PRENATAL SONOGRAPHIC FEATURES OF FETUSES IN TRISOMY 13 PREGNANCIES (III)

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SUMMARY

Prenatal ultrasound is a powerful tool for the detection of structural abnormalities of fetuses in trisomy 13 pregnancies. This article provides a comprehensive review of the prenatal sonographic features of trisomy 13 fetuses in the second and third trimesters, including cystic hygroma and nuchal edema, congenital heart defects, hydrops fetalis, omphalocele, diaphragmatic hernia, urinary tract abnormalities, and abnormal extremities and polydactyly. [*Taiwan J Obstet Gynecol* 2009;48(4):342–349]

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

Introduction

Prenatal ultrasound is a powerful tool for the detection of structural abnormalities of fetuses in trisomy 13 pregnancies [1]. This article provides a comprehensive review of the prenatal sonographic features of trisomy 13 fetuses in the second and third trimesters, including cystic hygroma and nuchal edema, congenital heart defects (CHD), hydrops fetalis, omphalocele, diaphragmatic hernia, urinary tract abnormalities, and abnormal extremities and polydactyly.

Cystic Hygroma and Nuchal Edema

Cystic hygroma is characterized by a bilateral septated cystic structure in the occipitocervical region. About 75% of second-trimester fetuses with cystic hygroma demonstrate chromosomal abnormalities, with Turner syndrome accounting for 80% of the cases [2]. Azar et al [2] found that 33 of 44 fetuses with cystic hygroma in the second trimester had chromosomal abnormalities, including Turner syndrome ($n=31$), trisomy 18 ($n=1$) and trisomy 21 ($n=1$). In a meta-analysis of 276 fetuses with prenatally diagnosed cystic hygroma, Snijders et al [3] reported chromosomal abnormalities in 68%, including 45,X ($n=163$), trisomy 21 ($n=26$), trisomy 18 ($n=13$) and other rearrangements ($n=11$). They also reported that cystic hygroma was diagnosed in 88% of fetuses with Turner syndrome ($n=65$), 2% of fetuses with trisomy 18 ($n=137$) and 1% of fetuses with trisomy 21 ($n=38$).

Nuchal edema is characterized by subcutaneous edema in the midsagittal plane of the neck, producing a characteristic tremor on ballottement of the fetal head. About one-third of fetuses with nuchal edema have chromosomal abnormalities, mainly trisomies 21, 18 and 13 [4]. Nicolaides et al [4] reported chromosomal abnormalities in 36.6% (53/145) of fetuses with nuchal edema, including trisomy 21 ($n=31$), trisomy 13 ($n=7$), trisomy 18 ($n=5$), Turner syndrome ($n=3$), triploidy ($n=2$), partial trisomy 4q ($n=1$), tetrasomy 12p ($n=1$), 4p deletion ($n=1$), 5q deletion ($n=1$) and 14q deletion ($n=1$). In a meta-analysis of 371 fetuses with prenatally diagnosed nuchal edema, Snijders et al [3] reported chromosomal abnormalities in 33% of the fetuses, including trisomy 21 ($n=85$), trisomy 18 ($n=9$), 45,X ($n=10$) and other rearrangements ($n=19$). They also reported nuchal edema in

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38% of fetuses with trisomy 21 ($n=38$), 22% with trisomy 13 ($n=54$), 5% with trisomy 18 ($n=137$), 6% with Turner syndrome ($n=65$), and 4% with triploidy ($n=50$).

