Prenatal Sonographic Features of Trisomy 18

Chih-Ping Chen¹,²,³*, Shu-Chin Chien⁴,⁵

Trisomy 18, the second most common autosomal trisomy, is associated with multiple severe structural defects. Most fetuses of trisomy 18 can have one or more sonographically detectable structural abnormalities. This article provides an overview of the common sonographic features of the fetal trisomy 18, with major and minor structural abnormalities including cardiac anomalies, malformations of the central nervous system, facial anomalies, gastrointestinal anomalies, limb anomalies, intrauterine growth restriction, choroid plexus cysts and increased nuchal translucency or cystic hygroma. Several diseases may have phenotypic overlaps with trisomy 18 syndrome, including trisomy 18-like syndrome, Pena–Shokeir syndrome type I and arthrogryposis multiplex congenita. In addition, sex bias is significantly observed in trisomy 18 live births, and prenatal selection against male fetuses has been documented to be associated with more complex congenital anomalies. Because of the lethal birth defects in trisomy 18, prenatal ultrasound is a valuable tool to detect a variety of congenital structural malformations of trisomy 18 throughout the gestation, and early sonographic identification of major structural defects and determination of the fetal sex can provide an appropriate genetic counseling and a more reasonable management for the pregnant women.

KEY WORDS — prenatal ultrasound, trisomy 18

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At least 11 trisomy 18 patients have been reported to have a long-term survival past the age of 10 years [10–12].

Nowadays, ultrasound and multiple maternal serum markers are clinically applied to detect fetuses with trisomy 18. The sensitivity of sonographic detection of fetuses with trisomy 18 was reported to be approximately 70–100% [13–16]. Prenatal sonographic features of trisomy 18 include congenital heart defects, malformations of the central nervous system (CNS), facial anomalies, gastrointestinal anomalies, defects of the limbs, intrauterine growth restriction (IUGR), choroid plexus cysts (CPCs) and increased nuchal translucency (NT) thickness or cystic hygroma. A detailed understanding of the various sonographic abnormalities for trisomy 18 fetuses can greatly improve prenatal detection of this serious congenital anomaly. In addition, differential diagnosis of trisomy 18 syndrome, including trisomy 18-like syndrome, Pena–Shokeir syndrome type I and arthrogryposis multiplex congenital (AMC), is discussed here (Table).

### Prenatal Sonographic Features

Sonographic findings associated with fetal aneuploidies can be classified as major structural anomalies or minor anomalies (or soft markers). Major structural anomalies related to trisomy 18 are anomalies of the cardiovascular system, CNS, extremities, face, and gastrointestinal system. Minor anomalies include IUGR (< 10th centile), increased fetal NT, nuchal cystic hygroma, CPC, absent fetal nasal bone, polyhydramnios, single umbilical artery, and umbilical cord cysts. Previous studies reported at least one abnormal sonographic finding seen in fetuses with trisomy 18 [15,17,18]. The prenatal sonographic detection of fetuses with trisomy 18 could be up to 100% by an experienced sonographer [15].

