Case report

FETAL TRIPLOIDY; TWO CASE REPORTS WITH PARTICULAR EMPHASIS ON ECHOCARDIOGRAPHIC ASSESSMENT AND LITERATURE REVIEW

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PRENAT CARDIO. 2013; DEC;3(4): 28-33.
DOI 10.12847/12135

Abstract

Triploidy is a disorder involving the occurrence of an additional set of chromosomes in cells. It is accompanied by multiple fetal and placental anatomical abnormalities. Triploidy typically leads to embryos or fetuses being miscarried in an early stage of pregnancy. Fetuses with this abnormality rarely survive until the third trimester. The case studies of two pregnancies diagnosed prenatally with triploidy are presented below in the context of the identified abnormalities and relevant literature.

Key words: *karyotype, triploidy, beta-hCG, hyperplacentosis, fetal anomalies, intrauterine growth restriction*

INTRODUCTION:

Triploidy involves the presence of an additional set of chromosomes in a cell (karyotype 69,XXY, 69,XXX or 69,XYY). It is a relatively frequent phenomenon associated with approx. 2% of conceptions. However most embryos/fetuses with triploidy abort before the 20th week of pregnancy and live births occur in 1 in 50 000 deliveries. [1,2,3,4] Modern obstetrics seldom provides an opportunity to observe the course of a pregnancy with an abnormal karyotype in the form of triploidy.

The present paper presents descriptions of ultrasound and echocardiographic examinations, cytogenetic analysis and clinical characteristic of two fetuses with triploidy, as well as a current review of literature on the subject.

How to cite this article:
Rybak-Krzyszkowska M, Moczulska H, Pilch P, Gach A, Tomczyk R, Korabel J, Respondek Liberska M.
Fetal triploidy - two case studies with particular emphasis on echocardiographic assessment and literature review.
Prenat Cardio. 2013 Dec;3(4):28-33

CASE DESCRIPTION:

Case 1.

25-year-old pregnant woman (Grav. II Para. II) was referred to the Maternity Outpatient Clinic of the University Hospital in Krakow at 15 weeks of gestation on the basis of an irregular image of the placenta in an ultrasound examination and the presence of high levels of beta-hCG. The patient was admitted for hospital diagnostics. The level of beta-hCG at admission was 638 047 mIU/ml. Ultrasound examination described placental thickening, with fetal biometry consistent with gestational age calculated based on the last menstrual period. Fetal anatomy was described as normal in relation to the gestational age. A single choroid plexus cyst was diagnosed. Diagnostic amniocentesis was performed in order to mark the fetal karyotype and the result was 69,XXY, indicating an abnormal male karyotype. The patient underwent genetic consultation, with pregnancy termination being the one possible course of action at that stage, in accordance with Polish regulations, however, the patient decided to continue with the pregnancy.

The patient visited the Maternity Outpatient Clinic of the University Hospital of Krakow again at 24 weeks of pregnancy. The level of beta-hCG was 200 000mIU/ml. Ultrasound examination indicated hyperplacentosis: the placenta was 8 cm thick with some characteristics of molar pregnancy. The fetal profile was abnormal with a shorter nasal bone; an enlarged tongue and prominent lips, widely separated nostrils and equinovarus of both feet were additionally described. The fetal growth profile was abnormal: according to biometry, fetal size was consistent with 22 weeks and 4 days. Shortened fetal long bones were