Nicolaides et al [5] found nuchal edema in 22.6% (7/31) of fetuses with trisomy 13. Wladimiroff et al [6] found cystic hygroma in 11.8% (2/17) of fetuses with trisomy 13, all of whom were diagnosed before 20 weeks' gestation. Lehman et al [7] found nuchal thickening/cystic hygroma in 21.2% (7/33) of fetuses with trisomy 13, six of whom were diagnosed at 12–20 weeks' gestation, while one was diagnosed at 20–32 weeks' gestation. De Vigan et al [8] found cystic hygroma in 15.5% (9/58) of fetuses with trisomy 13. Tongsong et al [9] found nuchal edema in 6.7% (1/15) of fetuses with trisomy 13, while Papp et al [10] found nuchal thickening > 6 mm in 21.4% (6/28) of fetuses with trisomy 13. The mean frequency of nuchal edema/cystic hygroma/nuchal thickening in trisomy 13, based on the six published series on second- and third-trimester fetal trisomy 13 fetuses, is 17.6% (32/182).

About 50% of first-trimester fetuses with cystic hygroma demonstrate chromosome abnormalities, with autosomal trisomies accounting for 60% of the cases and Turner syndrome accounting for 30%. Ville et al [11] reported chromosomal abnormalities in 28.6% (16/56) of fetuses with first-trimester cystic hygroma, including trisomy 18 ($n=6$), trisomy 21 ($n=5$), 45,X ($n=4$) and 47,*XXX* ($n=1$). Johnson et al [12] reported chromosomal abnormalities in 60.3% (41/68) of fetuses with first-trimester cystic hygroma, including trisomy 21 ($n=16$), trisomy 18 ($n=9$), trisomy 13 ($n=2$), 45,X ($n=9$), der(10)t(4;10) ($n=1$), t(1;18) ($n=1$), mosaic 46,XY/45,X ($n=1$), mosaic 46,XY/47,XX, + mar ($n=1$) and der(18)t(7;18) ($n=1$). Trauffer et al [13] reported chromosomal abnormalities in 48.8% (21/43) of fetuses with first-trimester cystic hygroma, including trisomy 21 ($n=9$), trisomy 18 ($n=4$), trisomy 13 ($n=1$), Turner syndrome ($n=4$) and translocations ($n=3$). Malone et al [14] reported chromosomal abnormalities in 50.8% (67/132) of fetuses with first-trimester septated cystic hygroma, including trisomy 21 ($n=25$), Turner syndrome ($n=19$), trisomy 18 ($n=13$), trisomy 13 ($n=6$), triploidy ($n=3$) and mosaic deletion of chromosome 9 ($n=1$). Kharrat et al [15] reported chromosomal abnormalities in 59.5% (25/42) of fetuses with first-trimester cystic hygroma, including trisomy 18 ($n=10$), trisomy 13 ($n=6$) and 45,X ($n=9$). Graesslin et al [16] reported chromosomal abnormalities in 52.8% (38/72) of fetuses with first-trimester cystic hygroma, including trisomy 21 ($n=14$), trisomy 18 ($n=7$), trisomy 13 ($n=3$), Turner syndrome ($n=11$) and other rearrangements ($n=3$). In a meta-analysis, Molina et al [17] found chromosomal abnormalities in 53.1% (139/262) of fetuses with first-trimester cystic hygroma, including trisomies 21, 18 and 13 ($n=84$), Turner syndrome ($n=42$), and other rearrangements ($n=13$).

Congenital Heart Defects

CHD have been found in 90% of fetuses with trisomy 13 [18]. The most common CHD in trisomy 13 fetuses include ventricular septal defects, atrial septal defects, patent ductus arteriosus, overriding aorta, dextroposition, hypoplastic aorta, atretic mitral and/or aortic valves, pulmonary stenosis, and anomalous pulmonary venous return [19]. The reported frequencies of prenatally detected CHD in fetuses with trisomy 13 in the second and third trimesters has varied, ranging from 29.3% (17/58) [8] to 33.3% (5/15) [9], 45.2% (14/31) [5], 48.5% (16/33) [7], 50.0% (9/18) [20], 53.6% (15/28) [10], 57.4% (31/54) [21] and 70.6% (12/17) [6]. The mean frequency of prenatally detected CHD, based on the eight published series on trisomy 13, is 47.2% (119/252).

