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

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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, including the major structural abnormalities observed during the first trimester (omphalocele, holoprosencephaly, megacystis and congenital heart defects), the frequencies of second- and third-trimester sonographic features reported in previous studies, and the subtle sonographic findings observed during the second trimester (echogenic intracardiac foci, echogenic bowel, single umbilical artery, choroid plexus cysts and intrauterine growth restriction). [*Taiwan J Obstet Gynecol* 2009;48(3):210–217]

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

Introduction

Trisomy 13 syndrome or Patau syndrome is the third most common autosomal chromosomal trisomy after trisomy 21 and trisomy 18. Goldstein and Nielsen [1] reported the incidence of trisomy 13 to be 0.053 per 1,000 live births. In a 13-year incidence study of chromosomal abnormalities in Arhus, Denmark, Nielsen and Wohlert [2] found three cases of trisomy 13 among 34,910 newborn children, or an incidence of 0.09 per 1,000 live births, while Wyllie et al [3] found an incidence of 0.077 per 1,000 live births. In a literature survey, Benn and Hsu [4] found three cases of trisomy 13 among 68,159 live births, or an incidence of 0.04 per 1,000. Prenatal ultrasound is a powerful tool for the detection of structural abnormalities in trisomy 13 fetuses. The Table summarizes these structural abnormalities, the markers or subtle findings, and the placental abnormalities that may present on ultrasound throughout such pregnancies [5]. The placental abnormalities encountered in trisomy 13 pregnancies include reduced placental vascularization and smaller placental volume in the first trimester, and a partial molar appearance and placental mesenchymal dysplasia in the second trimester [6]. To date, at least six studies of fetuses with trisomy 13 have been reported [7–12]. This article provides a comprehensive review of sonographic screening for structural abnormalities in trisomy 13 fetuses during the first trimester and the subtle sonographic findings in the second trimester.

Sonographic Screening for Structural Abnormalities Associated with Trisomy 13 in the First Trimester

Papageorghiou et al [13] found that 92 of 181 (50.8%) trisomy 13 fetuses who underwent ultrasound examination during the first trimester had omphalocele, holoprosencephaly (HPE) and/or megacystis. Watson et al [12] found that six of eight fetuses with trisomy 13 identified at 10–13 weeks of gestation had abnormal sonographic findings, including cystic hygroma in four

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Table. Prenatal ultrasound features of trisomy 13

Fetus
- Structural abnormalities
  - First trimester: holoprosencephaly, omphalocele, megacystis, and congenital heart defects
  - Second and third trimesters:
    - Brain: holoprosencephaly, brachycephaly, microcephaly, Dandy-Walker complex, posterior fossa abnormalities, ventriculomegaly, and spina bifida
    - Face: cyclopia, ethmocephaly, cebocephaly, premaxillary agenesis, cleft lip/palate, micrognathia, and hypoplastic nasal bone
    - Neck: cystic hygroma and nuchal edema
    - Heart: ventricular septal defects, atrial septal defects, patent ductus arteriosus, double-outlet right ventricle, hypoplastic left ventricle, mitral or aortic atresia, pulmonary stenosis, and anomalous venous return
    - Chest: diaphragmatic hernia
    - Abdominal wall: omphalocele
    - Urinary tract: renal cystic dysplasia, multicystic kidneys, enlarged and echogenic kidneys, hydronephrosis, and ureteral obstruction and duplication
    - Limbs: postaxial polydactyly of the hands and feet, clenched or overlapping digits, prominent calcaneus, and rocker-bottom feet
- Markers or subtle findings
  - First trimester: increased nuchal translucency thickness, fetal tachycardia, absent nasal bone, abnormal ductus venosus flow, smaller crown-rump length, smaller trunk and head volume, increased frontomaxillary facial angle in the presence of holoprosencephaly, and smaller gestational sac volume
  - Second trimester: echogenic intracardiac foci, echogenic bowel, pyelectasis, single umbilical artery, choroid plexus cysts, mild ventriculomegaly, and intrauterine growth restriction

