Triploidy in a Live-Born Extremely Low Birth Weight Twin: Clinical Aspects

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Abstract

Triploidy is a rare chromosomal aberration characterized by a karyotype with 69 chromosomes. Triploid fetuses usually are miscarried in early pregnancy. We present a case of a triploid twin and a genetically unaffected co-twin, conceived through in vitro fertilization. A discordant growth was registered at 20 weeks of gestation. Cesarean section was performed at $35^{5/7}$ gestational week. The second twin was extremely growth restricted female (780 g) with oligohydramnios and severe respiratory distress, and died at 20 hours of age. The autopsy revealed unilobar left lung, bilobar right lung, and cysts of the terminal bronchioles. Quantitative fluorescent polymerase chain reaction detected triploidy compatible pattern. So, early intrauterine growth restriction may be a sign of triploidy, which must be proven by pre or postnatal genetic testing.

Keywords
- triploidy
- intrauterine growth restriction
- lung anomaly
- twin pregnancy

Introduction

Triploidy is a chromosomal abnormality characterized by a karyotype with 69 chromosomes, that is, there is an extra haploid set of chromosomes.[1] This extra haploid set may be of maternal (digynic) or paternal (diandric) origin. The most common type at the conception is the diandric triploidy, where the fertilization of a normal haploid ovum occurs by a single diploid spermatozoon (monospermic) or by two haploid spermatozoa (dispermic). It accounts for up to 90% of partial molar pregnancies, most of them spontaneously aborted.[2–5] It is estimated that triploidy occurs in 1 to 3% of all conceptions, and most of the affected pregnancies are miscarried between 7 and 17 weeks of gestation.[6,7] The frequency of triploid embryos after conventional in vitro fertilization (IVF) is even higher, approximately 20%.[8] Fetuses with triploidy who proceed to live births are with multiple malformations and die at an early postnatal stage.[9] The frequency of this chromosome abnormality is extremely low in all live births (1/20–50,000)[7] but higher (1/5,000) among infants with very low birth weight (0.02%).[10] Single cases with longer survival of more than a month are reported in the literature.[11,12] Twin pregnancies consisting of a triploid fetus and a healthy fetus are an uncommon phenomenon.[2,13] A twin pregnancy that ends near term with a live birth of a triploid and a healthy twin is even rarer.

We describe a rare case of a live-born triploid twin with clinical features of a digynic phenotype. This case report aims to make the neonatologist and obstetricians aware of this uncommon condition.

Case Presentation

This was the first pregnancy of a 31-year-old woman conceived through conventional IVF. A combined first-trimester screening was not performed. The fetal morphology ultrasound at a postmenstrual age of 20 gestational weeks (GW) showed discordant growth of the twins: one of them was

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with significant intrauterine growth restriction (IUGR), and the other was appropriate for the gestation age. The fetal echocardiography at 21 GW showed structurally normal hearts in both twins, with the presence of aberrant right subclavia in the hypotrophic fetus increasing the risk for Down syndrome by 1.5 to 2%. Genetic amniocentesis for chromosomal disorders was recommended, but the family refused this option due to the risk of miscarriage. Few days before birth, the mother had a subfebrile temperature of 37.4 to 37.8°C, *Enterococcus spp.* infection in vaginal swabs, and thrombocytopenia. Fetal ultrasound showed diamniotic dichorionic twin pregnancy, extreme IUGR, and oligohydramnios with almost absence of amniotic fluid in the second twin. Cesarean section was performed at $35^{5/7}$ GW because of the severe discordant fetal growth and fetal distress (diastolic blood flow of zero) in the hypotrophic twin. The placenta of the growth-retarded twin was smaller relative to the unaffected baby with macroscopically normal appearance; however, a microscopic placental examination was not performed. Both twins were females. The first one was with a birthweight of 2,830 g, length 47 cm, head circumference 32 cm, and the second one had 780 g, 35 cm, 23 cm, respectively. In addition to the severe IUGR, the second twin had abnormal facial features (widely spaced eyes, frontal bossing, low nasal bridge, low-set malformed ears, and small jaw), low-set umbilicus, long fingers, and bilateral single transverse palmar creases. No syndactyly was observed (►**Fig. 1**). The 1-minute Apgar score was 3, the umbilical artery pH 7.37, Bass excess (BE) (−1.6), and only single gasps were present despite stimulation. Respecting the parents' request, active resuscitation was started: bag/mask ventilation, intubation, and positive pressure ventilation. After initial stabilization, both twins were transferred to the neonatal intensive care unit (NICU).

