Prenatal Sonographic Features of Trisomy 13

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Fetuses with trisomy 13 are characterized by many associated congenital anomalies including defects of the brain, face, heart, and limbs. The complex anomalies usually result in early embryo death or intrauterine fetal death in the late stages. Only 5–10% of live births have a longer survival time after delivery but these patients are often mentally retarded. Prenatal sonography has been reported to detect more than 90% of trisomy 13 fetuses with major structural defects in the second trimester. In recent years, the addition of soft markers to the sonographic screening for fetal trisomy 13 in the first trimester has been significantly beneficial. This article provides an overview of the common sonographic features of fetal trisomy 13 with major structural abnormalities including brain defects, midline facial defects, cardiac anomalies, genitourinary anomalies, limb anomalies and abdominal wall defects, and minor structural abnormalities including increased nuchal translucency thickness, echogenic intracardiac focus, fetal tachycardia, and megacystis. Several diseases may have phenotypic overlaps with trisomy 13 syndrome including Meckel-Gruber syndrome, pseudotrismy 13 syndrome, Smith-Lemli-Opitz syndrome, Pallister-Hall syndrome, and hydrolethalus syndrome. Due to the seriousness of this congenital anomaly, increased understanding of the different sonographic markers will improve the detection of trisomy 13 and prenatal ultrasound is a valuable tool in detecting a variety of congenital structural malformations of this lethal syndrome throughout gestation.

KEY WORDS — prenatal ultrasound, trisomy 13

Introduction

Chromosomal abnormalities occur in 0.1–0.2% of live-born infants. The incidence of trisomy 13 live births has been reported to range from 1/5,000 to 1/30,000 [1–8]. Trisomy 13 was first described by Patau et al [9] in 1960 and is the third most common trisomy following trisomies 21 and 18. Trisomy 13 represents the presence of an extra chromosome 13 resulting from a free copy or translocation. Molecular analysis of the free extra chromosome 13 revealed that in more than 80% of patients, it resulted from a maternal meiotic nondisjunction [10]. Clinically, it manifests many associated congenital anomalies including malformations of the brain, craniofacial defects, heart defects, limb defects, and severe mental retardation. The complex malformations usually result in miscarriage or intrauterine fetal death.
throughout the gestation [11]. Even after birth, the majority of affected fetuses die shortly thereafter. Only 5–10% of live births have a longer survival time and the survivors often have mental retardation [1].

In obstetric practice, ultrasound is a valuable tool in the detection of fetal structural anomalies, and it has been reported to detect more than 90% of fetuses with trisomy 13 [12,13]. Here, we review the associated prenatal sonographic features in the detection of fetal trisomy 13. The common major sonographic abnormalities of fetal trisomy 13 include brain defects, midline facial defects, cardiac anomalies, genitourinary anomalies, limb anomalies, and abdominal wall defects, and minor sonographic abnormalities include increased nuchal translucency thickness (NT), echogenic intracardiac focus (EIF), fetal tachycardia, and megacystis. Early prenatal diagnosis is significantly beneficial to determination of the course of pregnancy. In addition, differential diagnoses including Meckel-Gruber syndrome, pseudotrisomy 13 syndrome, Smith-Lemli-Opitz syndrome, Pallister-Hall syndrome, and hydrolethala-lus syndrome are discussed. Both the prenatal sonographic features and differential diagnoses of trisomy 13 are summarized in Table 1.

**Prenatal Sonographic Features**

Prenatal ultrasound has been extensively applied in the assessment of fetal chromosomal aneuploidy for a long time. Clinically, two types of sonographic markers suggestive of aneuploidy are used. Type I markers represent major fetal structural abnormalities and type II markers, also called soft markers, are characterized by nonspecific and often transient fetal abnormalities.

**Type I Markers — Major Structural Abnormalities**

Currently, type I sonographic markers in the majority of fetuses with trisomy 13 include the anomalies of the brain, the face, the heart, the genitourinary tract, the limbs, and abdominal wall defects in the second trimester. Above 14 weeks of gestation, Picklesimer et al [14] found that all the major structural anomalies of trisomy 13 could be prenatally detected. With the advent of high-quality ultrasound equipment, many structural abnormalities of fetal trisomy 13 can be detected before the second trimester. In a first trimester scanning between 11 and 13+6 weeks of gestation, sonographic findings of holoprosencephaly (HPE), exomphalos, and/or megacystis can be seen in approximately 50% of trisomy 13 fetuses [15]. Clinically, most pregnant women prefer early identification of the major fetal structural defects and this service can significantly promote their autonomy.