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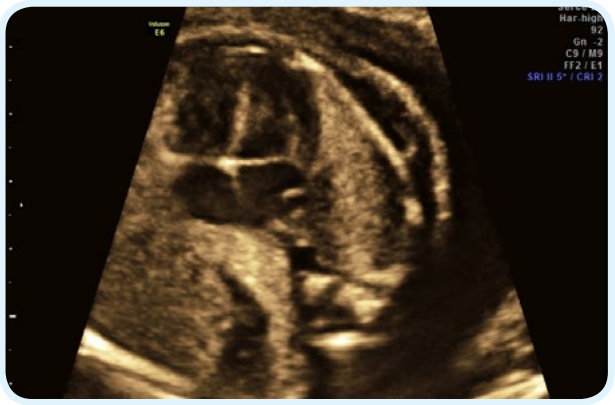
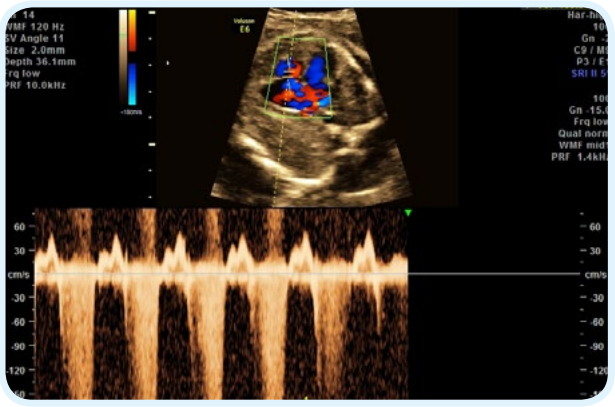
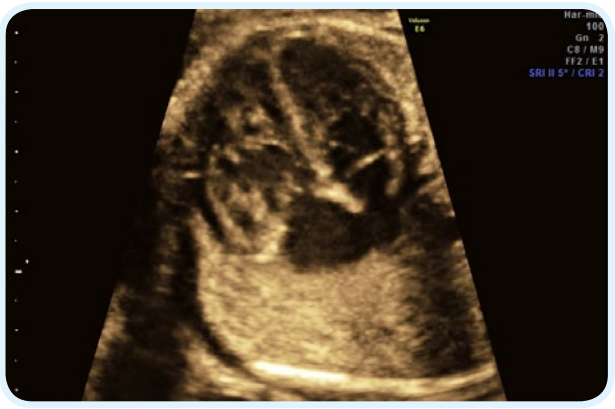
Submitted: 2015-09-21; accepted: 2015-09-27



Fot.1. Obraz czterech jam serca płodu w 24. tygodniu ciąży
Fot.1. Four chambers view, 24 weeks of gestation

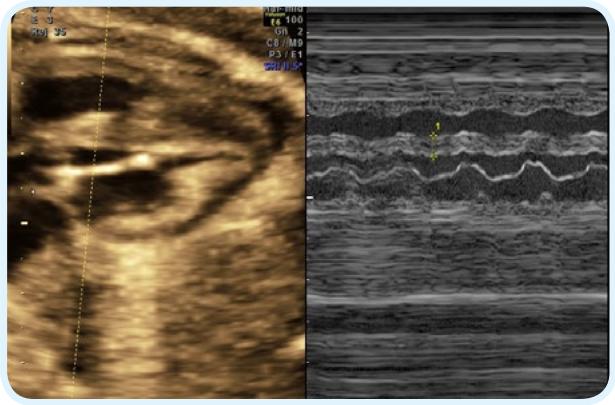


Fot.2. Niedomykalność zastawki trójdzielnej, 24. tydzień ciąży
Fot.2. Tricuspid regurgitation, 24 weeks of gestation

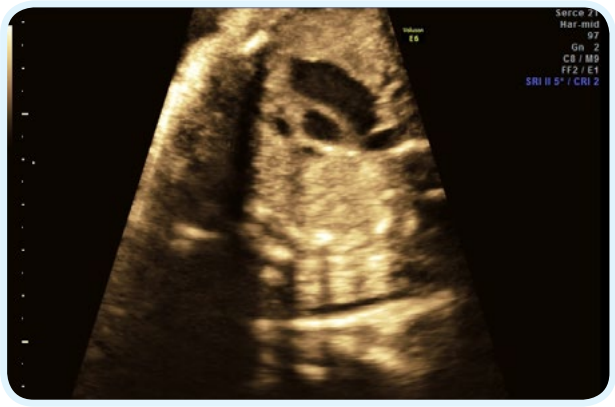


Fot.3. Hipertrofia prawej komory serca oraz wysięk w osierdziu, 30. tydzień ciąży
Fot.3. Hypertrophy of the right ventricle and pericardial effusion, 30 weeks of gestation

