4)
Facial clefts	15 (48.4)	12 (36.4)	15 (25.9)	5 (33.3)	12 (42.9)	19 (35.2)
Micrognathia	3 (9.7)	–	–	2 (13.3)	–	2 (3.7)
Nuchal edema/cystic hygroma	7 (22.6)	7 (21.2)	9 (15.5)	1 (6.7)	6 (21.4)	–
Hydrops fetalis	2 (6.5)	4 (12.1)	4 (6.9)	–	–	–
Omphalocele	7 (22.6)	5 (15.2)	3 (5.2)	2 (13.3)	1 (3.6)	–
Diaphragmatic hernia	2 (6.5)	–	–	2 (13.3)	–	–
Urinary tract abnormalities	20 (64.5)	11 (33.3)	12 (20.7)	4 (26.7)	12 (42.9)	9 (16.7)
Abnormal extremities	21 (67.7)	11 (33.3)	8 (13.8)	6 (40.0)	–	–
Polydactyly	–	7 (21.2)	–	–	2 (7.1)	6 (11.1)
Intrauterine growth restriction	15 (48.4)	16 (48.5)	–	4 (26.7)	–	–
Echogenic intracardiac focus	–	10 (30.3)	–	3 (20.0)	4 (14.3)	2 (3.7)
Echogenic bowel	–	–	–	–	5 (17.9)	–
Choroid plexus cysts	1 (3.2)	–	–	1 (6.7)	3 (10.7)	–
Single umbilical artery	–	8 (24.2)	–	2 (13.3)	–	5 (9.3)

– = not described.

with HPE, including trisomy 13 (*n* = 38), trisomy 18 (*n* = 3), trisomy 21 (*n* = 1), triploidy (*n* = 1), 6q+ (*n* = 1), del(18p) (*n* = 1), del(13q) (*n* = 1), r(13) (*n* = 1), r(21) (*n* = 1), t(1;2)(p13;p21) (*n* = 1) and der(15)t(3;15)(q13.2;q26.3) (*n* = 1). Whiteford and Tolmie [25] reported chromosomal abnormalities in 34.0% (17/50) of registered births with HPE, including trisomy 13 (*n* = 13), del(13q) (*n* = 2) and del(7q) (*n* = 2), while Odent et al [26] found chromosomal abnormalities in 38.8% (100/258) of HPE cases, including trisomy 13 (*n* = 64), trisomy 18 (*n* = 8), triploidy (*n* = 8), abnormalities of 7q (*n* = 9) and other rearrangements. Bullen et al [23] detected chromosomal abnormalities in 37.7% (20/53) of fetuses with HPE, including trisomy 13 (*n* = 15), trisomy 18 (*n* = 2), del(13q) (*n* = 2) and del(2p) (*n* = 1), and Blaas et al [27] found abnormalities in 36.7% (11/30) of such fetuses, including trisomy 13 (*n* = 5), r(13) (*n* = 1), del(13q) (*n* = 1), triploidy (*n* = 1), partial monosomy 14q (*n* = 1), partial monosomy 11p (*n* = 1) and t(8;14)(q21.1;q24.1) (*n* = 1). Chen et al [14] found chromosomal abnormalities in 57.6% (34/59) of fetuses with HPE, including trisomy 13 (*n* = 19), mosaic trisomy 13 (*n* = 1), i(13q) (*n* = 1), trisomy 18 (*n* = 4), triploidy (*n* = 2), del(7q) (*n* = 1), concomitant dup(3p) and del(2q) (*n* = 2), concomitant dup(3p) and del(7q) (*n* = 2), del(18p) (*n* = 1), and del(14)(q13q21.1) (*n* = 1). Trisomy 13 accounts for up to 75% of the chromosomal abnormalities associated with HPE [22–25]. In a meta-analysis of 132 fetuses with prenatally detected HPE, Snijders et al [28] reported chromosomal abnormalities in 33%

of cases, including trisomy 13 ($n=30$), trisomy 18 ($n=7$) and other rearrangements ($n=7$). In their study, the prevalence was 4% in fetuses with apparently isolated HPE and 39% in those with additional abnormalities. They also reported that HPE was observed in 39% of fetuses with trisomy 13 ($n=54$) and 3% of fetuses with trisomy 18 ($n=137$).