#### Table. Prenatal sonographic features of trisomy 18 and differential diagnosis

<table>
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<td>ventricular septal defects, atrial septal defects, double-outlet right ventricle, patent ductus arteriosus, hypoplastic left ventricle, tetralogy of Fallot, transposition of great vessels, endocardial cushion defects, mitral atresia, and coarctation</td>
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<td>cerebellar hypoplasia, holoprosencephaly, anencephaly, agenesis of corpus callosum, ventriculomegaly, hydrocephaly, strawberry-shaped head, brachycephaly, microcephaly, encephalocele, spina bifida and other neural tube defects</td>
<td>multiplex congenital</td>
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<td>facial clefts, cyclopia, hypotelorism, short ear length, micrognathia, prominent occiput, and absence or hypoplasia of nasal bone</td>
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Cardiac anomalies
A wide spectrum of cardiac defects associated with trisomy 18 include ventricular septal defects (VSD), atrial septal defects (ASDs), double-outlet right ventricle (DORV), patent ductus arteriosus (PDA), hypoplastic left ventricle, tetralogy of Fallot (TOF), transposition of great vessels, endocardial cushion defects, mitral atresia, coarctation, and others. In the pathologic series of trisomy 18, cardiac anomalies were universal and all the trisomy 18 cases manifested various forms of complex structural malformations [19–22]. In a combined pathologic series, the three most common defects were VSD (52%), coarctation (19%) and TOF (10%) [23]. However, prenatal echocardiography can detect most but not all cases of trisomy 18 with congenital heart defects throughout the gestation. Based on the experience of the sonographers, the quality of ultrasound equipment and diagnosis at gestational weeks, prenatal sonographic detection of congenital cardiac malformations of trisomy 18 have been reported with wide ranges. In a large study of 174 trisomy 18 fetuses between 10 and 33 weeks of gestation in London, cardiac anomalies were found in 118 of 162 cases (72.8%) by prenatal echocardiography, of which ASD (29/162, 17.9%), VSD (13/162, 8%) and coarctation (21/162, 13%) were the most frequent findings [23]. In addition, they found that cardiac malformations could be diagnosed reliably, even in the late first trimester. In an analysis of 30 trisomy 18 fetuses in Korea, cardiac anomalies were prenatally detected in 17 fetuses (57%) throughout the gestation and in 15 fetuses (50%) above 16 weeks of gestation. Almost all the fetuses had VSD (16/17, 94%) [17]. In a retrospective study of 89 trisomy 18 fetuses in Taiwan, 20 cases (20/89, 22.47%) were found to have CNS anomalies manifesting cerebellar hypoplasia, hydrocephalus-premaxillary agenesis, HPE, and neural tube defects. These defects were often detected prenatally in the second or third trimester [27]. In the report, cerebellar hypoplasia is the most common sign characterized by Dandy–Walker malformation and an enlarged cisterna magna. The abnormal sign of an enlarged cisterna magna is often detected after 24 weeks of gestation [14].

CNS anomalies
In trisomy 18, the reported associated CNS anomalies include cerebellar hypoplasia, holoprosencephaly (HPE), anencephaly, agenesis of corpus callosum, ventriculomegaly, hydrocephaly, encephalocoele, microcephaly, spina bifida, neural tube defects, and others. In a European study of 120 trisomy 18 cases, they found 16 cases (16/120, 13.3%) with CNS anomalies, including hydrocephalus (5.0%), HPE (1.7%), and others (6.7%) [16]. In a study of 25 trisomy 18 cases, 17 cases (17/25, 68%) had CNS anomalies, including an enlarged cisterna magna (20%), ventriculomegaly (16%), strawberry-shaped head (12%), brachycephaly (12%) and HPE (8%) [18]. In a study of 38 trisomy 18 cases, CNS anomalies were the most common anomalies in 33 cases (87%), compared with cardiac anomalies in 32 cases (84%) [15]. In a retrospective study of 89 trisomy 18 fetuses in Taiwan, 20 cases (20/89, 22.47%) were found to have CNS anomalies manifesting cerebellar hypoplasia, hydrocephalus-premaxillary agenesis, HPE, and neural tube defects. These defects were often detected prenatally in the second or third trimester [27]. In the report, cerebellar hypoplasia is the most common sign characterized by Dandy–Walker malformation and an enlarged cisterna magna. The abnormal sign of an enlarged cisterna magna is often detected after 24 weeks of gestation [14]. In a review of 70 trisomy 18 cases, the authors found 25 cases (25/70, 35.7%) having
CNS anomalies with abnormal head shape (12.9%), posterior fossa abnormality (11.4%), and ventriculomegaly (11.4%) [25].

**Facial anomalies**

Orofacial abnormalities are common among trisomy 18 patients [28]. The perinatal facial anomalies of trisomy 18 include facial clefts, cyclopia, hypotelorism, short ear length, micrognathia, prominent occiput, and absence or hypoplasia of nasal bone. When ocular anomalies or midline facial defects are seen in association with HPE, chromosomal aneuploidy should be highly considered. In different study settings, prenatal sonographic findings of facial anomalies can be detected in approximately 14.3–37% of trisomy 18 fetuses after the second trimester, and facial clefts are the most frequent [17,18,25]. Median and bilateral cleft-lips and palates, are the most common types [29]. In addition, absent fetal nasal bone was detected in 68 out of 124 fetuses with trisomy 18 (54.8%) at 11–13 +6 weeks of gestation [30,31].

**Gastrointestinal anomalies or abdominal wall defects**

The common gastrointestinal defects of fetal trisomy 18 include omphalocele, congenital diaphragmatic hernia (CDH), and esophageal atresia with tracheoesophageal fistula. The most frequent chromosomal anomaly associated with omphalocele is trisomy 18, especially the central type of omphalocele [32,33]. Prenatal detection of omphalocele in fetal trisomy 18 was reported, ranging from 7.1% to 36% throughout gestation [17,18,25]. The early diagnosis of omphalocele is often easy by prenatal ultrasound, but we should be cautious about the diagnosis prior to completion of the physiologic herniation. In a study of 33 fetuses with CDH, six fetuses (6/33, 18.1%) had chromosomal abnormalities, especially trisomy 18 [34].