Placenta
- First trimester: reduced placental vascularization and smaller placental volume
- Second trimester: partial molar appearance and placental mesenchymal dysplasia

cases, HPE in one case and irregularly large yolk sac in one case. Bronshtein et al [14] suggested that detailed first-trimester ultrasound examination of fetuses with abnormal nuchal translucency (NT) could shorten the parental decision-making process and spare parents a prolonged period of diagnostic uncertainty and anxiety, particularly when a structural anomaly was clearly diagnosed. In a study of 23 first-trimester fetuses with increased NT thickness ≥ 3.5 mm, Bronshtein et al [14] found severe anomalies in eight, mild anomalies in six, trisomy 13 in two, and trisomy 21 in one. In their study, one trisomy 13 fetus with NT thickness of 5.2 mm at 11^{+4} weeks of gestation had cleft lip and palate, congenital diaphragmatic hernia, HPE, hypoplastic left heart, micrognathia, and truncus arteriosus. Another trisomy 13 fetus had NT thickness of 6.0 mm at 12 weeks of gestation, and had cleft lip and palate, HPE and proboscis, while one trisomy 21 fetus with NT thickness of 4.4 mm at 13^{+3} weeks of gestation had hydronephrosis.

Omphalocele

Papageorghiou et al [13] found omphalocele in 28.2% (51/181) of trisomy 13 fetuses in the first trimester. Frequencies of omphalocele in trisomy 13 fetuses in the second and third trimesters of 3.6% (1/28) [11], 11.1% (2/18) [15], 13.3% (2/15) [10], 15.2% (5/33) [8], 22.6% (7/31) [7] and 29.4% (5/17) [16] have been reported. Chromosomal abnormalities have been reported in 10–12% of neonates with omphalocele and in 30% of fetuses with omphalocele [17–22]. When the diagnosis is made in early pregnancy, the incidence of aneuploidy can increase to 61.1% (11/18) at 12–16 weeks of gestation [23] and 66.7% (12/18) at 11–14 weeks of gestation [20]. The chromosomal abnormalities in 11 fetal omphaloceles reported by Blazer et al [23] were trisomy 18 ($n=5$), trisomy 21 ($n=2$), triploidy ($n=2$), trisomy 13 ($n=1$) and 45,X ($n=1$). The reported chromosomal abnormalities in the 12 fetal omphaloceles reported by Snijders et al [20] were trisomy 18 ($n=10$), trisomy 13 ($n=1$) and triploidy ($n=1$). In a meta-analysis of chromosomal abnormalities associated with omphalocele, Chen [24] found that 36.2% (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).

Holoprosencephaly

Papageorghiou et al [13] found HPE in 26.5% (48/181) of trisomy 13 fetuses in the first trimester. Frequencies of

16.7% (3/18) [15], 17.9% (5/28) [11], 35.5% (11/31) [7], 39.4% (13/33) [8] and 46.7% (7/15) [10] have been reported for HPE in trisomy 13 fetuses in the second and third trimesters. Blaas et al [25] found chromosomal abnormalities in 36.7% (11/30) of fetuses with prenatally detected HPE, and trisomy 13 in 45.5% (5/11). Reported frequencies of chromosomal abnormalities in fetuses with HPE in other studies have included 28.9% (11/38) [26], 33.3% (4/12) [27], 34.0% (17/50) [28], 38.8% (100/258) [29], 41.3% (50/121) [30], 42.9% (6/14) [31] and 57.6% (34/59) [32]. In a meta-analysis of chromosomal abnormalities associated with HPE, Blaas et al [25] suggested that the frequency was 34.7% (92/265) or more. Using modern, high-frequency transvaginal transducers, HPE can be diagnosed in the first trimester [33–48]. Sepulveda et al [41] suggested that failure to identify the "butterfly" sign (a cross-sectional view of the fetal brain, including visualization of both choroid plexuses) was a warning sign for HPE in the first trimester. Kim et al [44] and Timor-Tritsch et al [45] successfully used three-dimensional inversion-rendering mode to evaluate early fetal ventricles in HPE in the first trimester.