Frequencies of 16.7% (3/18) [29], 17.9% (5/28) [30], 18.5% (10/54) [31], 25.9% (15/58) [32], 35.5% (11/31) [33], 39.4% (13/33) [34] and 46.7% (7/15) [35] have been reported for HPE in fetuses with trisomy 13. In the seven published series on second- and third-trimester fetal trisomy 13, the mean frequency of HPE in trisomy 13 was 27.0% (64/237).

Brachycephaly

Brachycephaly is characterized by relative shortening of the occipital diameter, and is associated with Down syndrome and Roberts syndrome [28]. Nicolaides et al [33] reported brachycephaly in 16.1% (5/31) of fetuses with trisomy 13. In a series of 461 fetuses with chromosomal abnormalities at the Harris Birthright Research Center for Fetal Medicine, Snijders et al [28] found brachycephaly in 15% of fetuses with trisomy 21 ($n=155$), 29% with trisomy 18 ($n=137$), 26% with trisomy 13 ($n=54$), 10% with triploidy ($n=50$) and 32% with Turner syndrome ($n=65$).

Microcephaly

Microcephaly occurs in approximately 1 per 1,000 births and may be caused by chromosomal abnormalities, genetic syndromes, hemorrhage, infection, teratogens or radiation [28]. Nicolaides et al [33] reported microcephaly in 9.7% (3/31) of fetuses with trisomy 13, compared with 12.1% (4/33) reported by Lehman et al [34]. Snijders et al [28] reported microcephaly in 24% of trisomy 13 fetuses ($n=54$) and in 1% of fetuses with trisomy 18 ($n=137$), and suggested that most fetuses with trisomy 13 and microcephaly usually have HPE.

DWC and Posterior Fossa Abnormalities

DWC refers to a spectrum of abnormalities of the cerebellar vermis, cystic dilation of the fourth ventricle, and enlargement of the cisterna magna, including Dandy-Walker malformation (DWM; complete or partial agenesis of the cerebellar vermis and enlarged posterior fossa), Dandy-Walker variant (DWV; partial agenesis of the cerebellar vermis without enlargement of the posterior fossa), and mega-cisterna magna.

DWM occurs in approximately 1 per 25,000–35,000 pregnancies [36] and is associated with chromosomal abnormalities, Mendelian mutations, environmental factors, maternal diabetes, teratogens, congenital infections, and multifactorial disorders [37–39]. The frequency of chromosomal abnormalities in DWM has been reported as 14.5% [40], 46% [41] and 55% [42], with trisomy 18, trisomy 13 and triploidy being the most common aneuploidies. Hydrocephalus has been observed in 53% of cases [43], absent corpus callosum in 19% [36], associated developmental abnormalities of the central nervous system in 50% [44], and extracranial abnormalities in 60% [43]. Up to 18 different chromosomal abnormalities and 40 genetic syndromes have been associated with DWM [38]. Enlargement of the cisterna magna observed in the third trimester is a clue to aneuploidy, especially trisomy 18 [45].