**Limb anomalies**

The reported associated skeletal anomalies of fetal trisomy 18 include clubfeet, rocker-bottom feet, clenched hands, polydactyly, syndactyly, arthrogryposis, and limb deficiency. Trisomy 18 was shown to have specific influence on the development of preaxial component of the upper limb and the tendency of hypoplasia or aplasia of the thumb and radius [35]. Abnormalities in the upper extremities and hands were reported in about 95% (36/38) of trisomy 18 fetuses [15]. Perinatal findings of preaxial polydactyly include forms ranging from a pedunculated supernumerary digit on the thumb to a well-developed extra thumb, and the polydactyly may occur, either on the left or right hand [29]. In a sonographic diagnosis of trisomy 18 at mid-trimester, abnormal hands or feet can be detected in 40% of fetuses (10/25) [18]. In another review of 70 trisomy 18 fetuses, the sonographic detection of limb anomalies with clenched hands and clubfeet was only 5.7% (4/70) in the second trimester, because evaluation of limb defects was not a routine assessment in the setting at that time. In a study of 30 trisomy 18 fetuses, 14 fetuses (14/30, 47%) were detected with limb anomalies throughout the gestation, of which 12 fetuses were above 16 weeks of gestation [17]. Sonographic findings of fetal radial aplasia could be missed by prenatal two-dimensional ultrasound [36], and three-dimensional ultrasound is supposed to be a valuable adjunct to prenatal diagnosis of radial agenesis [37]. The poor sonographic detection of limb anomalies may be associated with maternal obesity, unfavorable fetal postures, earlier sonographic scanning, and suboptimal visualization of fetuses.

**IUGR**

IUGR is defined as less than 10th centile of predicted fetal weight for gestational age. It may be diagnosed at different trimesters. In a study of 47 trisomy 18 fetuses, IUGR was the most common sonographic abnormality in trisomy 18 fetuses with an incidence of 51% throughout the gestation, and the rate was up to 89% for those older than 24 weeks of gestation [14]. In another study of 70 trisomy 18 fetuses, only 11.4% were found with IUGR in the second trimester [25]. In the first trimester screening, smaller than expected crown-rump lengths (CRLs) in association with trisomy 18 have been reported, and the restricted growth rate may be affected earlier.
in trisomy 18 fetuses than in either trisomy 13 or triploidy [38,39].

**CPCs**

Fetal CPCs are fluid-filled cystic lesions within the choroid plexus. It may appear transiently owing to early fetal development and commonly resolves in the mid-trimester. In the general population, the prevalence of isolated CPC is around 1% [40,41]. In pregnancies complicated by isolated CPCs, the prevalence of trisomy 18 is very low (0.13–0.9%) [41,42]. The sizes, bilaterality and complexity of the CPCs related to aneuploidy remain controversial. In trisomy 18 fetuses, CPCs were seen in 25–50% of cases, and most of them had other associated abnormal features [14,15,17]. In clinical practice, invasive genetic diagnosis is recommended when prenatal ultrasound detects an additional major or minor anomaly in a fetus with CPCs in the mid-trimester [43].

**Increased NT thickness and cystic hygroma**

In the first trimester, NT refers to the sonographic finding of a subcutaneous collection of fluid behind the fetal neck. It is the sonographic measurement of a maximal thickness of the echolucent zone between the inner side of the fetal skin and the outer side of the soft tissue covering the cervical spine or the occipital bone during 11–13+6 weeks of gestation, as proposed by the Fetal Medicine Foundation (FMF) [44]. Increased fetal NT, equal to or above the 95th centile of a reference range, is significantly associated with chromosomal abnormalities [45]. The most sensitive sonographic finding for trisomy 18 was increased NT (75%) under 16 weeks of gestation [17]. In a multicenter study coordinated by the FMF, increased fetal NT was identified in 74.8% (89/119) of trisomy 18 fetuses [31]. First trimester screening, with a combination of fetal NT and maternal serum proteins of free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A), can identify approximately 90% of chromosomal aneuploidies including trisomy 18, which represents a screen positive rate of 1% [31].