On admission, the second twin was put on conventional mechanical ventilation with a period of high-frequency oscillations because of persisting hypoxemia, and broad-spectrum antibiotics were started. The laboratory tests showed thrombocytopenia, high red blood cell indices (mean corpuscular volume and mean corpuscular hemoglobin), and hypoproteinemia. The number of leukocytes, red blood cells, and hemoglobin was within reference ranges. Microbiological examinations were performed on both twins in the first hour of life: blood cultures, gastric and tracheobronchial aspirates, and ear canal, nose, throat, and rectum swabs were tested. Methicillin-resistant Staphylococcus epidermidis (MRSE) was detected in the ear canal specimens in both babies, while the other samples were sterile. The chest X-ray of the growth restricted twin showed Grade IV hyaline membrane disease, and after brief counseling, endotracheal administration of exogenous surfactant was made. Total 7 hours after birth, severe hemorrhagic syndrome occurred: pulmonary hemorrhage, stomach bleeding, thrombocytopenia, and anemia. Transfusions of packed erythrocytes and platelets, fresh frozen AB plasma were applied. Further attempts of stabilization included active cardiopulmonary resuscitation with norepinephrine and cardiac massage. Despite interventions and resuscitation efforts, the baby died at the age of 20 hours.

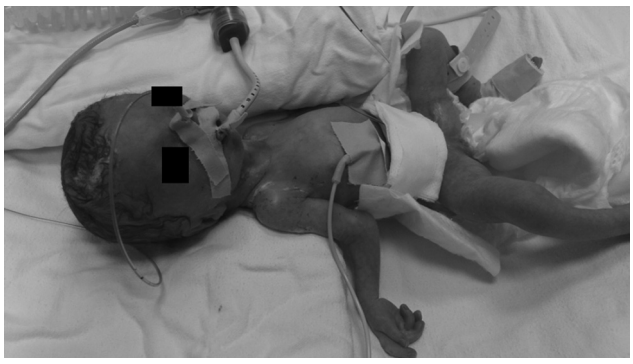

Fig. 1 Photo of the triploid newborn with severe intrauterine growth restriction ($35^{5/7}$gestational week, birthweight 780 g, and 1 hour of age).

The quantitative fluorescent-polymerase chain reaction (QF-PCR) analysis on DNA conducted on the abnormal twin, and extracted from the patient's blood sample detected triploidy: trisomic triallelic (1:1:1) or diallelic (2:1 or 1:2) patterns for informative short tandem repeats on all chromosomes (►**Fig. 2**). The results from QF-PCR on blood were not suspicious for mosaicism, but this test cannot exclude low-level mosaicism (<10–15%). Mosaic cell lines can be detected by karyotyping, which was not possible to perform in our case because the QF-PCR results became available after the infant's death, and there were no live cells or tissues from the patient at that point. The mother resisted further genetic testing, so the parental origin of the extra chromosomes could not be proved too. Based on typical clinical features (IUGR, discordant fetal growth, small placenta), we concluded that this was a digynic type of triploidy. The autopsy revealed complex congenital lung anomaly including unilobar left lung, bilobar right lung, and bilateral cysts of the terminal bronchioles. Histopathological features of hyaline membrane disease and interstitial pneumonia were present. The other organs were morphologically normal, including the brain, and their development was corresponding to gestational age ($35^{5/7}$ GW).Q1

