● Case Report

DOUBLE ANEUPLOIDY WITH KARYOTYPE 48,XXY,+18 IN FIRST TRIMESTER FETUS - CASE REPORT

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Abstract

Double anueploidy, involving both trisomy 18 and Klinefelter syndrome at the same time, is a rare event, in which the features of Edwards syndrome dominate the clinical picture. We describe a patient, who was diagnosed in the 8th gestational week with a seemingly normal intrauterine pregnancy with "chorionic bump". In the 12th week the following abnormalities were diagnosed by ultrasound: Increased nuchal translucency (4.7 mm), increased anteroposterior diameter of the fourth ventricle and increased diameter of the third ventricle of the brain, mesocardia and cardiomegaly. The CVS karyotype revealed 48,XXY,+18 karyotype. In our opinion, the increased anteroposterior diameter of the fourth ventricle of the brain in this fetus was probably an early manifestation of the Dandy-Walker malformation (unproven because of early pregnancy termination), which is typical of Edwards syndrome fetuses. We consider the increased anteroposterior diameter of the fourth ventricle of the brain in the first trimester fetus as an indication for fetal karyotyping and further detailed imaging studies.

Key words: *aneuploidy, first trimester, fourth ventricle*

35 years-old multigravida (36 years-old at the EDD, whose first pregnancy resulted in a birth of a healthy child , whereas the second pregnancy ended in early miscarriage) presented for ultrasound scan at 8+5 week of menstrual age. The anteverted uterus, with smooth contours and homogeneous echostructure, and the size corresponding to the date of the last menstrual period was observed on ultrasound. Within the uterus the outline of the gestational sac, the size of which corresponded to

9 weeks

was seen. The chorion localized to the posterior uterine wall and within it an oval structure of mixed echogenicity, corresponding to the "chorionic bump", with the diameter of 14 mm was observed.

Inside the gestational sac the outline of the living fetus with normal morphology, whose CRL corresponded to 8 + 1 week was visible. In the location of the right ovary a thin-walled two-chambered sonolucent cyst with smooth contours corresponding to the functional change was noted. According to the existing standards, the patient was scheduled for the 11-14 week scan.

13th week

The patient reported again at 13 + 1 weeks according to LMP. On the ultrasound examination the previously described "chorionic bump symptome" (Photo 1); sign was not observed this time, and the living fetus with an average of biometric parameters at 12 + 2 weeks and with the following abnormalities was revealed:

- Increased nuchal translucency (NT)= 4.7 mm (Photo. 2);
- Increased anteroposterior diameter of the fourth ventricle (Photo. 3, 4, 5)
- Increased diameter of the third ventricle of the brain, (Photo. 6);
- The outlines of the abnormally positioned four extremities with reduced mobility and signs of arthrogryposis (bilateral pterigia in the axillary regions) (Photo. 7, 8);
- Slight ulnar deviation of wrists;
- Mesocardia and cardiomegaly (Photo. 9), with asymmetry of the width of the ventricles, atypical relations of the great vessels and pericardial effusion;
- Two-vessel umbilical cord, with intestine-containing omphalocele (Photo. 10, 11, 12);
- Increased bowel echogenicity;
- Nasal bones with no evident hypoplasia;
- Cyst of the right ovary, as in the previous examination

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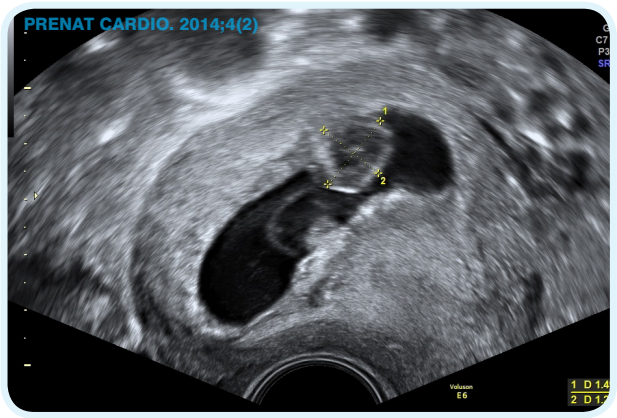