Lehman et al [7] reported that 48.5% (16/33) of fetuses with trisomy 13 had CHD, including hypoplastic left heart ($n=7$) and ventricular septal defects ($n=6$). Picklesimer et al [20] reported cardiovascular defects in 53% of fetuses with trisomy 13 ($n=18$), including ventricular septal defects ($n=3$), atrioventricular canal defects ($n=2$) and hypoplastic left heart ($n=4$). Papp et al [10] reported that 53.6% (15/28) of fetuses with trisomy 13 had CHD, including ventricular septal defects ($n=4$), dilated right chamber ($n=4$), outflow tract abnormalities ($n=2$), hypoplastic left ventricle ($n=2$), coarctation of the aorta ($n=1$), truncus arteriosus communis ($n=1$) and tricuspid regurgitation ($n=1$). Papp et al [10] also showed that 9.4% (5/53) of fetuses with trisomy 13 presented with CHD as the only sonographic feature. Watson et al [21] reported that 57.4% (31/54) of fetuses with trisomy 13 had CHD, including an atrial septal defect/ventricular septal defect/atrioventricular canal ($n=11$), multiple anomalies/complex ($n=10$), a single ventricle ($n=6$), an axis shift ($n=3$) and tetralogy of Fallot ($n=1$).

CHD have been found in 1% of the general population [18]. When CHD is identified in early infancy, there is a 5–10% frequency of chromosomal abnormalities [22,23]. Chromosomal abnormalities that are commonly associated with CHD include trisomy 21, trisomy 18, trisomy 13, tetrasomy 22p (cat-eye syndrome), tetrasomy 12p (Pallister-Killian syndrome), 45,X (Turner syndrome), 4p deletion (Wolf-Hirschhorn syndrome),

7q11.23 deletion (Williams syndrome), 20p12 deletion (Alagille syndrome), 22q11.2 deletion (DiGeorge syndrome), distal 11q deletion, 8p deletion involving 8p22.23, and 3p deletion involving 3p25 [24]. Most chromosomal abnormalities are associated with an increased incidence of CHD. For instance, CHD have been found in more than 90% of fetuses with trisomy 18, 90% with trisomy 13, 50% with trisomy 21, 67% with trisomy 22, 40% with cat-eye syndrome, about 40% with Wolf-Hirschhorn syndrome, about 20% with cri-du-chat syndrome, about 50% with mosaic trisomy 8, more than 50% with mosaic trisomy 9, about 25% with 13q deletion, more than 50% with partial trisomy 14q, less than 50% with 18q deletion, 14% with 49,XXXXY, and 35% with Turner syndrome [18].

