Prenatal Sonographic Features of Triploidy

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Fetuses with triploidy tend to die in early pregnancy, with few surviving to term. The survivors are profoundly growth-restricted and severely malformed and often die within a few days of birth. Triploid fetuses clinically exhibit a wide spectrum of sonographically detectable abnormalities. This article provides an overview of the common sonographic abnormalities of triploid fetuses, including extra-fetal anomalies (such as an enlarged and cystic placenta, oligohydramnios, and enlarged maternal ovaries with multicystic change) and fetal structural anomalies (such as intrauterine growth restriction, increased fetal nuchal translucency thickness, central nervous system anomalies, facial anomalies, genitourinary anomalies, cardiac anomalies, gastrointestinal anomalies, and limb defects). Recognition of these different sonographic features is useful in predicting the parental origin of triploidy. Clinically, several diseases that have a phenotypic overlap with triploidy include complete mole with a coexistent fetus in dizygotic twins, a normal fetus with placental mesenchymal dysplasia, trisomies 13 and 18, and Neu-Laxova syndrome. Because of the serious and lethal birth defects, prenatal ultrasound is a valuable tool in detecting the variety of extra-fetal and fetal structural malformations associated with triploidy throughout gestation; prenatal recognition of these sonographic features is of great help in early karyotypic confirmation, enabling appropriate genetic counseling and reasonable obstetric treatment.

KEY WORDS — prenatal ultrasound, triploidy

Introduction

Triploidy is a genetic disorder with three complete haploid sets of chromosomes (69,XXX, 69,XXY, or 69,XYY). The extra haploid set of chromosomes may be of paternal or maternal origin. Based on the phenotypes and parental origins of the extra haploid set, triploid fetuses can be classified into two types: diandric triploidy (type I) and digynic triploidy (type II) [1,2]. The prevalence of triploid pregnancy is approximately 1% of all human conceptions [3], around 0.03% at 10–14 weeks of gestation [4], and 0.002% at 16–20 weeks of gestation [5]. Most triploid conceptions end as spontaneous abortions in early development. Very few triploid fetuses survive to term [6]; the survivors are profoundly growth-restricted and severely malformed and often die within a few days after delivery.

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Clinically, triploid fetuses may manifest broad spectrums of phenotypic features, including placental changes, intrauterine growth restriction (IUGR), increased fetal nuchal translucency thickness (NT), and anatomic defects of the brain, face, heart, and limbs [7,8]. No uniform sonographic features are reported in association with triploidy in previous studies of limited numbers of triploid fetuses, and the absence of prenatal fetal anomalies cannot exclude a diagnosis of triploidy [9,10]. A recent study of second-trimester sonographic detection of 70 triploid cases found that fetal anatomic defects could be identified in 65 cases (92.9%) [2]. Due to the significantly increased death rate of triploid fetuses prenatally and neonatally, and the risk of maternal complications in association with triploidy, it is important to make an accurate diagnosis as early as possible during pregnancy. The aim of this article is to review the common sonographic characteristics for early prenatal detection of triploidy. Prenatal recognition of these sonographic features is of great help in early karyotypic confirmation and in predicting parental origin, and enables appropriate genetic counseling and obstetric treatment. The differential diagnosis of fetuses with triploidy is also discussed (Table).

Prenatal Sonographic Features

Sonographic findings associated with triploid fetuses can be classified as extra-fetal anomalies such as an enlarged and cystic placenta, oligohydramnios, and enlarged maternal ovaries with multicystic change, and as fetal structural anomalies that include IUGR, increased fetal NT, central nervous system (CNS) anomalies, facial anomalies, genitourinary anomalies, cardiac anomalies, gastrointestinal anomalies, and limb defects.

Extra-fetal anomalies

Placenta
Abnormal placentas with varying sonographic appearances, ranging from an enlarged size with multicystic components (grapelike vesicles in the placenta) to partial moles, were found in 28.6–55% (11/20) of triploid pregnancies [2,4,11]. Triploid pregnancies associated with abnormal placentas with large and hydropic change, consistent with partial moles, are often seen in diandric triploidy. In contrast, digynic triploid fetuses are often seen with normal-looking but small placentas.

Amniotic fluid
Approximately 40–60% of triploid fetuses were seen in association with moderate to profound oligohydramnios; polyhydramnios was rarely reported, with a frequency of only 5% in triploid fetuses [2,8,9,11,12]. Renal dysplasia or decreased renal blood flow as a consequence of IUGR was considered to be the cause of oligohydramnios [9,11].