Nyberg et al [42] reported chromosomal abnormalities in 54.5% (18/33) of a selected population of 33 fetuses with enlarged cisterna magna, including trisomy 18 ($n=12$), trisomy 13 ($n=3$), Turner syndrome ($n=1$) and other rearrangements ($n=2$), and found that the presence of associated anomalies and absence of ventricular dilation were most strongly correlated with chromosomal abnormalities. Chang et al [46] found chromosomal abnormalities in 53.1% (17/32) of fetuses with DWV (trisomy 13 [$n=9$], trisomy 21 [$n=3$], trisomy 18 [$n=2$], triploidy [$n=1$], and other rearrangements [$n=2$]), and in 31.6% (6/19) of fetuses with DWM (trisomy 21 [$n=1$], trisomy 18 [$n=1$], triploidy [$n=1$], tetraploidy [$n=1$], mosaicism [$n=2$], and clinical Down syndrome [$n=3$]). Ulm et al [47] found chromosomal abnormalities in 50.0% (7/14) of fetuses with DWC (DWM [$n=12$] and DWV [$n=2$]) before 21 weeks of gestation, including trisomy 18 ($n=3$), triploidy ($n=2$), trisomy 13 ($n=1$) and other rearrangement ($n=1$). Ecker et al [41] reported abnormalities in 45.8% (11/24) of fetuses with DWM (triploidy [$n=7$], trisomy 13 [$n=2$], trisomy 18 [$n=1$], and translocation [$n=1$]), and in 32.3% (10/31) of fetuses with DWV (trisomy 18 [$n=4$], trisomy 13 [$n=1$] and translocations [$n=5$]). In a meta-analysis of 101 fetuses with enlarged posterior fossa, Snijders et al [28] reported chromosomal abnormalities in 44% of cases, including trisomy 18 ($n=22$), trisomy 13 ($n=10$) and other rearrangements ($n=8$). They also reported that posterior fossa cysts were observed in 15% of the fetuses with trisomy 13 ($n=54$), 10% with trisomy 18 ($n=137$), 6% with triploidy ($n=50$) and 1% with

trisomy 21 (n=155). Nicolaides et al [33] found posterior fossa cysts in 19.4% (6/31) of fetuses with trisomy 13, and Lehman et al [34] reported enlarged cisterna magna in 15.2% (5/33) of fetuses with trisomy 13, two of whom were diagnosed at 12–20 weeks of gestation, and three at 20–32 weeks of gestation. Tongsong et al [35] found enlarged cisterna magna in 6.7% (1/15) of fetuses with trisomy 13, and Papp et al [30] reported posterior fossa cysts in 7.1% (2/28) of fetuses with trisomy 13. Watson et al [31] reported DWM in 7.4% (4/54) of fetuses with trisomy 13 and found abnormal posterior fossa with enlarged cisterna magna without an absent vermis in an additional 7.4% (4/54). In the five published series on second- and third-trimester fetal trisomy 13, the mean frequency of DWC and posterior fossa abnormalities in trisomy 13 was 13.7% (22/161).

Ventriculomegaly

Ventriculomegaly has a prevalence of about 5–25 per 10,000 births and may be associated with chromosomal abnormalities, genetic defects, intrauterine hemorrhage, infection and NTDs [28]. In a meta-analysis of 690 fetuses with prenatally detected ventriculomegaly, Snijders et al [28] reported chromosomal abnormalities in 13% of cases, including trisomy 18 (n=23), triploidy (n=14), trisomy 21 (n=13), trisomy 13 (n=10) and other rearrangements (n=14). In their study, the prevalence was higher in cases with additional abnormalities than in those with no other detectable abnormalities (17% *vs.* 2%), and higher in cases with mild-to-moderate ventriculomegaly than in those with severe ventriculomegaly (19% *vs.* 6%). They also reported ventriculomegaly in 18% of fetuses with triploidy (n=50), 16% with trisomy 21 (n=155), 14% with trisomy 18 (n=137), 9% with trisomy 13 (n=54), and 2% with Turner syndrome (n=65).

Nicolaides et al [33] found ventriculomegaly in 9.7% (3/31) of fetuses with trisomy 13. Lehman et al [34] reported lateral ventricular dilation in 9.1% (3/33) of fetuses with trisomy 13, of whom two were diagnosed at 12–20 weeks of gestation, and three at 20–32 weeks of gestation. De Vigan et al [32] reported hydrocephalus in 5.2% (3/58) of fetuses with trisomy 13. Tongsong et al [35] reported ventriculomegaly in 20.0% (3/15) of the fetuses with trisomy 13, Picklesimer et al [29] in 33.3% (6/18), Papp et al [30] in 39.3% (11/28) and Watson et al [31] in 16.7% (9/54). In the seven published series on second- and third-trimester fetal trisomy 13, the mean frequency of ventriculomegaly in trisomy 13 was 16.0% (38/237).