Wladimiroff et al [25] detected CHD by ultrasound in 13 of 230 fetuses and detected chromosomal abnormalities in 38.5% (5/13) of the fetuses with CHD, including trisomy 18 (n=3), trisomy 21 (n=1) and trisomy 13 (n=1). Copel et al [26] detected CHD by ultrasound in 34 of 502 fetuses, and chromosomal abnormalities in 32.4% (11/34) of the fetuses with CHD, including trisomy 18 (n=4), trisomy 21 (n=2), trisomy 13 (n=1), trisomy 9 (n=1), 47,XXY (n=1), and 45,X (n=1). Paladini et al [27] detected CHD by ultrasound in 31 of 469 fetuses, and chromosomal abnormalities in 48.4% (15/31) of the fetuses with CHD, including trisomy 21 (n=6), trisomy 18 (n=4), trisomy 13 (n=4) and triploidy (n=1). In their study, fetuses with cardiac and extracardiac anomalies carried a higher risk of aneuploidy than those with isolated cardiac anomalies (71.4% [10/14] *vs*. 29.4% [5/17]), and atrial septal defects and ventricular septal defects were the cardiac anomalies most often associated with aneuploidies (77% *vs*. 71%, respectively). Brown et al [28] found that 34.4% (43/125) of fetuses with CHD had chromosomal abnormalities, including trisomy 18 (n=16), trisomy 21 (n=9), trisomy 13 (n=6), 45,X (n=4), triploidy (n=2) and other rearrangements (n=6). The karyotype was abnormal in 63.5% (33/52) of the fetuses with coexisting noncardiac anomalies, compared with 13.7% (10/73) of those fetuses without coexisting noncardiac anomalies. In a meta-analysis of 829 fetuses with prenatally detected CHD, Snijders et al [3] reported chromosomal abnormalities in 29% of the cases, including trisomy 21 (n=68), trisomy 18 (n=82), trisomy 13 (n=30), 45,X (n=30) and other rearrangements (n=31). In their study, chromosomal abnormalities were found in 16% of the cases with apparently isolated heart defects and 65% of those with additional abnormalities. Snijders et al [3] also reported that CHD were observed in 52% of fetuses with trisomy 18 (n=137), 48% with Turner syndrome (n= 5), 43% with trisomy 13 (n=54), 26% with trisomy 21 (n=155), and 16% with triploidy (n=50). Chaoui et al [29] detected CHD by ultrasound in 203 of 2,716 fetuses and chromosomal abnormalities in 22.7% (46/203) of the fetuses with CHD, including trisomy 18 (n=15), trisomy 21 (n=13), trisomy 13 (n=5), 45,X (n=5), triploidy (n=2) and other rearrangements (n=6). In their study, 8/15 of the fetuses with trisomy 18 had a ventricular septal defect, 9/13 with trisomy 21 had an atrioventricular septal defect, and 5/5 with 45,X had a left heart outflow obstruction, but the fetuses with trisomy 13, triploidy and other rearrangements did not have typical cardiac defects. Chaoui et al [29] additionally found that the aneuploidy incidences for specific CHD were 55% for an atrioventricular septal defect, 43% for a ventricular septal defect, 43% for aortic coarctation, 36% for tetralogy of Fallot, 36% for double outlet right ventricle, and none for isomerism, transposition of the great arteries, pulmonary atresia or stenosis.

Prenatal diagnosis of an atrioventricular septal defect is associated with a 50% risk of aneuploidy, mainly trisomy 21. Delisle et al [30] found that 57.9% (22/38) of fetuses with an atrioventricular septal defect had chromosomal abnormalities, including trisomy 21 (n=19), trisomy 18 (n=1), trisomy 13 (n=1) and mosaic trisomy 19q (n=1). Huggon et al [31] found that 49.1% (107/218) of fetuses with an atrioventricular septal defect had chromosomal abnormalities, including trisomy 21 (n=86), trisomy 18 (n=13), trisomy 13 (n=4), 48,XYY,+21 (n=1), 8q deletion (n=1), unbalanced translocation of 14/21 (n=1), 22q11 microdeletion (n=1) and unknown fragment to 12 (n=1).

Song et al [32] found chromosomal abnormalities in 28.1% (94/334) of fetuses with major CHD, including trisomy 21 (n=41), trisomy 18 (n=18), trisomy 13 (n=9), 45,X (n=7), 22q11.2 deletion (n=7) and other rearrangements (n=10). In their study, chromosomal abnormalities were not found in fetuses with aortopulmonary window (0/1), anomalous pulmonary venous connection (0/2), ectopia cordis (0/4), heterotaxy (0/32), single ventricle (0/12) or transposition of the great arteries (0/15). In contrast, chromosomal abnormalities were found in fetuses with: (1) aortic stenosis (1/9, 11.1%), including trisomy 18 (n=1); (2) atrioventricular septal defect (39/53, 73.6%), including trisomy 21 (n=34), trisomy 18 (n=3), 45,X (n=1) and 3p+ (n=1); (3) coarctation of the aorta/arch interruption (7/19, 36.8%), including trisomy 21 (n=1), trisomy 18 (n=1), trisomy 13 (n=1) and del(14)(q32.1) (n=1); (4) double outlet right ventricle (12/28, 42.9%), including trisomy 18 (n=5), trisomy 13 (n=5), 47,XXY,der(13;14)(q10;q10) (n=1) and 47,XX,+der(Y)t(Y;14)(q12;q22) (n=1); (5) hypoplastic left heart syndrome (6/66,