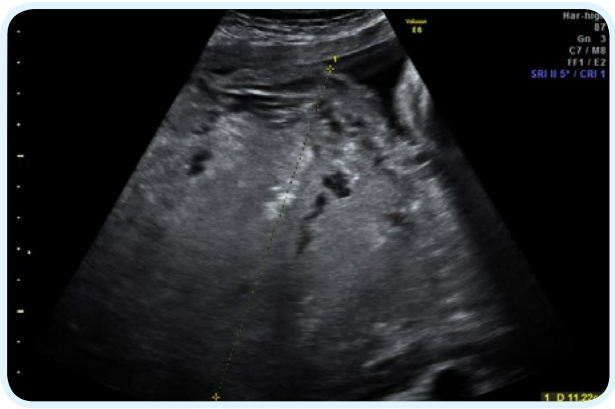
found, and microcephaly was diagnosed: biparietal diameter and head circumference were consistent with 21 weeks' gestation. Echocardiographic examination (Dr A. Wójtowicz) indicated enlargement of the heart with a HA/CA ratio of 0.39, as well as an abnormal heart axis of +45 degrees. The setting and movement of the atrioventricular valves was regular with a slight dominance of the right heart structures. The origin of large vessels was described as consistent (LVOT 5.1mm Z-score 2.31; RVOT 6mm Z-score 3.04). A regular image of three vessels could be seen in the superior mediastinum. Doppler examination revealed tricuspid regurgitation (Photo 1, 2).



Fot.4. Hipertrofia przegrody międzykomorowej, 30. tydzień ciąży
Fot.4. Septal hypertrophy, 30 weeks of gestation



Fot.5. Nieprawidłowy obraz trzech naczyń, 30. tydzień ciąży
Fot.5. Abnormal three vessel view, 30 weeks of gestation



Fot.6. Łożysko – 11 cm, 34. tydzień ciąży
Fot.6. Placenta – 11 cm, 30 weeks of gestation

The patient was consulted at the Clinic of Endocrinology for symptoms of hyperthyroidism, where she was prescribed 50mg Propylthiouracil twice daily, achieving gradual relief of symptoms. The arterial pressure profile was normal. No other abnormalities were found during the study.

During a subsequent visit to the Clinic of Pathological Pregnancy in the 30th week of pregnancy, irregularities in the image of the superior mediastinum were observed with the pulmonary artery (PA) dominating. Also a poststenotic dilation of the pulmonary artery (10mm Z-score 1.85; RVOT 6.7mm Z-score 0.74) and a pulmonary artery flow Vmax of up to 125cm/second were observed. The heart was