Nuchal cystic hygroma or nuchal edema is characterized by abnormal fluid accumulation behind the fetal neck after the second trimester or occasionally in the first trimester. The definitive sonographic findings include bilateral cystic structures or posterior cystic structures with thick septations, which are often associated with hydrops and adverse outcome. Hyett et al [46] hypothesized that nuchal cystic hygromas in trisomic fetuses may have resulted from the mechanism of hemodynamic changes due to the underlying cardiac anomalies. In a large database in Europe, cystic hygroma was the most frequent sonographic finding of trisomy 18 fetuses throughout the gestation (26/120, 21.7%) [16]. Ville et al [47] reported 56 cystic hygromas between 9 and 14 weeks of gestation and found chromosomal abnormalities in 29%, of which trisomy 18 (38%) was the most common karyotype.

**Differential Diagnosis**

Cytogenetic analysis is required for a definite diagnosis of fetal trisomy 18. The common structural abnormalities of fetal trisomy 18 remind us to consider several other diseases, such as trisomy 18-like syndrome, Pena–Shokeir syndrome type I and AMC.

**Trisomy 18-like syndrome (OMIM 601161)**

Shashi et al [48] reported a newborn with complex congenital heart defects and minor anomalies, suggestive of trisomy 18. Her parents were consanguineous. Normal karyotype was demonstrated in blood lymphocytes, skin fibroblasts, and kidney tissue, except for only 17% of mosaic trisomy 18 in the liver tissue. They concluded that mosaicism for trisomy 18 in the liver might result from a laboratory error, and a new autosomal recessive malformation syndrome was proposed, considering the history of parental consanguinity.

**Pena–Shokeir syndrome type I (OMIM 208150)**

Pena–Shokeir syndrome type I, also called fetal aki-nesia deformation sequence, was first described by Pena and Shokeir [49]. It is an autosomal recessive...
and lethal disorder, characterized by multiple neurogenic arthrogryposis, facial anomalies, and pulmonary hypoplasia. Pulmonary hypoplasia often results in early neonatal death. Primary motor neuropathy is reported as a cause of the syndrome, and the associated neuropathologic findings are cerebellar hypoplasia, thin cerebral and cerebellar cortices, marked paucity of anterior horn cells in the spinal cord, and diffuse muscle atrophy. Prenatal diagnosis was first reported in 1985, with the findings of polyhydramnios, abnormal skull shape, nuchal edema, and a similarly abnormal fetus in a previous pregnancy [50]. Pena–Shokeir syndrome type I and trisomy 18 syndrome can have similar prenatal sonographic findings, such as polyhydramnios, arthrogryposis and rocker-bottom feet [51]. The distinguishable sonographic features between them are: scalp edema and lung hypoplasia in fetuses with Pena–Shokeir syndrome type I, and cardiac arrhythmias, prominent occiput, micrognathia and omphalocele in fetuses with trisomy 18.

**AMC**

AMC, with an incidence of 1/3,000, is a heterogeneous group of disorder [52]. It manifests as congenital nonprogressive joint contractures in the upper and lower limbs and/or the vertebral column, lung hypoplasia, growth restriction, and facial anomalies with normal intelligence [53,54]. Pathologic categories of AMC include myopathies, neuropathies, connective tissue disorders, and exogenous effects such as a limited intrauterine space. AMC may be caused by either environmental factors or genetic disorders. Several types involving single gene defects are discussed here.

Autosomal dominant AMC syndrome (OMIM 108110) is characterized by various kinds of congenital contractures, amyoplasia, and a round face with a frontal midline capillary hemangioma and slightly small jaw [55,56]. There are four types of autosomal recessive AMC syndromes. Lethal congenital contracture syndrome type 1 (OMIM 253310), mapping to 9q34, is characterized by marked fetal hydrops, multiple congenital contractures with akinesia, micrognathia, the Pena–Shokeir phenotype with lung hypoplasia, atrophy of the muscle, and paucity of anterior horn motor neurons in the spinal cord [57–59]. Lethal congenital contracture syndrome type 2 (OMIM 607598), mapping to 12q13, is characterized by multiple joint contractures, micrognathia, markedly distended urinary bladder, and craniofacial anomalies [60]. Compared with type 1, type 2 lacks fetal hydrops, pterygia, and fractures. Mid-trimester sonographic features, attributing to fetal akinesia, limb contractures, hydramnios and distended urinary bladder, have been reported in type 2 [61]. AMC with neurogenic type (OMIM 208100), mapping to 5q35, is a nonlethal type, and females are less affected than males because of the possibility of incomplete penetrance in females [62,63]. Arthrogryposis–renal dysfunction–cholestasis syndrome (OMIM 208085), caused by mutations in VPS33B gene mapping to 15q26.1, manifests as a neurogenic AMC with neonatal jaundice and renal dysfunction, and those affected often die within the first year of life [64,65]. X-linked distal AMC (OMIM 301830), mapping to Xp11.3–q11.2, manifests as congenital joint contractures, hypotonia, chest deformities, facial dysmorphism, severe fetal muscle weakness and loss of anterior horn cells in males [66,67]. Several female carriers can have mild features [68].