9.1%), including trisomy 13 ($n=1$), 45,X ($n=3$), t(1;4)(p13.1;p15.3) ($n=1$) and inv(1)(q42.12q42.13) ($n=1$); (6) pulmonary stenosis or atresia with intact ventricular septum (3/24, 12.5%), including trisomy 21 ($n=1$), trisomy 18 ($n=1$) and der(12)t(4;12) (p15;q24) ($n=1$); (7) tricuspid atresia (2/14, 14.3%), including trisomy 18 ($n=1$) and mosaic trisomy 22 ($n=1$); (8) tetralogy of Fallot (13/33, 39.4%), including trisomy 21 ($n=3$), trisomy 18 ($n=4$), trisomy 13 ($n=1$), 22q11.2 deletion ($n=3$), 49,XXXXY ($n=1$) and mosaic trisomy 14 ($n=1$); (9) truncus arteriosus (7/9, 77.8%), including trisomy 18 ($n=1$), trisomy 13 ($n=1$), 22q11.2 deletion ($n=3$), 92,XXYY ($n=1$) and mosaic rec(1),dup(1q) ($n=1$); (10) tricuspid valve dysplasia (including Ebstein's anomaly) (2/12, 16.7%), including trisomy 21 ($n=2$); and (11) vascular ring (2/2=100%), including trisomy 18 ($n=1$) and 22q11.2 deletion ($n=1$). In the seven cases with 22q11.2 deletion, Song et al [32] found that three had truncus arteriosus, three had tetralogy of Fallot, and one had a vascular ring.

Hydrops Fetalis

Hydrops fetalis occurs in approximately 1 per 1,000 births and may be the consequence of fetal or maternal disorders such as hematologic, cardiovascular, renal, pulmonary, gastrointestinal, hepatic, metabolic, chromosomal, neoplastic, infectious, placental or umbilical cord disorders [3]. In a meta-analysis of 600 fetuses with nonimmune hydrops fetalis, Jauniaux et al [33] reported chromosomal abnormalities in 15.7% (94/600) of fetuses, including trisomy 21 ($n=36$), Turner syndrome ($n=33$), trisomy 18 ($n=7$), triploidy ($n=5$), trisomy 13 ($n=3$), trisomy 16 ($n=1$) and other chromosomal rearrangements (mosaicism, translocations, deletion of the short arm of chromosome 13, and pericentric inversions) ($n=9$). Snijders et al [3] found that hydrops fetalis was diagnosed in 80% of fetuses with Turner syndrome ($n=65$), 20% with trisomy 21 ($n=155$), 7% with trisomy 13 ($n=54$), 4% with trisomy 18 ($n=137$), and 2% with triploidy ($n=50$). The reported frequencies of hydrops fetalis in fetuses with trisomy 13 range from 6.5% (2/31) [5] to 6.9% (4/58) [8] and 12.1% (4/33) [7].