Megacystis

Papageorghiou et al [13] found megacystis in 11.6% (21/181) of trisomy 13 fetuses in the first trimester. Fetal megacystis at 10–14 weeks of gestation is defined by a longitudinal bladder diameter of ≥ 7 mm [49,50]. Sebire et al [49] detected fetal megacystis in 15 of 24,492 (1/1,633) pregnancies and chromosomal abnormalities in three of the 15 cases (20%). These included trisomy 18 ($n=1$), trisomy 13 ($n=1$) and unbalanced translocation involving chromosomes 14 and 20 ($n=1$). They also found that in the majority of chromosomally normal fetuses with mild or moderate enlargement of the bladder (longitudinal bladder diameter, 8–12 mm), there was spontaneous resolution by 20 weeks of gestation with no obvious adverse effects. They also found progressive obstructive uropathy in all fetuses with severe megacystis (longitudinal bladder diameter, ≥ 17 mm). Favre et al [51] reported chromosomal abnormalities in four of 15 fetuses (26.7%) at 11–15 weeks of gestation, including trisomy 13 ($n=2$), trisomy 18 ($n=1$) and trisomy 21 ($n=1$). Liao et al [50] found that 30 of 145 fetuses (20.7%) with megacystis at 10–14 weeks of gestation had chromosomal abnormalities, including trisomy 13 ($n=17$), trisomy 18 ($n=7$), trisomy 21 ($n=2$), triploidy ($n=1$), trisomy 4 ($n=1$), mosaic trisomy 15 ($n=1$), and unbalanced translocation involving chromosomes 14 and 20 ($n=1$). They also expected a significantly higher number of aneuploid fetuses with trisomy 13 and trisomy 18, but not trisomy 21 in cases of megacystis. Liao et al [50] demonstrated that in fetuses with megacystis and a longitudinal bladder diameter of 7–15 mm, the risk of aneuploidy was 23.6% (26/110), compared with a risk of 11.4% (4/35) in those with a longitudinal bladder diameter of > 15 mm. Liao et al [50] additionally found that increased NT thickness was present in about 75% of aneuploid and about 30% of euploid fetuses with megacystis. About 90% of euploid fetuses with a longitudinal bladder diameter of 7–15 mm had spontaneous resolution, but all fetuses with a longitudinal bladder diameter > 15 mm had progressive obstructive uropathy. Boissier et al [52] reported that three of 12 (25%) fetuses with fetal megacystis in the first trimester had chromosomal abnormalities, including trisomy 18 ($n=2$) and trisomy 21 ($n=1$). Sepulveda [53] concluded that early detection of megacystis should include karyotyping and follow-up scans, and that vesicocentesis should be managed promptly in cases with progressive enlargement of the fetal bladder, while serial vesicocentesis with vesicoamniotic shunting or cystoscopic procedures should be offered as an alternative to termination of pregnancy, if the condition did not resolve.

Congenital heart defects (CHD)