Type of anomaly	Types of anomaly by literature review	Types of anomaly by Pokrzywnicka et al.	Case 1	Case 2
Genetic gender	69, XXY; 69,XXX, mozaicism	69,XXY male	69,XXY male	69,XXX female
Beta-HCG	Differential data	?	High levels	?
Hyperplacentosis	55% cases	?	yes	no
Amniotic fluid abnormalities	50-60% cases	?	Polyhydramnions	Oligohydramnions
Intrauterine growth restriction	66-100% cases	nie / no	nie / no	tak / yes
Craniofacial anomalies: -micrognathia -hypertelorism -macroglossia -cleft lip/palate -large posterior frontanelle -face dysmorfic feactures	Very often	tak / yes	tak / yes	?
Central nervous system anomalies: -atrophy of the cortex -agenesis of corpus callosum -neural tube defect	36-45% cases	no	no	?
Genitourinary tract anomalies: -dysplasia/agenesis of the kidney -policystic kidney -defect of scrotum, penis -hypospadias -cryptorchidism - ambiguous genitalia	15% cases	yes	Ambiguous genitalia	Policystic kidney
Congenital cardiovascular system defects: -ASD -VSD -ARSA -TGA -PS	5-33% cases	VSD	Pulmonary stenosis	?
Cardiomegaly		Cardiomegaly	Cardiomegaly	Cardiomegaly
Limb defects: -syndactyly -talipes equinovarus -palmar crease	52% cases	yes	yes	?
Gastrointestinal tract anomalies: -duodenal atresia -agenesis of the gallbladder	rare	no	no	no
Intrauterine demise	19	no	no	yes
Delivery of alive newborn	1	yes	yes	no
Weight (g)	?	700	1940	?
Apgar score	?	1/2/5	7	?
Hematologic abnormalities -decreased number of RBC -increased RBC indices	?	yes	yes	?
Hypotony	?	yes	yes	?
First-day death	?	yes	yes	

Table 1. List of the most commonly reported anatomical abnormalities given in the literature concerning fetuses with triploidy in comparison with those of the cases reported herein

still enlarged, with an HA/CA ratio of 0.39. Additionally, hypertrophy of the right ventricle and hypertrophy of the interventricular septum were described: the interventricular septum being 5mm wide (Photo 3, 4, 5). A similar image was observed at 34 weeks' gestation.

A biometry examination identified that the tendency for abnormal growth observed in earlier examinations was still present. The growth profile of fetal abdominal circumference was consistent with gestation period, however, further gradual inhibition of growth of fetal head circumference and length of long bones was observed. The dimensions of the head were smaller by 5/6 weeks, representing over 6 SD for the given gestation period, whereas the measurements of long bones were smaller by 5 weeks, representing 4.5 SD. The placenta was observed to have thickened further to 11 cm (Photo 6).

To treat the patient's hypertension, 2x250mg methyldopa per day was prescribed, which normalized the pressure.

General examination of the patient's urine remained regular. The level of beta-hCG was 160 000mIU/ml at 34 weeks.

In week 36, the patient prematurely and spontaneously delivered an infant weighing 1940g and measuring 43cm. Initially the general condition of the infant was average, with an Apgar score of 7. Physical examination indicated intrauterine hypotrophy, signs of prematurity, general swelling, cyanosis and considerable swelling of the right lower extremity (birth injury) as well as reduced muscle tone. A neonatal examination indicated the following symptoms of dismorphy: receding jaw, large tongue, gothic palate, large posterior fontanelle (2.5x2.5cm), low set ears, epicanthic fold, eyes set wide apart and a wide base of the nose (Photo 7).

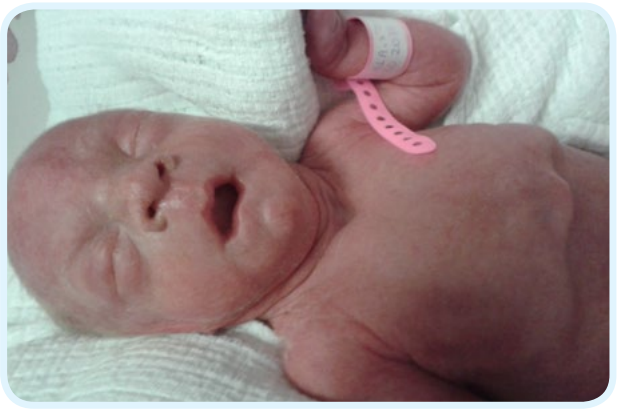
Additionally described were ambiguous genitalia (micropenis, undeveloped scrotum), syndactily (toes IV and V of left foot), brachydactyly, equinovarus of both feet, individual subcutaneous nodules on heels and transverse palmar creases. Transfontanelle ultrasonic examination indicated no abnormalities besides an underdeveloped brain structure.