Photo 1. Chorionic bump symptome

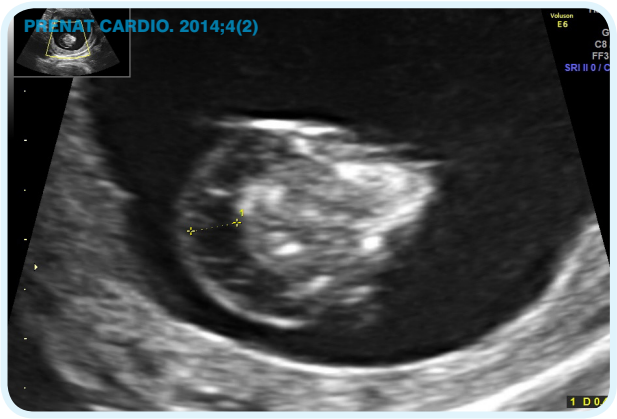

Photo 2. Nuchal edema-transverse section

In the light of the observed fetal malformations the patient was offered fetal karyotyping by CVS, for which she gave informed, written consent. The ultrasound examination was performed using GE Voluson E6 scanner, with RAB 4-8D and RIC 5-9D volumetric probes.

CYTOGENETIC TESTING

In order to obtain the tissue for cytogenetic studies transabdominal chorionic villus sampling under continuous ultrasound guidance was performed.

The obtained villi were placed in a Petri dish containing RPMI (Life Technologies, USA) with heparin (Polfa, Poland). The villi were separated under the inverted microscope from maternal tissue fragments, and then divided into two portions and transferred to two vessels containing BIOAMF complete culture medium (Biological Industries, Israel). One portion of the material was analyzed using the so-called direct method (short-term culture) by which chromosomes are analyzed in the cells released

from the cytotrophoblast. The metaphase spreads obtained from the short-term culture can be derived from fetal cells only, due to the lower mitotic potential of maternal cells, which may be found in the biopsy material[1,2]. Therefore the direct method stands for the confirmation of the fetal origin of the examined cells[3]. The second portion of the sample was subjected to the so-called long-term culture, in which the cells from the

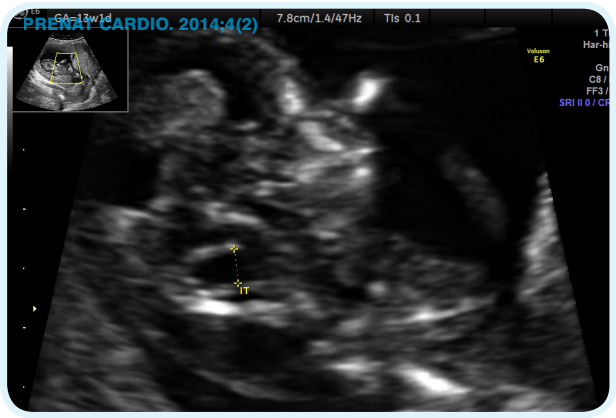

Photo 3. Increased antero-posterior diameter of the fourth ventricle of the brain - longitudinal section

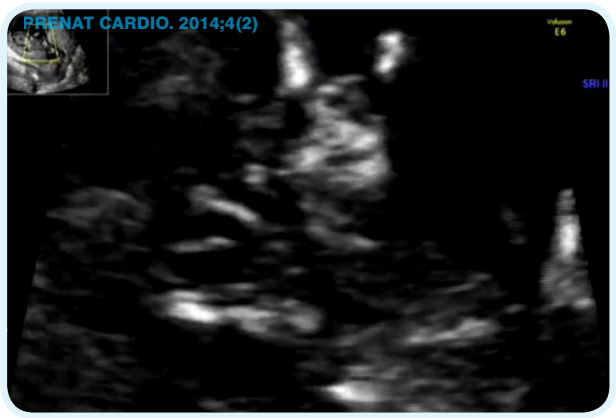

Photo 4. Increased antero-posterior diameter of the fourth ventricle of the brain - longitudinal section