Neural tube defects

Trisomy 13 can be associated with spina bifida, encephalocele, and anencephaly. Spina bifida is the most common NTD associated with trisomy 13. Encephalocele and anencephaly have occasionally been reported. Byrne and Warburton [48] reported trisomy 13 in an aborted embryo with encephalocele. Phadke and Thakur [49] reported prenatal diagnosis of iniencephaly, alobar HPE and cyclopia in a fetus with mosaic trisomy 13, and Halder et al [50] reported mosaic trisomy 13 in a fetus with iniencephaly, anencephaly, facial clefts, single umbilical artery, dilated right side of the heart, and club foot. Several studies have shown that NTDs occur in about 8% of trisomy 13 cases [51–53]. Rodriguez et al [51] found three cases of spina bifida among 34 trisomy 13 patients (8.8%). Wyllie et al [52] found one meningocele and two encephaloceles among 36 trisomy 13 patients (8.3%). In a study of 25 mid-trimester trisomy 13 fetuses, Seller [53] found that 8.0% (2/25) had spina bifida, while Watson et al [31] reported spina bifida in 3.7% (2/54) of second-trimester fetuses with trisomy 13.

Facial Cleft

Facial clefts, such as cleft lip and/or cleft palate, occur in approximately 1 per 700 live births and are related to genetic and environmental factors [28]. The incidence of facial clefts shows marked racial and geographic variation. For instance, the incidence among Caucasians, such as the population in the United Kingdom, is 0.7–0.9 per 1,000 deliveries, while the incidence is higher (1.5–2.0 per 1,000 deliveries) among Asians, and lower (0.5 per 1,000 deliveries) among blacks [54,55]. Chromosomal abnormalities occur in < 1% of babies with facial clefts [56], but in 30–50% of fetuses with facial clefts [28,57–59]. Nicolaides et al [57] reported chromosomal abnormalities in 48.4% (31/64) of fetuses with facial clefts, including trisomy 13 (n=15), trisomy 18 (n=10), trisomy 21 (n=1), triploidy (n=1), deletion or translocation (n=2) and other rearrangements (n=2). In a meta-analysis of 118 fetuses with prenatally diagnosed facial clefts, Snijders et al [28] reported chromosomal abnormalities in 40%, including trisomy 13 (n=25), trisomy 18 (n=16) and other rearrangements (n=6), while in a study of 461 fetuses with chromosomal abnormalities [28], they reported facial clefts in 39% of fetuses with trisomy 13 (n=54), 10% with trisomy 18 (n=137), 2% with triploidy (n=50) and 1% with trisomy 21 (n=155).

Trisomy 13 accounts for up to 50–70% of chromosomal abnormalities associated with facial clefts [28,57–60]. Clementi et al [59] reported 74 fetuses with prenatally detected facial clefts and chromosomal abnormalities, including trisomy 13 (n=41), trisomy 18 (n=13), autosomal deletions (n=5), trisomy 21 (n=3), triploidy (n=4) and other rearrangements (n=8), while Stoll et al [61] reported 27 fetuses with prenatally detected facial clefts and chromosomal abnormalities, including trisomy 13 (n=11), trisomy 18 (n=13), del(4p) (n=1), r(15) (n=1), and dup(12p) (n=1).