Omphalocele

Chromosomal abnormalities have been reported in 10–12% of neonates with omphalocele and 30% of fetuses with omphalocele [34–39]. When the diagnosis is made in early pregnancy, the incidence of aneuploidy can increase to 61.1% (11/18) at 12–16 weeks' gestation [40] and 66.7% (12/18) at 11–14 weeks' gestation [37]. The chromosomal abnormalities in 11 cases of fetal omphalocele reported by Blazer et al [40] were trisomy 18 ($n=5$), trisomy 21 ($n=2$), triploidy ($n=2$), trisomy 13 ($n=1$) and 45,X ($n=1$), while the reported chromosomal abnormalities in 12 cases of fetal omphalocele reported by Snijders et al [37] were trisomy 18 ($n=10$), trisomy 13 ($n=1$) and triploidy ($n=1$). Nicolaides et al [34] found that 36.2% (42/116) of second- and third-trimester fetuses with omphalocele had chromosomal abnormalities, including trisomy 18 ($n=32$), trisomy 13 ($n=6$) and other rearrangements ($n=4$). In a meta-analysis of chromosomal abnormalities associated with omphalocele, Chen [41] found that 36.1% (415/1,148) of fetuses with prenatally detected omphalocele had chromosomal abnormalities, including trisomy 18 in 66.7% (277/415), trisomy 13 in 17.3% (72/415) and trisomy 21 in 6.3% (26/415) of fetal omphaloceles with aneuploidy. In a meta-analysis of 475 fetuses with prenatally detected omphalocele, Snijders et al [3] reported chromosomal abnormalities in 35% of fetuses, including trisomy 18 ($n=108$), trisomy 13 ($n=28$) and other rearrangements ($n=31$). Snijders et al [3] found that omphalocele was diagnosed in 31% of fetuses with trisomy 18 ($n=137$), 17% of fetuses with trisomy 13 ($n=54$), and 2% of fetuses with triploidy ($n=50$).

Papageorghiou et al [42] found omphalocele in 28.2% (51/181) of trisomy 13 fetuses in the first trimester. The reported frequencies of omphalocele in the fetuses with trisomy 13 in the second and third trimesters range from 3.6% (1/28) [10] to 11.1% (2/18) [20], 13.3% (2/15) [9], 15.2% (5/33) [7], 22.6% (7/31) [5] and 29.4% (5/17) [6]. The mean frequency of omphalocele in trisomy 13, based on the six published series on second- and third-trimester fetal trisomy 13, is 15.5% (22/142).

Diaphragmatic Hernia

The prevalence of congenital diaphragmatic hernia (CDH) is about 1 per 4,000 births [43]. Chromosomal abnormalities are detected in about 10% of cases with CDH [44–47]. Trisomies 13, 18 and 21, and 45,X are the most common aneuploidies associated with CDH [48–50]. Frequently reported structural chromosomal abnormalities associated with CDH include tetrasomy 12p (Pallister-Killian syndrome), del(15) (q26.1–q26.2), del(8)(p23.1), cytogenetic rearrangements of 8q23, del(4)(p16), +der(22)t(11;22)(q23;q11) and del(1)(q41–q42.12) [46,47,49,50]. Other reported chromosomal rearrangements associated with CDH include

duplication of 1q25–q31.2, deletion or duplication of 2q37, deletion of 3q22, deletion or duplication of 4q31, deletion of 5p15, deletion of 6p25, deletion of 6q25.3–qter, duplication of 8p21–p23.1, deletion of 8q22–q23, deletion of 9p24–pter, deletion of 11p13, duplication of 11q23.3–qter, duplication of 12p, and duplication of 14q32 [50]. CDH has been seen in patients with tetrasomy 21, trisomy 22, and trisomy 9 [49,51,52]. Autosomal deletions have been more commonly associated with CDH than autosomal duplications [53]. Lurie [53] has suggested that the segments 15q26, 8p23, 8q22, 4p16, 1q42 and 3q22 are candidates for the location of genes which, when deleted or truncated, may cause CDH, while the segments 22q11, 4q28.3q32, 1q25q31.2 and 2p23p25 are good candidates for the location of genes responsible for CDH in trisomic conditions. Candidate pathways and genes associated with CDH include the retinoid signaling pathway and the genes of *COUP-TFII* (OMIM 107773, 15q26), *FOG2* (OMIM 603693, 8q23), *GATA4* (OMIM 600576, 8p23.1), *WT1* (OMIM 607102, 11p13), and *SLIT3* (OMIM 603745, 5q35.1) [50]. Syndromic forms of CDH include Cornelia de Lange syndrome, craniofrontonasal syndrome, Donnai-Barrow syndrome, Fryns syndrome, Matthew-Wood syndrome, multiple vertebral segmentation defects (spondylocostal dysostosis and Jarcho-Levin syndrome), Simpson-Golabi-Behmel syndrome, and WT1-opathies (Denys-Drash syndrome, Frasier syndrome, and Meacham syndrome) [46,47,50].