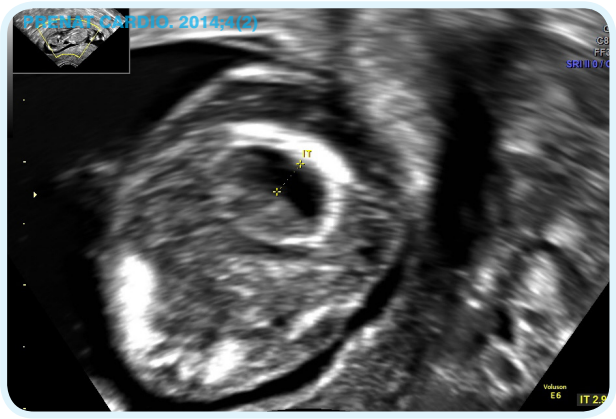

Photo 5. Increased antero-posterior diameter of the fourth ventricle of the brain - transverse section

extra-embryonic mesenchyme are cultured. Cultivation was

carried out in the incubator with the automatic control of carbon dioxide.

Cytogenetic preparations obtained from both cultures were stained using GTG banding (G-bands by trypsin using Giemsa). The assessment of the metaphase spreads from both types of cell culture was performed using Eclypse 80i microscope (Nikon) and LUCIA Cytogenetics-Karyo / FISH software (Precoptic). The karyotype of the villi was recorded in accordance with the principles of ISCN