The infant's general condition deteriorated dynamically, with progressing respiratory and circulatory failure. The infant died after 14 hours of life. Postmortem examination was not performed.

Case 2:

28-year-old prima gravida was admitted for examination. While an ultrasound examination at 13 weeks' gestation had not revealed any irregularities, a subsequent examination at 24 weeks indicated the size of the head was disproportionate to that of the fetal trunk, as well as the presence of oligohydramnios. For this reason, the pregnant woman was directed to the Department for Diagnoses and Prevention of Congenital Malformations, Polish Mother's Memorial Hospital - Research Institute in Lodz.

At 26 weeks of gestation, anhydramnios was diagnosed. The fetus was in a forced position, compressed against the uterus walls. The placenta was located on the front of the uterus with a thickness of 3cm (Grannum grade 1). The following fetal biometry abnormalities were found: a head circumference of 20.6 weeks, abdominal circumference of 17.4 weeks and a femur length of 19.2 weeks. Examination of anatomical structures was impeded. In the area of the kidneys, structures of unclear echogenicity with renal pelvises of 3mm each and two renal arteries were visualized. The image suggested policystic kidneys. The shapes of the skull bones were irregular. The structure of the central nervous system were without evidence of ventricular enlargement. The umbilical cord comprised two vessels. Echocardiographic examination indicated the presence of relative cardiomegaly (AP 15mm; HA/CA 0.42). Detailed assessment of the heart was impossible because of concurrent anhydramnios. Diagnostic amnioinfusion



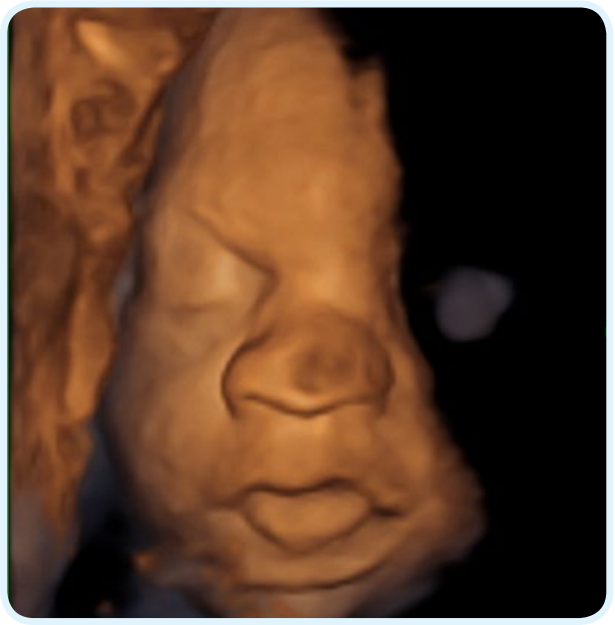
Fot.7. Newborn with dysmorphic features

and fetal karyotype evaluation were recommended. Fetal death in utero occurred at 28 weeks. The fetal karyotype results were abnormal: 69,XXX.

DISCUSSION:

Triploidy is one of the most frequent chromosome abnormalities in pregnancies. While its frequency is estimated to be 1-3% of all pregnancies[5], this rises to 15% in cases of spontaneous abortions with cytogenetic aberrations.[6] On the cellular level, triploidy is characterized by the presence of three (3n) instead of two (2n) haploid sets of chromosomes. Two variations of this abnormality can be identified: one with a single set of maternal chromosomes and two sets of paternal chromosomes (diandric triploidy) and another with a single set of paternal chromosomes and two sets of maternal chromosomes (digynic triploidy).[7]

Triploidy may occur as a result of three different mechanisms, [8] the most frequent being the fertilization of the oocyte by two spermatozoa, leading to the creation of a diandric embryo with the karyotype 69,XXX or 69,XXY.