Chromosomal abnormalities vary with the type of facial cleft [58,59,62]. Nyberg et al [58] reported chromosomal abnormalities in 30.8% (20/65) of fetuses and neonates with facial clefts (unilateral cleft lip [n=5], unilateral cleft lip and palate [n=15], bilateral cleft lip and palate [n=20], median cleft lip and palate [n=21], and cleft with amniotic bands [n=4]), including trisomy 13 (n=14), trisomy 18 (n=2), 45,X (n=1), mosaic trisomy 22 (n=1), del(6)(p22) (n=1), and der(10)t(10;15)(q21.2;q15) (n=1). They found chromosomal abnormalities in none of the cases with unilateral cleft lip (0/5), in 20.0% (3/15) with unilateral cleft lip and cleft palate (trisomy 18 [n=1], 45,X [n=1], and mosaic trisomy 22 [n=1]), 30.0% (6/20) with bilateral cleft lip and palate (trisomy 13 [n=4], del(6)(p22) [n=1] and der(10)t(10;15)(q21.2;q15) [n=1]), 52.4% (11/21) with median cleft lip and palate (trisomy 13 [n=10] and trisomy 18 [n=1]), and in none with cleft associated with amniotic bands (0/4). In their study, the types of facial clefts in the 14 cases with trisomy 13 included median cleft lip and palate (n=10) and bilateral cleft lip and palate (n=4), and the two cases with trisomy 18 had median cleft lip and palate (n=1) and unilateral cleft lip and palate (n=1).

Bergé et al [60] reported chromosomal abnormalities in 51.4% (36/70) of fetuses with prenatally detected facial cleft (cleft lip [n=3], unilateral cleft lip and palate [n=25], bilateral cleft lip and palate [n=29], median cleft [n=11], and isolated cleft palate [n=2]), including trisomy 13 (n=28), trisomy 18 (n=6), triploidy (n=1), and marker chromosome (n=1). They found chromosomal abnormalities in none of the fetuses with unilateral cleft lip (0/3), in 32.0% (8/25) with unilateral cleft lip and cleft palate (trisomy 13 [n=6], trisomy 18 [n=1] and triploidy [n=1]), 58.6% (17/29) with bilateral cleft lip and palate (trisomy 13 [n=12], trisomy 18 [n=4], and marker chromosome [n=1]), 81.8% (9/11) with median cleft lip and palate (trisomy 13 [n=8] and trisomy 18 [n=1]), and in 2 of 2 with isolated cleft palate (both trisomy 13). The types of facial clefts in the 28 cases with trisomy 13 in their study were bilateral cleft lip and palate (n=12), median cleft (n=8), unilateral cleft lip and palate (n=6) and isolated cleft palate (n=2), and in the six cases with trisomy 18 were bilateral cleft lip and palate (n=4), median cleft (n=1) and unilateral cleft lip and palate (n=1). The triploid case had unilateral cleft lip and palate, and the case with the marker chromosome had bilateral cleft lip and palate.

Frequencies of 25.9% (15/58) [32], 33.3% (5/15) [35], 33.3% (6/18) [29], 35.2% (19/54) [31], 36.4% (12/33) [34], 42.9% (12/28) [30] and 48.4% (15/31) [33] have been reported for facial clefts in fetuses with trisomy 13. In the seven published series on second- and third-trimester fetal trisomy 13, the mean frequency of facial cleft in trisomy 13 was 35.4% (84/237).

Micrognathia

Micrognathia occurs in approximately 1 per 1,000 births and is a nonspecific finding associated with a wide range of genetic syndromes and chromosomal abnormalities [63]. The risk of chromosomal abnormalities, mainly trisomy 18 and triploidy, may be as high as 38–66% in fetuses with micrognathia [57]. Nicolaides et al [57] reported that 66.1% (37/56) of fetuses with micrognathia had chromosomal abnormalities, including trisomy 18 (n=21), triploidy (n=9), trisomy 13 (n=3), deletion or translocation (n=3) and other rearrangements (n=1). Snijders et al [28] reported micrognathia in 53% of fetuses with trisomy 18 (n=137), 44% with triploidy (n=50), 9% with trisomy 13 (n=54) and 1% with trisomy 21 (n=155). Frequencies of 3.7% (2/54) [31], 9.7% (3/31) [33] and 13.3% (2/15) [35] have been reported for micrognathia in fetuses with trisomy 13. In three published series on second- and third-trimester fetal trisomy 13, the mean frequency of micrognathia in trisomy 13 was 7.0% (7/100).

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