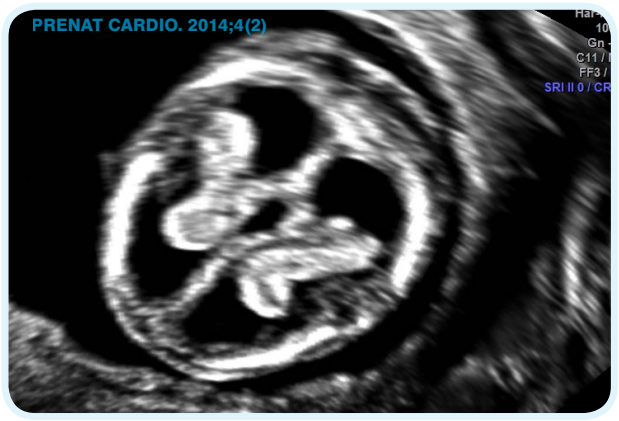

Photo 6. Dilated third ventricle of the brain

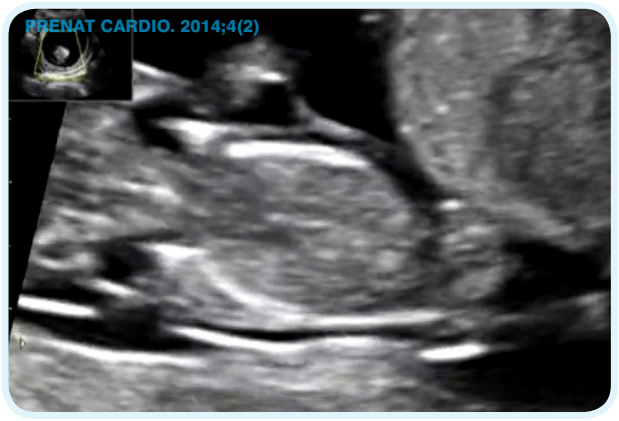

Photo 8. Pterigium in the axillary region

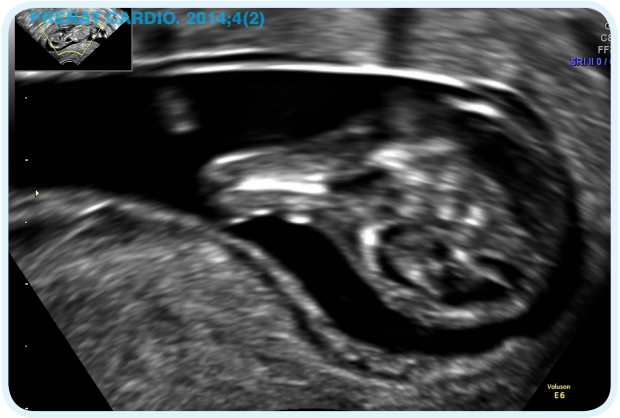

Photo 7. Pterigium in the axillary region

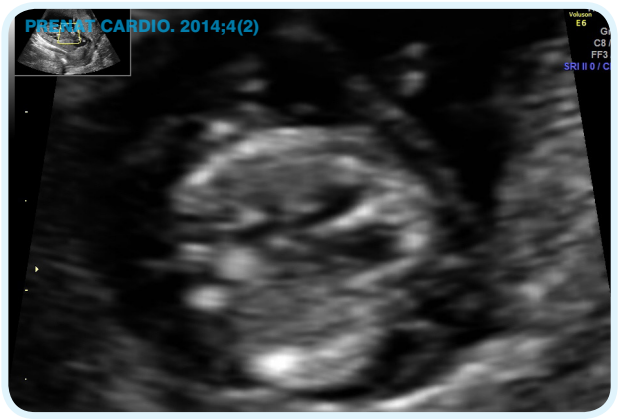

Photo 9. Cardiomegaly, mesocardia, subcutaneous edema

2013 (An International System for Human Cytogenetic Nomenclature).

The abnormal karyotype was diagnosed with the modal number of 48 chromosomes: coexistence of two different aneuploidies: trisomy 18, corresponding to the clinical symptoms of Edwards syndrome and X chromosome disomy, causing symptoms of Klinefelter syndrome in the male. The diagnosed karyotype 48, XXY + 18 is graphically represented in the form of karyogram (Photo. 13).

DISCUSSION

Double aneuploidy with simultaneous occurrence of additional X and 18 chromosomes is a very rare event, but that was several times reported in world literature. The clinical picture is dominated by the symptoms associated with trisomy 18, as Klinefelter syndrome related signs are linked primarily with the reproductive system, whose dysfunction becomes evident mainly after puberty or even later, which would be unlikely in our case, taking into account the high lethality of trisomy 18[4].

Normal height (body length in newborns), long limbs and normal penile length can be mentioned as clinical features atypical of Edwards syndrome, and associated with the X chromosome disomy "concealing" the symptoms of trisomy 18[5]. Definitive diagnosis is nonetheless based on cytogenetics.

Double aneuploidies in liveborn neonates involve the same chromosomes (13, 18, 21, X and Y), which occur in cases of "typical" (single) aneuploidy[6,7].

In the material obtained after spontaneous abortions double aneuploidy was found in more than 2% of all miscarriages with the additional involvement of the chromosomes 2, 8, 15 and 16[8].

Chorionic bump

The available literature explains the pathogenesis of the chorionic bump sign as the result of a hematoma in the deciduo-villous space or as a manifestation of the presence of an endometrial polyp which models the chorion (P. Jeanty, oral communication).

The presence of this symptom doubles the risk of miscarriage, but does not correlate with an increased risk of fetal defects [9,10].

Central nervous system

According to Chaoui et al. (2009) the 95th percentile of the anteroposterior diameter of the fourth ventricle of the brain for CRL = 57 mm is 2.2 mm, while in the described case the measured value was 2.9 mm, which corresponds to about seven standard deviations above the median for the given CRL value[11].

The enlargement of the anteroposterior diameter of the fourth ventricle of the brain is described as an early sign of Dandy-Walker malformation, which occurs in trisomy 18[12,13].

Due to the termination of pregnancy in the first trimester, it was not possible to verify the evolution of the fourth

ventricle enlargement into Dandy-Walker malformation, it can be surmised however, that that the final result would be like this.

On the basis of this case, we believe that the enlargement of the fourth ventricle of the brain during the first trimester of pregnancy should be considered as an indication for further testing, including fetal karyotyping and genetic ultrasound examination and fetal echocardiography in later pregnancy.

Genetic counseling

The constellation of findings in the fetus, even before performing invasive diagnostics, was associated with poor prognosis for normal development, and even for survival of the child after birth, and the patient was accordingly counseled.

The aim of the cytogenetic study was to find out the cause of fetal malformations, which suggested genetic background of the abnormal phenotype, which is important not only from the point of view of planning the further obstetrical care and parents decisions concerning the fate of pregnancy, but also for genetic counseling about the risk of recurrence of the condition in children in subsequent pregnancies and even other relatives.