**Brain anomalies**

The brain anomalies in trisomy 13 patients include HPE, agenesis of the corpus callosum, cerebellar anomalies, hydrocephalus, ventriculomegaly, enlarged cisterna magna, and microcephaly [13]. HPE is a severe malformation in the brain and is caused by impaired midline cleavage of the embryonic pro-sencephalon resulting in different degrees of fusion of the lateral ventricles [16]. The variable phenotypes of HPE can be classified as alobar type, semilobar type, lobar type, and a middle interhemispheric fusion variant. Alobar HPE is characterized by total absence of interhemispheric fissure, the third ventricle, falx cerebri, neurohypophysis, and olfactory bulbs. Semilobar HPE is characterized by partial separation of posterior cerebral hemispheres with presence of occipital lobe and usually the absence of olfactory bulbs and corpus callosum. Lobar HPE is characterized by complete division of cerebral hemispheres with a variable degree of fusion at the cingulated gyrus [17]. Genetic and nongenetic factors can both result in the development of fetal HPE. In cases with HPE of an abnormal karyotype, trisomy 13 is the most frequent, and approximately 70% of fetuses with trisomy 13 can manifest HPE [7,18]. Prenatal diagnosis of HPE was first described by Kurtz et al in 1980 [19]. The most specific sonographic findings in trisomy 13 with alobar HPE are single fused lateral ventricle, fusion
of the thalami, and no visible midline structures in the midtrimester. The associated findings often include the presence of a dorsal sac and midline facial anomalies such as cyclopia, hypotelorism, anophthalmia, arhinia, proboscis, and midline facial clefts [20,21]. In a sonographic scanning of 28 trisomy 13 fetuses between 13 and 25 weeks of gestation, brain anomalies were detected in 18 fetuses (18/28, 64.3%), of which ventriculomegaly and HPE were the most common [22]. Recently, first-trimester sonographic screening for fetal trisomy 13 has reported that HPE can be detected as early as 9 + 2 weeks' gestation with improved ultrasound equipment [23]. Sepulveda et al proposed that failure to identify the “butterfly” sign which describes visualization of the choroid plexus in both lateral ventricles is a warning sign of HPE in the first trimester [24].

### Facial anomalies

Normally developed facial features depend on the normal development of the underlying brain structures. Because of the common brain anomalies in fetuses with trisomy 13, midline facial defects are also frequently seen. The facial anomalies associated with alobar HPE are invariably characterized by a wide range of midline facial defects ranging from a single incisor to cyclopia and clinically these features can be classified as cyclopia, ethmocephaly, cebocephaly, and median cleft lips [17,25,26]. The main facial features in cyclopia include median monoophthalmia, synophthalmia or anophthalmia, and absent or single proboscis. Ethmocephaly manifests extreme hypotelorism and a proboscis above the orbits. Cebocephaly is characterized by ocular hypotelorism and single nostril nose. Features in the case

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**Table 1. Prenatal sonographic features of trisomy 13 and differential diagnoses**

**Prenatal sonographic features**

- **Type I markers — major structural anomalies**
  - Brain anomalies: holoprosencephaly, agenesis of the corpus callosum, cerebellar anomalies, hydrocephalus, ventriculomegaly, enlarged cisterna magna, and microcephaly.
  - Facial anomalies: cyclopia, ethmocephaly, cebocephaly, median cleft lips, a single incisor, and absent or hypoplastic nasal bone.
  - Cardiac anomalies: 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.
  - Genitourinary anomalies: pyelectasis, renal cystic dysplasia, multicystic kidneys, enlarged and echogenic kidneys, hydronephrosis, ureteral obstruction, and duplication.
  - Limb anomalies: postaxial polydactyly of the hands and feet, clenched or overlapping digits, prominent calcaneus, and rocker bottom or club feet.
  - Abdominal wall defects: omphalocele, bladder extrophy.