Maternal ovaries
The presence of enlarged maternal ovaries with multiple cysts, also termed theca-lutein cysts, is highly associated with a complete molar pregnancy, hormonal stimulation for artificial reproductive techniques, and multiple gestations. Despite its rarity, the appearance of theca-lutein cysts in early pregnancy can be seen in association with triploid gestations [11,13], with an incidence of approximately 10% of triploid pregnancies [2,10]. The presence of ovarian theca-lutein cysts supposedly relates to the abnormal elevation of maternal serum $\beta$-human chorionic gonadotrophin ($\beta$-HCG) levels produced by trophoblastic hyperplasia; high circulating serum levels of this protein are common in triploid gestations [4,14].

Fetal structural anomalies

Intrauterine growth restriction
IUGR is defined as predicted fetal weight below the 10th percentile for gestational age. It is the most distinguishable sonographic feature of fetal triploidy, with a reported incidence of 55–100% in different series, and with an average growth lag (difference from that expected by dates) of 2–6 weeks [2,4,8–12]. Symmetrical IUGR is more common in fetuses with diandric triploidy, and asymmetrical IUGR is often seen in fetuses with digynic triploidy. Asymmetrical growth restriction is observed in triploid fetuses,
with the trunk being more severely compromised than the head at 11–13\(^{-6}\) weeks of gestation [15]. The occurrence of IUGR is potentially evident as early as 10 weeks’ gestation [8,16,17]. Pircon et al suggested that IUGR could be the result of either first-trimester IUGR with subsequent normal growth or delayed ovulation and/or fertilization [10].

*Increased nuchal translucency thickness*

Increased fetal NT, characterized as a nonspecific and transient fetal anomaly, has been significantly associated with chromosomal abnormalities including triploidy. Early detection of triploidy leads to the identification of more than 65% of triploid fetuses with increased fetal NT [4]. A recent review found that increased NT is commonly seen in fetuses with diandric triploidy and that normal NT is commonly detected in fetuses with digynic triploidy [18].

*Central nervous system anomalies*

CNS anomalies are the second most common sonographic features following IUGR, with a reported frequency of approximately 50% of triploid cases [2,9–12]. The reported associated CNS anomalies include ventriculomegaly, Dandy–Walker malformation or variant, agenesis of the corpus callosum, holoprosencephaly (HPE), interhemispheric cyst, posterior fossa cyst, encephalocele, neural tube defects, and others. Second-trimester sonographic diagnosis of 70 triploid fetuses identified 24 cases with ventriculomegaly, five with spina bifida, five with Dandy–Walker malformation, and two with HPE [2]. First-trimester sonographic diagnosis of 18 triploid fetuses identified four cases with HPE (22.2%, 4/18) and one case with posterior fossa cyst (1/18) [4]. In a prenatal sonographic study of 20 triploid fetuses, CNS anomalies were observed in 45% (9/20) of cases, including four cases with open neural tube defects, two with isolated ventriculomegaly, one with corpus callosum agenesis and an interhemispheric cyst, one with encephalocele, and one with microcephaly [11]. Prenatal sonographic findings of CNS anomalies in 13 triploid fetuses included six cases with bilateral cerebral ventriculomegaly (6/13) and four with Dandy–Walker malformation or Dandy–Walker variant (4/13), which is suggested to be an additional sonographic marker for fetal triploidy [19].

*Facial anomalies*

Facial anomalies seen in prenatal triploids include microcephaly or relative macrocephaly, low-set ears, micrognathia, hypertelorism, facial clefts, cyclopia, proboscis, single nostril, and others [11,20,21]. Second-trimester sonographic diagnosis of 70 triploid fetuses identified 17 cases with micrognathia and one case with cleft lip and palate [2]. When ocular anomalies or midline facial defects are seen in association with HPE, chromosomal aneuploidy including triploidy should be strongly suspected.

*Genitourinary anomalies*

Genitourinary anomalies associated with triploidy include renal cystic dysplasia, hydronephrosis, ambiguous external genitalia, hypospadias, and others. Second-trimester sonographic diagnosis of 70 triploid fetuses identified eight cases (11.4%) with renal malformations [2]. Genital maldevelopment was detected in male fetuses with triploidy [22]. Prenatal sonographic detection of 20 triploid fetuses identified 3 cases with urinary anomalies of cystic kidneys and dilated renal pelvis. Postmortem examination of these 20 triploid fetuses revealed additional genitourinary anomalies, including renal agenesis, renal hypoplasia, renal cystic dysplasia, horseshoe kidney, and bicornuate uterus; these abnormalities may have been missed because of poor sonographic scans [11].