In the described fetus the underlying cause of malformations was regular trisomy of chromosome 18, being itself a random event, with the risk increased because of the maternal age, with additional incidental occurrence of X-chromosome polysomy and probably accidental coincidence of chorionic bump sign.

The risk of re-occurrence of aneuploidy in such cases is only slightly higher than the age-related risk in the given patient.

It should be emphasized at this point that in a significant number of cases of fetal malformation the underlying causes are structural chromosome aberrations (often submicroscopic), inherited from the parents, who are phenotypically healthy, but who are carriers of a balanced translocation or other rearrangement, which involves a high risk of recurrence of unbalanced karyotype in subsequent offspring. Neglecting to study fetal karyotype deprives patients of the warning about the high risk of

recurrence of the disease in future pregnancies and denies the patient the opportunity to carry out targeted diagnosis in a subsequent pregnancy

In cases of fetal structural aberrations parental karyotyping and genetic counseling of the family is necessary.

Portion of cases of fetal malformations are associated with monogenic mutations, of which particularly those X-linked or with autosomal recessive mode of inheritance have a particularly high recurrence risk.

In genetic counseling in unexplained fetal malformation cases it is necessary to highlight the possibility of undetected recessive disorder with high recurrence risk

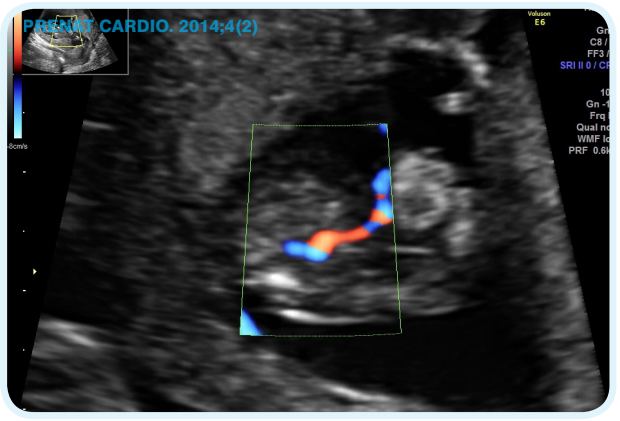

Photo 10. Two-vessel umbilical cord

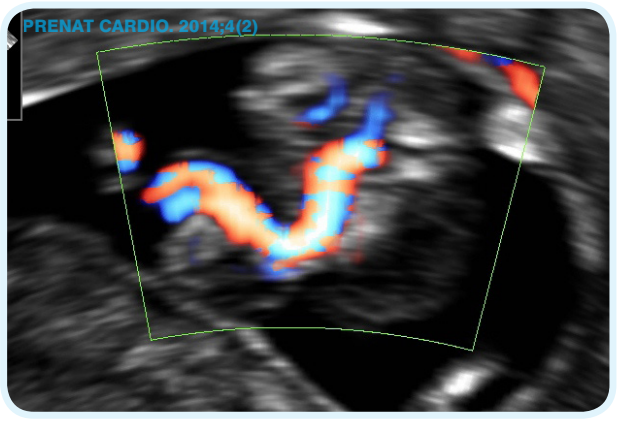

Photo 11. Two-vessel umbilical cord

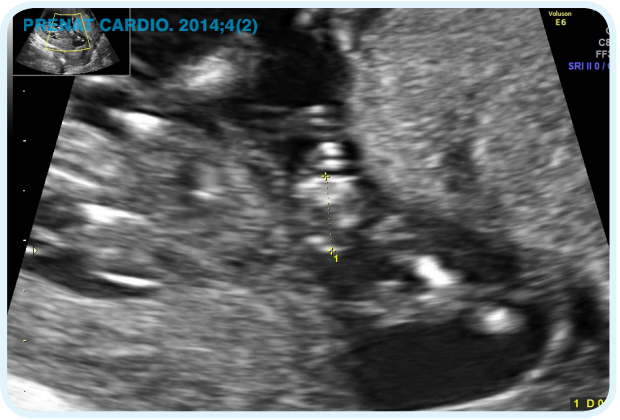

Photo 12. Omphalocele

to parents and to discuss with them possible diagnostic options in subsequent pregnancies.

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Photo 13. Long term culture karyogram