The frequency of CDH in trisomy 13 has been reported to be 6–13% [3,5,9]. Snijders et al [3] found that CDH was diagnosed in 10% of fetuses with trisomy 18 ($n=137$), 6% of fetuses with trisomy 13 ($n=54$), and 2% of fetuses with triploidy ($n=50$). Nicolaides et al [5] found CDH in 6.5% (2/31) of fetuses with trisomy 13, and Tongsong et al [9] found CDH in 13.3% (2/15) of fetuses with trisomy 13.

The frequency of trisomy 13 in prenatally detected CDH has been reported as 8–30%. In a meta-analysis of 173 fetuses with prenatally diagnosed CDH, Snijders et al [3] found chromosomal abnormalities in 18% of fetuses, including trisomy 18 ($n=18$) and other rearrangements ($n=14$). Thorpe-Beeston et al [54] reported chromosomal abnormalities in 30.6% (11/36) of fetuses with prenatally diagnosed CDH, including trisomy 18 ($n=6$), trisomy 13 ($n=3$), triploidy ($n=1$) and del(8) ($n=1$). Bollmann et al [44] reported chromosomal abnormalities in 13.6% (6/44) of fetuses ($n=33$) and neonates ($n=11$) with CDH, including trisomy 18 ($n=4$), partial trisomy of chromosome 5 ($n=1$) and 45,X ($n=1$). Howe et al [55] reported chromosomal abnormalities in 31.6% (12/38) of fetuses prenatally diagnosed with CDH, including trisomy 18 ($n=2$), del(4)(p16) ($n=2$), mosaic trisomy 14 ($n=1$), +dic(15) (q11.2) ($n=1$), +mar(16) ($n=1$), t(6;8)(q24;q23) ($n=1$), del(12) ($n=1$), t(1;21)(p32;q22) ($n=1$), der(15)t(15;17)(q24.3;q23.3) ($n=1$) and del(8)(p23.1) ($n=1$). Dillon et al [56] reported chromosomal abnormalities in 8.5% (17/201) of fetuses prenatally diagnosed with CDH, including trisomy 18 ($n=5$), trisomy 13 ($n=3$), trisomy 22 ($n=1$), del(3)(q14) ($n=2$), del(3)(q11) ($n=1$), del(3)(q22) ($n=1$), t(13q;14q) ($n=1$), Turner syndrome ($n=1$) and r(9) ($n=1$). Tonks et al [45] reported chromosomal abnormalities in 28.1% (27/96) of fetuses prenatally diagnosed with CDH, including trisomy 18 ($n=9$), trisomy 13 ($n=6$), +der(22)t(11;22)(q23;q11) ($n=2$), del(2)(q33q35 or q35q37) ($n=1$), del(15)(q26.1) ($n=1$), tetrasomy 12p ($n=1$), marker chromosome ($n=1$), balanced inversion or translocation ($n=2$), additional material of unknown origin ($n=2$), der(2)t(2;8)(q37;q11.2) ($n=1$) and der(7)t(2;7)(q37;q36) ($n=1$). Stoll et al [57] reported chromosomal abnormalities in 30% (21/70) of babies with CDH and associated anomalies, including trisomy 18 ($n=10$), trisomy 13 ($n=2$), trisomy 21 ($n=1$), tetrasomy 12p ($n=2$) and autosomal partial deletions and/or duplications ($n=6$).