The first twin was a girl appropriate for gestation age, with 1-minute/5-minute Apgar's score of 6/8. Due to respiratory distress, she was transferred to the NICU too, intubated at the age of 2 hours, and received two endotracheal applications of exogenous surfactant. The clinical and radiological findings were compatible with congenital pneumonia and secondary surfactant deficiency. A maternal–fetal infection has also been discussed: C-reactive protein levels were significantly elevated, MRSE from ear canal swab was proven (the same strain as in the co-twin), the other peripheral specimens, blood culture, gastric, and tracheal aspirates were sterile. No congenital anomalies were registered, and 15 days after birth, the baby was discharged from the hospital.

Discussion

Triploidy in a human newborn was first reported 1967 by Bernard et al[14] and Edward et al.[15] Butler et al reported the first live-born infant with complete triploidy.[16] Among chromosomal disorders, the triploidy is the most commonly

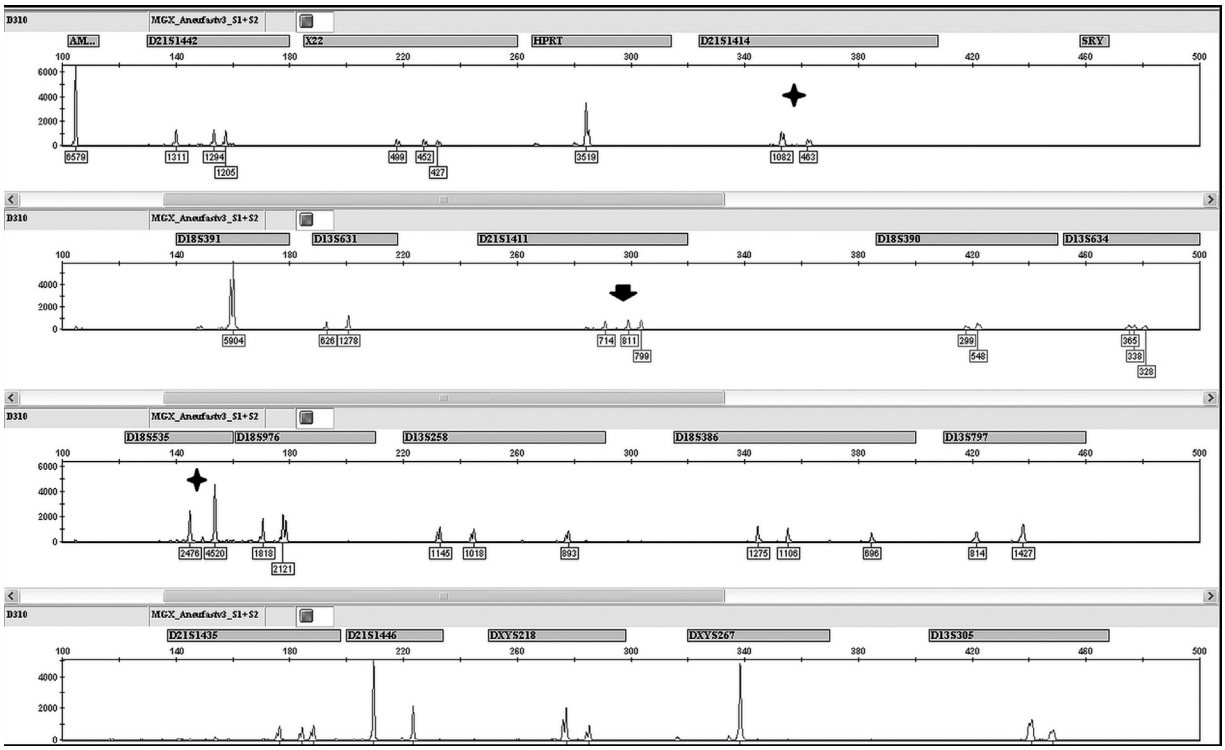

Fig. 2 Quantitative fluorescent polymerase chain reaction electropherogram of the patient showing triploidy—trisomic triallelic or diallelic patterns for informative STRs on all chromosomes. In the trisomic triallelic pattern, three copies of a chromosome are indicated by the presence of three peaks for corresponding chromosome-specific STRs with the same fluorescence intensity and a ratio between the areas of 1:1:1 (e.g., D21S1411), black arrow. The trisomic diallelic pattern produces two unbalanced fluorescent peaks with an area ratio of 2:1 or 1:2 (e.g., D21S1414 and D18S535), black stars. STR, short tandem repeat.

observed chromosomal aberration at conception and its frequency may be as high as 1 to 3%.[6,9] Most triploid pregnancies are miscarriaged in the first trimester or later so that the frequency of triploidy in cases that underwent amniocentesis is approximately 1:3,300.[6] Here, we present the first case of twin pregnancy after IVF for our country, in which one of the fetuses was triploid and the other one was unaffected. Cesarean section was performed at 35 GW due to fetal distress of one twin. Both twins were born alive and needed active resuscitation.