*Cardiac anomalies*

Postmortem examination of cardiac anomalies in triploid fetuses revealed ventricular septal defects, atrial septal defects, pulmonary stenosis, aberrant right subclavian artery, truncus arteriosus, and others [11]. Prenatal sonographic detection of cardiac anomalies differs significantly among studies. Second-trimester sonographic diagnosis of 70 triploid fetuses identified 22 cases (31.4%) with cardiac anomalies [2]. However, only one case with cardiac anomalies was detected prenatally from 20 cases of triploidy [11].
Gastrointestinal anomalies or abdominal wall defects
The gastrointestinal defects associated with triploidy include omphalocele, gastroschisis, collapsed stomach, congenital diaphragmatic hernia (CDH), duodenal obstruction, and others. The occurrence of omphalocele could be suggestive of triploidy [22], while 10–18% of triploid fetuses had associated omphalocele or gastroschisis [23]. First-trimester sonographic diagnosis of 18 triploid fetuses identified three cases with exomphalos (16.7%, 3/18) [4]. Another first-trimester study revealed fetal exomphalos in 12.5% of fetuses with triploidy [24]. Second-trimester sonographic diagnosis of 70 triploid fetuses identified four cases with omphalocele, five with collapsed stomach, and one with CDH [2]. CDH was prenatally diagnosed in a digynic triploid fetus [25]. Prenatal sonographic detection of duodenal obstruction as a “double bubble” sign was associated with a triploid fetus [26].

Limb defects
Postmortem examination of limb defects in triploid fetuses revealed syndactyly, clinodactyly, simian crease, flexion deformity, bowed legs, talipes equinovarus, hitchhiker’s toe, wide gap between toes, and prominent heels [11]. In 65 triploid fetuses with anatomic defects, malformed hands were prenatally detected in 34 cases (52.3%, 34/65), of which syndactyly of the third and fourth digits was the most common, and 5 cases had talipes equinovarus (7.7%, 5/65) [2]. However, few limb anomalies are recognized by prenatal sonography, with the possible causes of oligohydramnios, unfavorable fetal postures, suboptimal visualization of fetuses, maternal obesity, and the earlier sonographic scanning.

Molecular Analysis and Clinical Manifestations
Based on molecular polymorphism studies of the parental extra haploid set in triploidy, the majority of triploid conceptions are diandric, resulting from fertilization of a normal ovum with either a diploid sperm or two sperms. Less than 20% of triploids are digynic, resulting from a double maternal contribution with a meiosis I or II error of the ovum [27,28]. The triploid karyotype may be 69,XXX, 69,XXY, or 69,XYY from a supernumerary paternal haploid set and 69,XXX, or 69,XXY from an extra maternal haploid set. The incidence of 69,XYY is extremely low; very few 69,XYY conceptions survive beyond the second month of pregnancy [3]. The maternal contribution is reported to be essential for normal embryonal growth and development; importantly, the paternal contribution controls the growth of extraembryonic tissue such as the placenta [29,30].

Clinically, two distinct fetal phenotypes and different levels of first-trimester or second-trimester maternal serum markers have been delineated in association with triploidy [1,2,31]. Fetuses of diandric triploidy (type I) are characterized by a relatively well-grown fetus with or without microcephaly, extremely high levels of free β-HCG and α-fetoprotein (α-FP), increased fetal NT, and a large cystic placenta with partial molar changes that may affect the mother with varying degrees of preeclampsia during pregnancy or persistent trophoblastic disease after delivery [18,32,33]. Fetuses with digynic triploidy (type II) present with severe asymmetrical IUGR, relative macrocephaly, low levels of pregnancy-associated plasma protein-A and free β-HCG, normal fetal NT, and an apparently normal but small placenta. Despite these differences, there is still phenotypic overlap between the two types [2,18].

Differential Diagnosis
Prenatal sonographic features of triploid partial molar pregnancy include fetal and placental changes. Similar sonographic findings may be seen in several types of pregnancy, including complete mole with a coexistent fetus (CMCF) in dizygotic twins, a normal fetus with placental mesenchymal dysplasia (PMD), trisomies 13 and 18, and Neu–Laxova syndrome (NLS). In addition, a triploid fetus may be mistaken for a normal fetus with growth restriction.
Table. Prenatal sonographic features of triploidy and differential diagnosis

Prenatal sonographic features
Extra-fetal anomalies
- Enlarged placentas with multicystic spaces to partial moles or small placenta
- Oligohydramnios
- Theca-lutein cysts in maternal ovaries
Fetal structural anomalies
- Intrauterine growth restriction
- Increased fetal nuchal translucency thickness
Central nervous system anomalies
- Ventriculomegaly, Dandy-Walker malformation, agensis of corpus callosum, holoprosencephaly, interhemispheric cyst, posterior fossa cyst, encephalocele, neural tube defects, and others
Facial anomalies
- Microcephaly or relative macrocephaly, low-set ears, micrognathia, hypertelorism, facial clefts, cyclopia, proboscis, single nostril, and others
Genitourinary anomalies
- Renal cystic dysplasia, hydronephrosis, ambiguous external genitalia, hypospadias, and others
Cardiac anomalies
- Ventricular septal defects, atrial septal defects, pulmonary stenosis, and others
Gastrointestinal anomalies or abdominal wall defects
- Omphalocele, gastroschisis, collapsed stomach, congenital diaphragmatic hernia, duodenal obstruction, and others
Limb defects
- Syndactyly (especially the third and fourth digits), flexion deformity, talipes equinovarus, hitchhiker's toe, and others