- **Type II markers — soft markers**
  - Increased nuchal translucency thickness
  - Echogenic intracardiac focus
  - Fetal tachycardia
  - Megacystis

**Differential diagnoses**

- Meckel-Gruber syndrome
- Pseudotrisomy 13 syndrome
- Smith-Lemli-Opitz syndrome
- Pallister-Hall syndrome
- Hydroethalalus syndrome
of median cleft lips also include ocular hypotelorism and flat nose. The variable and less severe facial malformations associated with semilobar or lobar HPE include hypotelorism, coloboma of the iris, unilateral or bilateral cleft lip and/or palate, microphthalmia, flat nose, and other anomalies [17,25,26]. In a prenatal detection of 28 trisomy 13 fetuses, midline facial defects were the most common (12/28, 42.9%) and usually associated with the underlying brain defects (11/12, 92%) [22]. Absent or hypoplastic nasal bone has been suggested as a marker for identification of fetal aneuploidy in the first and second trimesters [27–29]. It can be detected in approximately 34–55% of fetuses with trisomy 13 [30,31]. Because of lack of relationship between absent nasal bone and first trimester biochemical markers in trisomy 13 fetuses, it could be expected to increase the detection of this aneuploidy after incorporating the study of the characteristics of the absent nasal bone into the existing first trimester screening program [32].

**Cardiac anomalies**
Congenital heart defects are common in fetuses with trisomy 13, including 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 [13,33]. Cardiovascular anomalies were prenatally detected in 15 (53.6%) out of 28 trisomy 13 fetuses, of which ventricular septal defects were the most common (4/15, 26.7%) [22].

**Genitourinary anomalies**
The frequently associated genitourinary anomalies in trisomy 13 fetuses, occurring unilaterally or bilaterally, include multicystic kidneys, enlarged and echogenic kidneys, renal cystic dysplasia, hydronephrosis, ureteral obstruction, and duplication [13]. These abnormalities may be seen in approximately one third of trisomy 13 fetuses [13]. In another study of 28 trisomy 13 fetuses, renal anomalies were prenatally detected in 42.9% (12/28), of which the two common findings were pyelectasis (8/12, 66.6%) and renal cystic dysplasia (4/12, 33.3%) [22].

**Limb anomalies**
The limb defects described in trisomy 13 include postaxial polydactyly of the hands and feet, clenched or overlapping digits, prominent calcaneus, and rocker bottom or club feet, of which postaxial polydactyly was the most frequent in Lehman et al’s report [13]. An epidemiologic analysis revealed 155 cases with the suspected or proved trisomy 13 cases having postaxial polydactyly and only 15 cases having preaxial polydactyly [34]. However, in a recent study of 28 trisomy 13 fetuses, prenatal detection of a limb defect with postaxial polydactyly was only documented in two cases (2/28, 7.1%) [22]. The difficulty in prenatal sonographic detection of limb anomalies may be strongly associated with maternal obesity, unfavorable fetal postures, earlier sonographic scanning, and suboptimal visualization of fetuses.

**Abdominal wall defects**
Abdominal wall defects in fetuses with trisomy 13 may have omphalocele and bladder extrophy [13]. Omphalocele may be the manifestation of a chromosomal abnormality. In a study of 40 fetuses with central type of omphalocele, trisomy 13 was the second most frequent chromosomal abnormality (5/40, 12.5%) after trisomy 18 (29/40, 72.5%) [35]. In a large ultrasound screening at 11–14 weeks of gestation, the frequency of fetal omphalocles with trisomy 13 was 9.1% [36]. Although the early diagnosis of omphalocele is often easy by prenatal ultrasound, we should caution about the diagnosis before the completion of the physiologic herniation in the first trimester.

**Type II Markers — Soft Markers**
The most common soft markers in trisomic fetuses include a thickened nuchal fold, EIF, fetal tachycardia, megacystis, intrauterine growth restriction, echogenic bowel, single umbilical artery, shortened femurs or humerus, renal pelvic dilation, and choroid plexus cysts. Although these findings are seen in normal fetuses, they can be found in a higher
percentage of fetal aneuploidy, and their presence has become an important element of risk adjustment in early pregnancy. Similar to other trisomies, soft markers on prenatal ultrasound have been increasingly applied in screening of fetal trisomy 13. The more commonly studied soft markers for trisomy 13 include an increased fetal NT, an EIF, fetal tachycardia, and megacystis.