The extra haploid set of chromosomes in triploid pregnancies may be maternal (digynic triploids) or paternal (diandric triploids). According to previous studies, the frequency of the triploid genotypes is as follows: 31 to 49% (with 69, XXX), 49 to 68% (with 69, XXY), and 0 to 3% (with 69, XYY). The low frequency of 69, XYY chromosomal status suggests that this karyotype leads to low viability and early abortion of the zygote, or the mechanism through which it occurs is very rare.[11] The triploidy can be classified into two phenotypes with distinct placental, sonographic, and clinical findings.[9] Phenotype 1, the diandric triploidy (extra haploid set from father), is associated with a relatively well-grown fetus with either proportionate head size or slight microcephaly, an enlarged and partially multicystic placenta, elevated levels of maternal serum β-human chorionic gonadotropin (β-hCG), and partial hydatidiform mole. The majority of such pregnancies are aborted early in gestation.[17] The phenotype 2 is the digynic triploidy where the additional chromosomes are of maternal origin. It is characterized by severe fetal IUGR, relative macrocephaly, a small noncystic placenta, and decreased levels of β-hCG.[9] Multiple congenital anomalies have been reported in both types such as syndactyly, gastroschisis, encephalocele, myelomeningocele, adrenal hypoplasia, heart defects, etc.[2,18] Severe growth restriction is pathognomonic for the digynic triploidy. Zaragoza et al[17] have analyzed 91 cases of human triploid fetuses according to the origin of the additional haploid chromosome set and reported that the majority of the triploid embryos (69%) were diandric in origin because of dispermy. Many of the phenotypic features in our patient are quite characteristic for digynic triploidy syndrome: severe IUGR, facial abnormalities (hypertelorism, microretrognathia, and dysplastic low set ears) arachnodactyly. Syndactyly, which is a common finding in most of the reports, was not observed in our case.[2,9]

Some studies describe triploid pregnancies are complicated by preeclampsia, thrombocytopenia, hemorrhagic disorders, hyperemesis, pulmonary edema, and thromboembolic phenomena.[19,20]In our case, the mother had no evidence of preeclampsia; however, thrombocytopenia, growth discordance of the twins with IUGR, and oligohydramnios of the triploid fetus were present.