CHD have been found in more than 80% of fetuses with trisomy 13 [54,55]. The commonest CHDs 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 [55]. Frequencies of CHD in trisomy 13 fetuses in the second and third trimesters have been reported as 33.3% (5/15) [42], 45.2% (14/31) [7], 48.5% (16/33) [8], 50.0% (9/18) [15], 53.6% (15/28) [11], and 70.6% (12/17) [16]. Becker and Wegner [56] found that the overall detection rate for major CHD on the 11–13^{+6}-week scan was 84.2% (32/38), with 37.5% (3/8) for NT < 2.5 mm and 96.7% (29/30) for NT ≥ 2.5 mm. In a study of pregnancies with risk factors for fetal CHD, such as NT ≥ 4 mm, a first-degree relative with CHD, or suspicion of CHD or extracardiac abnormality on the 10–14-week scan, Huggon et al [57] found chromosomal abnormalities in 31.5% (70/222) of fetuses with a normal heart on echocardiography (trisomy 21 [$n=47$], trisomy 18 [$n=9$], trisomy 13 [$n=4$], 45,X [$n=3$], and others [$n=7$]). In contrast, chromosomal abnormalities were present in 69.2% (18/26) of fetuses with atrioventricular septal defect (trisomy 21 [$n=14$], trisomy 18 [$n=1$], trisomy 13 [$n=2$], and others [$n=1$]), in 71.4% (5/7) of fetuses with hypoplastic left heart syndrome (trisomy 18 [$n=1$] and 45,X [$n=4$]), in 80.0% (8/10) of fetuses with ventricular septal defect (trisomy 21 [$n=2$], trisomy

18 [*n*=5], and trisomy 13 [*n*=1]), in 92.6% (25/27) of fetuses with disproportion (trisomy 21 [*n*=3], trisomy 18 [*n*=5], trisomy 13 [*n*=4], and 45,X [*n*=13]), and in 94.7% (18/19) of fetuses with isolated tricuspid valve regurgitation (trisomy 21 [*n*=14], trisomy 18 [*n*=2], 45,X [*n*=1], and others [*n*=1]). In the study by Huggon et al [57], seven of the 11 trisomy 13 fetuses (63.6%) had confirmed cardiac abnormalities on echocardiography.

Echogenic Intracardiac Focus (EIF)

EIF is the subjective sonographic finding of an echogenic spot over the capillary muscle, and its detection depends on the resolution of the ultrasound equipment, the operator's experience, and the fetal position. EIF is a common sonographic finding in the second trimester and is observed in 3–4% of normal fetuses [58,59]. Roberts and Genest [60] reported that mineralization of the cardiac papillary muscle was observed in 15.9% (20/126) of fetuses with trisomy 21 and 39.1% (9/23) of fetuses with trisomy 13, compared with only 2% of normal fetuses. Lehman et al [8] reported that EIF was found in 38.9% (7/18) of fetuses with trisomy 13 at 12–20 weeks of gestation, and Bromley et al [61] found EIF in 18.2% (4/22) of fetuses with trisomy 21, compared with 4.7% (62/1,312) of normal fetuses. However, racial differences exist in the frequency of sonographically identified EIF in second-trimester fetal hearts [62]. Shipp et al [62] found incidences of EIF of 30.4%, 5.9%, 10.5% and 11.1% for Asian, black, white and unknown women, suggesting that EIF is a normal condition that occurs in about one-third of fetuses of Asian women. Frequencies of 3.7% (2/54) [12], 14.3% (4/28) [11], 20% (3/15) [10] and 30.3% (10/33) [8] have been reported in fetuses with trisomy 13.