**Increased NT**
In the first trimester, the term “fetal NT” refers to the sonographic finding of a subcutaneous collection of fluid behind the fetal neck. Previous studies provide evidence that increased fetal NT is significantly associated with chromosomal abnormalities [37]. Currently, the Fetal Medicine Foundation, a registered charity in the United Kingdom, proposed that the optimal gestational age for the measurement of fetal NT is from 11 to 13 + 6 weeks of gestation. The corresponding fetal crown–rump length (CRL) is between 45 mm and 84 mm. Increased NT is defined by the vertical thickness equal to or above the 95th centile of a reference range. The 95th centile of NT increased linearly with fetal CRL from 2.1 mm at a CRL of 45 mm to 2.7 mm for a CRL of 84 mm, whereas the 99th centile did not change with CRL, and it was approximately 3.5 mm [38]. Kagan et al [39] reported that NT thickness was 4.5 mm or more in approximately 60% of trisomy 13 fetuses. In addition, maternal serum proteins including free β-human chorionic gonadotropin (β-hCG) and pregnancy associated plasma protein-A (PAPP-A) are decreased in trisomy 13 fetuses [40]. Nicolaides reported that first trimester screening by a combination of fetal NT and PAPP-A and free β-hCG can identify approximately 90% of chromosomal aneuploidies including trisomy 13, which represents a screen positive rate of 1% [31]. After the second trimester, nuchal cystic hygroma or nuchal edema can be seen in approximately 20% of fetuses with trisomy 13 [13].

**EIF**
An EIF is a subjective sonographic finding of an echogenic spot over the cardiac papillary muscle and its detection depends on a variety of factors including resolution of the sonographic equipment, the operator’s experience and the fetal posture. Approximately 3–4% of normal fetuses can be detected with EIFs in the second trimester [41,42]. Shipp et al [43] found three times more detections among Asian patients with EIFs compared with white patients. In a pathologic study, Roberts and Genest first suggested an association between aneuploidy and mineralization of the papillary muscle, which was observed in 2% of normal fetuses compared with 39% of those with trisomy 13 [44]. Clinically, most trisomy 13 fetuses with EIFs also had detection of other structural anomalies, except for one trisomy 13 fetus who had multiple EIFs as the only abnormal finding on prenatal ultrasound [45].

**Fetal tachycardia**
In first trimester studies, fetal tachycardia was reported to be associated with trisomy 13 [46,47]. Fetal heart rate in normal pregnancy is observed to increase from about 110 beats per minute (bpm) at 5 weeks of gestation to 170 bpm at 9 weeks due to cardiac structural development and then gradually to decrease to 150 bpm by 14 weeks, suggestive of functional maturation of the parasympathetic system [48,49]. Fetal heart rate was reported to be above the 95th centile of the normal range in 67% of trisomy 13 fetuses and the possible explanation of first-trimester fetal tachycardia of trisomy 13 is associated with congenital cardiac defects such as septal and/or valvular abnormalities [46].

**Megacystis**
By definition, fetal megacystis is defined by a longitudinal bladder diameter of 7 mm or more at 10–14 weeks of gestation and the incidence is about 1 in 1,500 pregnancies [50]. If a longitudinal diameter of the fetal bladder is measured as 7–15 mm during 10–14 weeks of gestation, there is a risk of approximately 25% that the fetus will have a chromosomal defect, mainly trisomies 13 or 18 [51]. Approximately 90% of fetuses with megacystis of a normal karyotype will spontaneously resolve without any adverse consequence of the urinary system.
Differential Diagnosis

The definite diagnosis of fetal trisomy 13 depends on cytogenetic analysis. Owing to these common structural abnormalities in fetal trisomy 13, differential diagnoses should include Meckel-Gruber syndrome, pseudotrisomy 13 syndrome, Smith-Lemli-Opitz syndrome, Pallister-Hall syndrome, and hydro lethals syndrome.

Meckel-Gruber syndrome or Meckel syndrome (MKS, OMIM 249000)

MKS was described initially in 1822 by Meckel [52] and redefined in 1934 by Gruber [53]. MKS is classified into three subtypes and the genetic loci have been mapped including MKS1 (OMIM 609883) on 17q21-q24 [54], MKS2 (OMIM 603194) on 11q13 [55], and MKS3 (OMIM 607361) on 8q21-q22 [56]. MKS is an autosomal recessive disorder manifesting a combination of polycystic kidneys, anomalies of the central nervous system (typically occipital encephalocele), hepatic ductal dysplasia and cysts, and postaxial polydactyly [57]. Clinical spectrums of MKS showed that cystic kidney dysplasia is the most common defect, whereas occipital encephalocele and polydactyly are found in only 50% [58]. Compared with trisomy 13, occipital encephalocele but not HPE is the major brain anomaly in MKS. In addition, oligohydramnios is often seen in MKS fetuses due to severe renal dysfunction.