Differential diagnosis of a triploid partial molar pregnancy
Complete mole with a coexistent fetus in dizygotic twins
A normal fetus with placental mesenchymal dysplasia
Trisomies 13 and 18
Neu-Laxova syndrome

and a small placenta with poor function resulting from constitution or intrauterine infection. Therefore, cytogenetic investigation is necessary for a definite diagnosis of fetal triploidy.

Complete mole with a coexistent fetus in dizygotic twins
The incidence of dizygotic twins with CMCF has been reported as 0.001–0.0046% pregnancies [34]. It has been reported to be associated with potential life-threatening maternal complications with pregnancy continuation, such as preeclampsia, hyperthyroidism, pulmonary edema, and gestational trophoblastic disease [35]. To distinguish a triploid partial mole from CMCF is difficult on histologic examination alone [36]. Additional genetic analyses of ploidy and DNA polymorphic markers can improve the diagnostic accuracy in molar pregnancy [37–40]. Genetic analysis of complete molar tissue often shows a diploid karyotype of only paternal origin, despite a rare occurrence of biparental complete moles observed as a familial case; most partial moles show a triploid karyotype [41,42].
Normal fetus with PMD
PMD is a rare condition of pregnancy characterized by placentomegaly and multicystic change and presents with sonographic features of molar change. It is also called pseudo-partial mole [43,44]. The condition is often associated with a karyotypically and phenotypically normal fetus and rarely with a growth-restricted fetus or a fetus with features of Beckwith–Wiedemann syndrome (BWS) [45]. Polyhydramnios may be present if the fetus has a swallowing difficulty as part of BWS. The histologic hallmarks include enlarged stem villi containing loose, moderate connective tissue with focal cistern-like formation and the absence of abnormal trophoblastic proliferation and stromal trophoblastic inclusions. Normal or slightly increased maternal serum β-HCG and α-FP levels during pregnancy may be seen in association with PMD [46,47]. Most cases are asymptomatic throughout gestation; hence, a detailed sonographic scan of fetal morphology for early recognition of fetal anomalies and karyotypic confirmation is important to avoid unnecessary termination of pregnancy in cases associated with a normal fetus.

Trisomies 13 and 18
Many similar fetal structural anomalies can be detected in fetuses with triploidy, trisomy 13, and trisomy 18, such as increased NT, IUGR, CNS anomalies, facial anomalies, cardiac anomalies, genitourinary anomalies, and gastrointestinal defects. Trisomy 18 is often associated with polyhydramnios in late gestation, but triploidy is often present with oligohydramnios. Despite that more than 90% of partial moles are associated with diandric triploidy, placental molar presentation with multiple fetal abnormalities can be observed in cases of trisomy 13 [48]; therefore, a definite diagnosis should be achieved by fetal karyotyping.

NLS (OMIM 256520)
NLS is an autosomal recessive disorder characterized by a lethal dysplasia with placental anomalies, severe IUGR, fetal edema, ectodermal dysplasia, and the cerebroarthrodigital complex with severe CNS anomalies [49]. The first case was reported in 1971 [50]; prenatal detection of the syndrome during the second trimester of gestation is possible [51]. Fetuses with NLS and triploidy may have similar structural anomalies, but the excessive deposition of subcutaneous tissue with edema is a hallmark feature of NLS on a sonographic scan. In addition, a history of parental consanguinity or prior affected child has been documented in cases of NLS.

Summary
With the advent of ultrasound equipment, the use of prenatal ultrasound has greatly improved the detection of triploid fetuses in obstetric practice. The increased understanding of different sonographic features is helpful in detecting triploid fetuses throughout gestation. Although several diseases have phenotypic overlaps with triploidy, major sonographic features that alert the physician to the possible diagnosis of triploidy are extra-fetal anomalies such as an enlarged and cystic placenta, oligohydramnios, and enlarged maternal ovaries with multicystic change, and fetal structural anomalies such as IUGR, increased fetal NT, CNS anomalies, facial anomalies, genitourinary anomalies, cardiac anomalies, gastrointestinal anomalies, and limb defects. These sonographic features are also useful in predicting the parental origin of triploidy. Clinically, several diseases may have phenotypic overlaps with triploidy; therefore, early sonographic identification of these anomalies in triploid fetuses is important in providing earlier karyotypic confirmation and enabling more reasonable management for pregnant women.

References