Echogenic Bowel

Papp et al [11] found echogenic bowel in 17.9% (5/28) of fetuses with trisomy 13. This condition occurs in approximately 1 per 200 mid-trimester fetuses [63,64]. It may be a normal condition during the second trimester, but has also been associated with intra-amniotic hemorrhage, severe uteroplacental insufficiency, cystic fibrosis, chromosomal abnormalities, and *in utero* infection with cytomegalovirus and toxoplasmosis [63,65]. In a study of karyotyped fetuses with echogenic bowel, after exclusion of fetuses with major anomalies, Al-Kouatly et al [65] found that 3.7% (5/136) had chromosomal abnormalities, including trisomy 21 (*n*=4) and trisomy 18 (*n*=1). Bromley et al [66] reported that echogenic bowel was found in 12.5% (6/48) of fetuses with trisomy 21, and that the risk of trisomy 21 in fetuses with isolated echogenic bowel was 1.4% (71/5,105). Echogenic bowel is associated with a six- to seven-fold increase in the risk of Down syndrome, or a risk in the range of 1–2% [67,68]. In a study of 50 fetuses with echogenic bowel, Bromley et al [66] found that 16% (8/50) of fetuses had chromosomal abnormalities, including trisomy 21 (*n*=6), trisomy 13 (*n*=1) and Turner syndrome (*n*=1), and that all aneuploid cases had additional anomalies. Snijders et al [63] observed that echogenic bowel was most commonly associated with placental insufficiency and intrauterine growth restriction (IUGR). In their study of 250 fetuses with echogenic bowel, the frequencies of chromosomal abnormalities in fetuses with IUGR, minor abnormalities and major abnormalities were 0% (0/91), 2.5% (3/122) (trisomy 21 [*n*=1], trisomy 18 [*n*=1], and triploidy [*n*=1]), and 35.8% (24/67) (trisomy 21 [*n*=6], trisomy 18 [*n*=6], trisomy 13 [*n*=6], triploidy [*n*=2] and other rearrangements [*n*=4]), respectively.

Single Umbilical Artery (SUA)

SUA has been found in 0.2–1.9% of deliveries [69–73]. Granese et al [74] reported a prevalence of 0.48% (61/12,672) for SUA on prenatal ultrasound at 16–23 weeks of gestation. SUA can be associated with congenital malformations of all major organ systems and with chromosomal abnormalities [75–80]. Prucka et al [81] reported that SUA existed in 2% (97/4,846) of pathologic specimens and that fetuses with SUA had significantly more chromosomal abnormalities (10.3% *vs.* 1.0%) and other congenital anomalies (27% *vs.* 8%). Martínez-Frías et al [82] found that the most commonly associated malformations were bilateral renal agenesis and imperforate anus, followed by unilateral renal agenesis and vertebral defects. SUA has been found in more than 50% of fetuses with trisomy 18 and 10–50% of fetuses with trisomy 13 [67].

In the first trimester, visualization of the umbilical arteries on either side of the bladder and continuous with the umbilical cord insertion to the fetus can be obtained by color flow mapping in an oblique, transverse section of the fetal abdomen including the umbilicus and the fetal bladder [83]. In a study of 717 fetuses immediately before chorionic villus sampling at 11–14 weeks of gestation, Rembouskos et al [83] found SUA in 3.3% (21/634) of fetuses with a normal karyotype, 11.4% (5/44) with trisomy 21, 77.8% (14/18) with trisomy 18 and 9.5% (2/21) with other chromosomal abnormalities. The authors also found that at 11–14

weeks of gestation, the most commonly associated major structural defects were omphalocele and megacystis, and the most common chromosomal abnormality was trisomy 18 in fetuses with SUA.

In a meta-analysis of 936 fetuses with SUA diagnosed in the second and third trimesters, Rembouskos et al [83] found that 79 fetuses (8.4%) had chromosomal abnormalities, including trisomy 18 ($n=33$), trisomy 13 ($n=15$), trisomy 21 ($n=5$), triploidy ($n=9$) and other rearrangements ($n=17$). In a study of fetuses with SUA diagnosed in the second trimester, Lubusky et al [84] found SUA in 4.8% (102/2,147) of cases, including 12.8% (5/39) with trisomy 21, 50% (8/16) with trisomy 18, 25% (1/4) with trisomy 13 and 7.25% (5/69) with other rearrangements. SUA has been reported to occur in 9.3% (5/54) [12], 13.3% (2/15) [10] and 24.2% (8/33) [8] of fetuses with trisomy 13.