Pseudotrisomy 13 syndrome (holoprosencephaly-polydactyly syndrome, OMIM 264480)

Patients with pseudotrisomy 13 syndrome manifest HPE, severe facial anomalies, postaxial polydactyly, and a normal karyotype [59]. Other congenital defects may include cerebellar hypoplasia, encephalocele, microphthalmia, cleft lip and palate, cardiac defects, ambiguous genitalia, malformations of the urinary and digestive system, malsegmentation of the lungs, and adrenal hypoplasia [60]. Neither HPE nor polydactyly is obligatory because affected sibs did not always show these malformations [61]. Several cases provide evidence that pseudotrisomy 13 syndrome is an autosomal recessive inheritance and carries a 25% risk of recurrence [62–65]. The phenotypes of trisomy 13 have a considerable overlap with pseudotrisomy 13 and the most powerful diagnosis in distinguishing trisomy 13 from pseudotrisomy 13 relies on fetal karyotyping.

Smith-Lemli-Opitz syndrome (SLOS, OMIM 270400)

SLOS is a metabolic syndrome of multiple congenital malformations characterized by psychomotor retardation, growth restriction, cleft palate, postaxial polydactyly, and rare craniofacial abnormalities including microcephaly, micrognathia, and HPE. The causative factor is deficiency of 7-dehydrocholesterol reductase (DHCR7) resulting from mutations in the DHCR7 gene mapping to 11q12-q13 [66]. The reductase is the final enzyme of the cholesterol biosynthetic pathway. Prenatal diagnosis of SLOS can be done by biochemical analysis of 7-dehydrocholesterol levels in amniotic fluid or chorionic villi and mutation analysis of the DHCR7 gene [67,68]. Since recently, steroid measurements in maternal urine are supposed to be a reliable basis for prenatal diagnosis [69].

Pallister-Hall syndrome (PHS, OMIM 146510)

PHS is defined by postaxial polydactyly, hypothalamic hamartoma, abnormal lung lobations, renal agenesis or dysplasia, epiglottic or laryngeal clefts, congenital heart defects, and intrauterine growth restriction. The syndrome is caused by frameshift, nonsense, and splicing mutations in the zinc finger transcription factor gene, GLI3, mapping to 7p13 [70]. The specific finding of hypothalamic hamartoma in PHS is different from HPE in trisomy 13 and magnetic resonance imaging is the most valuable diagnostic tool [71].

Hydro lethals syndrome (HYLS, OMIM 236680)

Hydro lethals syndrome, discovered in Finland, was characterized by midbrain anomalies with severe hydrocephalus, micropolygyria, facial clefts,
micrognathia, and polydactyly [72]. It is caused by mutations in the HYLS1 gene on 11q24.2 (OMIM 610693) [73]. In the brain, the foramen magnum is keyhole shaped and the hydrocephalus is external because the ventricles are open to the subarachnoid space. Clinically, polyhydramnios often occurs during the pregnancy and the characteristics of polydactyly are postaxiality in the hands and preaxiality in the feet.

### Conclusion

In the modern era, the use of prenatal ultrasound in aneuploidy risk estimation has improved clinical obstetric practice. Clinically, triple maternal serum screening with α-fetoprotein, free β-hCG, and unconjugated estriol in the second trimester is not useful in detecting trisomy 13 fetuses. Statistically, sonographic findings of structural defects can identify more than 90% of trisomy 13 fetuses throughout the gestation. Despite the fact that sonographic features of trisomy 13 may overlap with those of other syndromes, fetuses with brain defects, midline facial defects, cardiac anomalies, genitourinary anomalies, limb anomalies, and abdominal wall defects are strongly suggestive of trisomy 13 and further fetal karyotyping is warranted. In the first trimester screening for trisomy 13 fetuses, the addition of sonographic soft markers including increased fetal NT and absent or hypoplastic nasal bone demonstrably benefits pregnant women in obtaining more personalized risk assessment. Due to the lethal syndrome, prenatal ultrasound has been demonstrated to be a valuable tool in detecting a variety of congenital structural malformations of trisomy 13 throughout the gestation.

### References


52. Meckel JF. Beschreibung zweier, durch sehr aehnliche Bildungsabweichungen entsellter Geschwister. Dtsch Arch Physiol 1822;7:99–172. [In German]

53. Gruber GB. Beitraege zur Frage “gekoppelter” missbildungen. (Akrocephalo-Syndactylie und Dysencephalia splanchnocystica) Beitr Path Anat 1934;93:459–76. [In German]


58. Fraser FC, Lytwyn A. Spectrum of anomalies in the Meckel syndrome, or: “Maybe there is a malformation syndrome with at least one constant anomaly.” Am J Hum Genet 1983;33:642–8.