Fot.8. 3D image of the fetal face, 34 weeks of gestation

Triploidy may also occur through fertilisation of an egg cell by an abnormal binuclear spermatozoon whose genetic material was not reduced in the second meiotic division. The third mechanism is responsible for digynic triploidy and is caused by a haploid spermatozoon fertilizing a diploid egg cell created by a polar body which stopped dividing after the second or, more seldom, after the first meiotic division.

Clinical observations confirm that some triploid pregnancies stop developing at a very early stage, whereas others end with term delivery. This phenomenon can be explained by the mechanisms of cell division and chromosome segregation. The basis for regular chromosome segregation is the creation of the karyokinetic spindle around the centrosome. In the case of early zygote division, the father's centromere remains active, which may explain the different fates of digynic and diandric pregnancies.[9] In the case of digynic pregnancies, cell divisions happen normally, as the zygote has one active paternal centrosome and the maternal centrosome is inactive. However, in the case of diandric pregnancies, the additional active centrosome interferes with chromosome segregation, often leading to the creation of mosaicism and molar pregnancy. The described mechanism may explain why diandric pregnancies are usually lost at an earlier stage than digynic pregnancies.[10]

In some cases of diandric triploidy, the fetal triploidy can be accompanied by placental abnormalities in the form of partial hydatidiform mole. High beta-hCG levels are observed. Such pregnancies can be complicated by the development of hypertension and pre-eclampsia, which may cause a real threat to the mother's life.[3] Case 1 is a good demonstration of these literature observations.

As has been mentioned before, triploid pregnancies can be divided into diandric and digynic types. McFadden and Kalousek describe two different phenotypes of triploid fetuses. The first is diandric, where microcephaly is observed but the rate of fetal growth is not significantly disturbed and the placenta is usually large with cysts. Digynic, on the other hand, is usually characterized by a small placenta without cysts, and fetal development is characterised by asymmetric fetal growth rate restriction with relative macrocephaly (a high HC/AC ratio).[3] According to the literature, intrauterine fetal growth restriction occurs in 66-100% of triploid fetuses, which are usually 2 to 6 weeks smaller than expected.[11] Jauniaux et al. report that fetal triploidy can be suspected in case of partial hydatidiform mole or grave asymmetric fetal growth restriction with seemingly normal placenta , as seen in Case 2.[12]

Besides growth restriction, a series of defects can be observed in various systems in triploid fetuses. Jauniaux et al. describe 70 triploid fetuses, of which 65 manifested anatomical abnormalities. Table 1 presents the most frequent anatomical anomalies given by the literature on the subject compared with the cases described herein.[11,12,13]

Cardiac symptoms in a triploid patient were mentioned by Pokrzywnicka et al. Postmortem examination indicated an enlarged heart with mostly right ventricular hypertrophy, large atria, wide foramen ovale and an aortal origin overriding both ventricles.[14] Case 1 presented with pulmonary stenosis, a defect which may evolve in utero, and is fully manifested only after delivery. While the first symptom of a heart defect can be tricuspid insufficiency, which occurred in week 24 in the case described herein, a disproportion at the level of the three vessels of the mediastinum and faster blood flow through the pulmonary artery valve, or right ventricular hypertrophy may only occur in subsequent weeks of pregnancy. Fetal cardiomegaly was observed in Case 2, which ended in fetal demise. The question whether it was the only or the first cardiac symptom remains open, as no postmortem examination was performed. Fetal heart enlargement is a significant predictor which was not noticed before (Table 1).

The variety of symptoms observed in triploid fetuses indicates a need to consider triploidy in differential diagnosis of fetuses with multi malformation syndrome. The role of classic cytogenetic testing should also be emphasized, as it is often impossible to diagnose fetal triploidy with the help of quick modern diagnostic methods based on molecular biology techniques.

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Financing: The research was not financed from the external sources
Conflict of interest: The authors declare no conflict of interest and did not receive any remuneration