Choroid Plexus Cysts

Choroid plexus cysts (CPCs) occur in approximately 1% of karyotypically normal fetuses and about 50% of fetuses with trisomy 18 [85]. The reported frequency of CPCs in the normal population ranges from 0.3% to 3.6% [86–89]. CPCs are a normal condition during the second trimester and resolve by 26–28 weeks of gestation in more than 90% of cases, with no known pathologic association [63]. Sullivan et al [90] suggested that normal results of maternal serum biochemical tests and an absence of additional fetal anomalies on prenatal ultrasound could reliably exclude any underlying chromosomal abnormality. In a meta-analysis of 1,806 fetuses with CPCs, Snijders et al [63] reported a mean frequency of chromosomal abnormalities of 8%, including trisomy 18 ($n=121$), trisomy 21 ($n=18$) and other rearrangements ($n=11$), with a frequency of 1% for cases with isolated CPCs and 46% for those with multiple anomalies. They also found CPCs in 47% of fetuses with trisomy 18 ($n=137$), 8% with trisomy 21 ($n=155$) and 2% with trisomy 13 ($n=54$). Yoder et al [91] found a likelihood ratio of 13.8 (95% confidence interval, CI, 7.72–25.14; $p<0.001$) for trisomy 18 and 1.87 (95% CI, 0.78–4.46; $p=0.16$) for trisomy 21 in second-trimester fetuses with isolated CPCs. Frequencies of 3.2% (1/31) [7], 6.7% (1/15) [10] and 10.7% (3/28) [11] have been reported for CPCs in fetuses with trisomy 13.

IUGR

The frequency of chromosomal abnormalities in neonates with small gestational age is <10% [92–95]. However, early IUGR is a common prenatal feature of major chromosomal abnormalities, particularly triploidy, trisomy 18 and trisomy 13 [95]. In a study of 458 fetuses with IUGR at 17–39 weeks of gestation, Snijders et al [95] found chromosomal abnormalities in 19.4% (89/458) of cases, including triploidy ($n=36$), trisomy 18 ($n=32$), trisomy 21 ($n=8$), trisomy 13 ($n=5$), trisomy 22 ($n=1$) and other autosomal deletions or duplications ($n=7$). The frequency of chromosomal abnormalities varied with gestational age at presentation (38% at 18–25 weeks, 10% at 26–33 weeks, and 15% at 34–41 weeks), the presence of fetal anomalies (40% with fetal anomalies and 3% without fetal anomalies), amniotic fluid volume (95% with increased volume, 32% with normal volume, 10% with reduced volume, and 5% with absent volume), and Doppler findings (44% with absence of notch [–NT] and presence of end-diastolic frequencies [+EDF], 24% with –NT/–EDF, 12% with +NT/+EDF, and 8% with +NT/–EDF).

Triploid fetuses have early-onset asymmetrical IUGR with macrocephaly and increased head-to-abdominal circumference ratio, whereas fetuses with trisomy 18 and trisomy 13 have symmetrical IUGR before 30 weeks' gestation [63]. Dicke and Crane [96] found that mid-trimester IUGR was evident in 43% of fetuses with trisomy 13 ($n=9$) and 59% of fetuses with trisomy 18 ($n=22$), but not in fetuses with trisomy 21 ($n=43$). Snijders et al [63] found small gestational age in 100% of fetuses with triploidy ($n=50$), 74% with trisomy 18 ($n=137$), 61% with trisomy 13 ($n=54$), 55% with Turner syndrome ($n=54$), and 20% with trisomy 21 ($n=155$). Jauniaux et al [97] reported that 62.5% (10/16) of fetuses with triploidy had fetal crown-rump length below the fifth centile at 10–14 weeks of gestation. Bahado-Singh et al [98] reported that, in the first trimester, fetuses with trisomy 18 and trisomy 13 were growth restricted, with significant shortening of crown-rump length, but that fetuses with trisomy 21 were not associated with early-onset IUGR.

Frequencies of 26.7% (4/15) [10], 48.4% (15/31) [7] and 48.5% (16/33) [8] have been reported for IUGR in fetuses with trisomy 13.

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