In the published literature, there are various reports on major anomalies associated with triploidy. However, there are no obligate and typical clinical features of triploidy syndrome.[9] The pathological examination on autopsy of our patient revealed a rare congenital lung anomaly with absent lobation of the left lung, bilobar right lung, and bilateral cysts of the

terminal bronchioles. The other organs including the brain showed normal morphology and development corresponding to the gestational age. To our knowledge, this is the first near term live born 69,XXX triploid twin patient with the above described pulmonary anomaly and no significant malformations of other organs. Mittal et al reported postmortem findings of pulmonary hypoplasia in 12 cases (60%) and absent lobation of the lungs in six cases (30%) among 20 triploid fetuses.[18] In the study of Toufaily et al,[9] including 54 triploid fetuses >20 GW and newborns over 30 years (1972–2012), there were three cases with pulmonary hypoplasia and one with absent lobation of the lungs.[9] In both studies, these abnormalities were accompanied by severe co-malformations of the central nervous, cardiovascular, and/or genitourinary systems, which were not observed in our case. Other reported typical finding in triploid fetuses, such as syndactyly of the fingers (most often three to four) or toes (two to three), was also not present in our case.

The triploidy is almost always incompatible with life or with very short survival in live-born infants. Only singlet pregnancies with longer survival are published in the literature.[11,12] Iliopoulos et al[11] describe a case of an infant with a 69,XXX karyotype survived 164 days. Our patient was a girl twin with severe IUGR with a co-twin of appropriate growth for the gestational age. Since the reason for the severe IUGR was not clarified and no prenatal genetic diagnosis was available, respecting the family's request our neonatal team performed the necessary intensive care for the newborn. The DNA test (QF-PCR) established feature of triploidy compatible pattern without evidence of mosaicism (presumptive karyotype 69,XXX) however, the results became available after the infant's death.

If a triploid embryo is diagnosed prenatally at earlier gestation, pregnancy termination is an option. That requires an early prenatal diagnosis. First trimester combined screening has a high detection rate for common aneuploidies, but not for a broader range of chromosomal aberrations, including triploidy.[21,22] Noninvasive prenatal fetal testing (NIPFT) screens for common fetal chromosomal abnormalities by analyzing cell-free plasma DNA in maternal plasma. If the fetal fraction is low, the results are "noninformative." The fetal fraction is lower in cases of trisomy 13, trisomy 18, and digynic (maternal) triploidy (all of which tend to have smaller placentas). So professional society guidelines recommend that all cases with "no result" due to low fetal fraction should be followed up with invasive prenatal testing.[23,24] The management of twin pregnancies with a severe genetic defect of one fetus represents a significant challenge. Most guidelines for NIFPT have been developed based on single pregnancies; moreover, the results are noninformative for triploidy.[24] If the twin fetuses are all alive, chorionic villous sampling or amniocentesis of the growth-restricted fetus can be performed to confirm the diagnosis.

The present case has indicated seriousness of a medical challenge, and importance of genetic counseling and informed consent about in utero medical intervention or retention of the pregnancy condition. If the diagnosis of triploidy is confirmed early in pregnancy, most parents may opt for termination of pregnancy. But with twin pregnancies, the decision is difficult. Selective feticide of the triploid twin could improve the prognosis for the unaffected twin.[2] On the other hand, there is an increased risk of miscarriage for both fetuses. In our case, the parents refused even invasive genetic testing (amniocentesis) in pregnancy due to the increased risk of miscarriage. If the fetus with triploidy is born alive, symptomatic treatment and comfort care are recommended. The decision on the extent of treatment (comfort care or active resuscitation) should be made by the parents after receiving accurate and clear information about the disease and the prognosis. Psychological support should be provided to the family.

Conclusion

This report presents an extremely rare case of live-born twins conceived through IVF with triploid and diploid genetic makeup. Early detection of growth discordance in a twin pregnancy may indicate chromosomal abnormality of the growth-restricted fetus. The combination of IUGR with a complex congenital lung anomaly without other severe congenital anomalies in the live-born infant is unusual for triploidy syndrome and not expected by clinicians. Fetal diagnosis of triploidy can be suspected by ultrasound assessment of fetal morphology and should be confirmed by genetic prenatal diagnosis (chromosome analysis/DNA test). In an extremely rare case of triploidy live birth in which prenatal diagnosis is not performed, postnatal genetic tests should be done to confirm the suspected clinical and pathological features.

Conflict of Interest
None declared.

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