Urinary Tract Abnormalities

Fetal urinary tract abnormalities occur in approximately 2–3 per 1,000 pregnancies [3]. The frequently observed urinary tract abnormalities associated with fetal trisomy 13 include multicystic kidneys, enlarged and echogenic kidneys, renal cystic dysplasia, hydronephrosis, and ureteral obstruction and duplication [7]. Nicolaides et al [58] found that among 682 fetuses with renal defects including mild hydronephrosis ($n=276$), moderate/severe hydronephrosis ($n=206$), multicystic dysplasia ($n=173$) and renal agenesis ($n=27$), chromosomal abnormalities occurred in 85 fetuses (12.5%), including trisomy 18 ($n=20$), trisomy 21 ($n=19$), trisomy 13 ($n=18$), 45,X ($n=6$), triploidy ($n=5$), deletions ($n=9$), 47,XYY ($n=2$) and other rearrangements. In their study, trisomy 21 was the most common chromosomal abnormality (41%) associated with mild hydronephrosis, whereas trisomy 18 and trisomy 13 were the most common chromosomal abnormalities (48%) associated with moderate/severe hydronephrosis, multicystic dysplasia and renal agenesis. Snijders et al [3] found that mild hydronephrosis was diagnosed in 30% of fetuses with trisomy 21 ($n=155$), 16% of fetuses with trisomy 18 ($n=137$), 37% of fetuses with trisomy 13 ($n=54$), 4% of fetuses with triploidy ($n=50$), and 8% of fetuses with

Turner syndrome ($n=65$). They also found that the prevalences of other renal abnormalities in trisomy 21, trisomy 18, trisomy 13, triploidy and Turner syndrome were 7%, 12%, 24%, 6% and 6%, respectively.

The reported frequencies of urinary tract abnormalities in fetuses with trisomy 13 range from 16.7% (9/54) [21] to 20.7% (12/58) [8], 26.7% (4/15) [9], 33.3% (11/33) [7], 42.9% (12/28) [10], 47.1% (8/17) [6] and 64.5% (20/31) [5]. The mean frequency of prenatally detected urinary tract abnormalities, based on the seven published series on second- and third-trimester fetal trisomy 13, is 32.2% (76/236).

Abnormal Extremities and Polydactyly

Syndactyly of the third and fourth digits is associated with triploidy; clinodactyly with hypoplasia of the middle phalanx of the fifth digit is associated with trisomy 21; arthrogryposis, overlapping fingers, rocker-bottom feet and talipes are associated with trisomy 18; and polydactyly is associated with trisomy 13 [59]. Snijders et al [3] found that abnormalities of the hands and feet were diagnosed in 76% of fetuses with triploidy ($n=50$), 72% of fetuses with trisomy 18 ($n=137$), 52% of fetuses with trisomy 13 ($n=54$), 25% of fetuses with trisomy 21 ($n=155$), and 2% of fetuses with Turner syndrome ($n=65$). The reported frequencies of abnormal extremities in fetuses with trisomy 13 range from 13.8% (8/58) [8] to 33.3% (11/33) [7], 40.0% (6/15) [9] and 67.7% (21/31) [5].

Trisomy 13 is the most common abnormality associated with polydactyly. In a study of 338 syndromic polydactyly cases, Castilla et al [60] found trisomy 13 in 167 cases (49.4%), Meckel syndrome in 57 cases (16.9%), trisomy 21 in 31 cases (9.2%), hydrolethalus syndrome in 11 cases (3.3%), VATERL association in nine cases (2.7%), trisomy 18 in seven cases (2.1%), Ellis-van Creveld syndrome in seven cases (2.1%), and miscellaneous syndromes with less than four cases in each syndromic category. The reported frequencies of polydactyly in fetuses with trisomy 13 range from 7.1% (2/28) [10] to 11.1% (6/54) [21] and 21.2% (7/33) [7].

A detailed review on the frequencies of prenatal ultrasound features reported in six studies [5,7–10,21] of fetuses with trisomy 13 can be found in the Table in Chen [61].

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