**Sex Bias in Fetal Trisomy 18**

Sex bias in many congenital anomalies has been reported. In trisomy 18 live births, there is a significant excess of females. Statistically, the male to female ratio for live births with trisomy 18 is around 0.6 and for fetuses, it is around 0.9 [27,69]. However, there is little about the sex differences in trisomy 18 conceptuses. After conception, Huether et al [70] reported a prenatal male to female ratio of 0.9 for trisomy 18 before and after 16 weeks of gestation and of 0.69 at birth. In detailed statistics of 93 trisomy 18 fetuses throughout the gestation in Switzerland, the sex ratio was 1.02 between 10 and 15 weeks of gestation, 0.82 between 16 and 27 weeks and 0.52 between 28 and 43 weeks [69].
Spontaneous pregnancy loss rate of trisomy 18 was reported, ranging from 20% to 67% after amniocentesis [8,9,71–73]. In another study conducted after 18 weeks of gestation, the authors found that the risk for intrauterine demise in males was twice as high as the risk for intrauterine demise in females [69]. In addition to a substantial prenatal loss of trisomy 18 males, the remaining male survivors after birth seem to have a significantly shorter life span [9,28, 69,74–76]. In recent years, it is difficult to thoroughly understand the spontaneous outcome for different sex because of the increased elective abortions of trisomy 18 pregnancies after prenatal diagnosis [73].

To the best of our knowledge, the excessive loss of trisomy 18 male fetuses was associated with more severe congenital malformations, as observed by Chen [24]. In his report, the more complex structural abnormalities in trisomy 18 males included more complex CHD (57% in males vs. 33% in females), more associated CNS anomalies (50% in males vs. 33% in females), more associated omphalocele (21% in males vs. 0% in females), more associated CDH (14% in males vs. 7% in females), and more associated arthrogryposis (64% in males vs. 0% in females). Molecular analysis revealed a male preponderance caused by maternal meiosis II errors and a female preponderance caused by maternal meiosis I errors. But no significant difference was noted in the associated structural abnormalities between maternal meiosis I errors, maternal meiosis II errors and paternal errors [3].

**Conclusion**

With the advent of ultrasound equipment, the use of prenatal ultrasound has greatly improved the detection of aneuploid fetuses in obstetric practice. Traditionally, second trimester maternal serum screening test, combining α-fetoprotein, β-hCG and unconjugated estriol, can detect only 60% of trisomy 18 fetuses [77]. Prenatal sonographic detection of fetuses with trisomy 18 was reported to be approximately 70–100%, and the contribution of prenatal sonographic findings to the detection of trisomy 18 increases significantly with the fetal growth. Despite several diseases having phenotypic overlaps with trisomy 18 syndrome, fetuses with complex heart defects (such as septal and valvular defects), limb defects (such as preaxial polydactyly, clenched hand, arthrogryposis and limb deficiency), CNS anomalies (such as cerebellar hypoplasia, microcephaly, HPE, abnormal head shape, CPC, and facial clefts), gastrointestinal anomalies (such as omphalocele and CDH), and others (such as IUGR and cystic hygromas) are strongly suggestive of trisomy 18, and further fetal karyotyping is recommended. The addition of sonographic soft markers, including increased fetal NT and the absence of fetal nasal bones, to the first trimester screening for trisomy 18 fetuses can significantly enhance the detection rate. The increased understanding of the different sonographic markers is helpful in detecting trisomy 18 fetuses, and prenatal ultrasound is an established valuable tool to detect a variety of congenital structural malformations throughout the gestation. In addition, prenatal selection against male fetuses was documented to be associated with more complex congenital anomalies. Early sonographic identification of the major structural defects and determination of fetal sex in trisomy 18 can provide an appropriate genetic counseling and allow for a more reasonable management for the pregnant women.

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