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A rare occurrence of three consecutive autosomal trisomic pregnancies in a couple without offspring

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Summary

Background: Trisomies are the most common chromosomal abnormalities, being a major cause of pregnancy loss in the first trimester. Data from preimplantation embryos support the concept of recurrent aneuploidy in women with recurrent abortion. *Case:* The authors report a rare case with three different consecutive trisomic pregnancies: 47,XY,+21, 47,XX,+9, and 47,XX,+18. All pregnancies resulted from the same relationship and no consanguinity was present. Standard clinical cytogenetic analysis indicated that both members had normal peripheral blood karyotype, with no evidence of mosaicism in either patient or her partner. *Conclusion:* The present report supports the hypothesis that some women have a higher risk for nondisjunction than others of the same age. Counseling a couple with recurrent trisomies is difficult and future research on genetics of cell division are required to assist them.

Key words: Recurrent trisomies; Pregnancy; Prenatal ultrasound; Meiosis nondisjunction.

Introduction

Trisomies are the most common chromosomal abnormalities in human pregnancy and occur in approximately 4% of clinically recognized pregnancies. Moreover, 30% of spontaneous miscarriages caused by numerical chromosome abnormalities have a trisomy and it is associated with increased maternal age, rising from very low incidence at age 20–24 up to 35% at age 40–44 years. This chromosomal imbalance is usually not compatible with life and will result in a miscarriage in the first trimester in most cases, making it the leading cause of pregnancy loss in this period [1, 2]. Only three autosomal trisomies [13, 18, 21] and the three sex chromosome trisomies (XXY, XXX, and XYY) are compatible with live birth. Data from preimplantation embryos support the concept of recurrent aneuploidy in women with recurrent abortion [3]. The authors report a rare case with three different consecutive autosomal trisomic pregnancies in a couple with normal karyotype and no living offspring.

Case Report

A 40-year-old woman, gravida 2, para 0, was referred to Prenatal Diagnostic Unit (PDU), Emergency University Hospital, Craiova, Romania for the first trimester genetic, extended structural sonographic evaluation and genetic counseling.The patient had no medical or surgical history. The pregnancy evolution was clinically normal up to this point. Detailed two-dimensional, three-dimensional, and four-dimensional ultrasound examination was performed, using a Voluson 730 E8 machine at 11+6 weeks of amenorrhea. Corpus luteum was present on the right ovary. Many abnormalities were noted in terms of genetic markers and structural features: generalized subcutaneous edema, large nuchal translucency (9.7 mm), absent nasal bone (Figures 1a and 1b), and facial angle (90.78^0). The cardiac sweep was consistent with complete atrio-ventricular septal defect data. Also spatial-temporal image correlation datasets were obtained. Spectral Doppler interrogation showed holosystolic regurgitation at the site of the common A-V valve and absent a wave at the site of Arantius ductus venousus. Normal images were obtained in terms of: intracranial translucency value, choroid plexus symmetry, anterior bony palate, orbits, surface rendering face, abdominal insertion of umbilical cord, situs, stomach image, diaphragm, spine, bilateral limbs, bladder, three-vessels cord, amniotic fluid, cervical length, uterine arteries pulsatility index. Crown-rump length (CRL) was consistent with menstrual dates (55.4 mm). She was screened positive for trisomy 21 at the combined test. After counseling, the couple accepted the invasive maneuver (chorionic villus sampling). Conventional karyotyping confirmed trisomy 21 (Figure 2a) and the couple requested surgical termination of pregnancy (TOP). The evolution after TOP was uneventful.

After eight months, the patient self-referred to the PDU for another dating scan, at 9+6 WA, after several days of vaginal spotting. The examination revealed missed abortion: medium gestational sac (GS) diameter 20 mm (corresponding at 6+3WA), opaque yolk sac (YS), and no visible embryo (Figure 1c). Corpus luteum present on the left ovary. TOP by aspiration technique was performed, with normal postoperative evolution. Cytogenetic analysis of product of conception showed a non-mosaic trisomy 9 pattern (karyotype 47,XX,+9) (Figure 2b).

After another three months, the patient presented again to the PDU, for a new pregnancy dating scan, at 10+0 WA. The CRL of the embryo was 22.5 mm (corresponding to 9+0 weeks embryo) and the embryonic heart rate was 178 beats/minute. There was a normal

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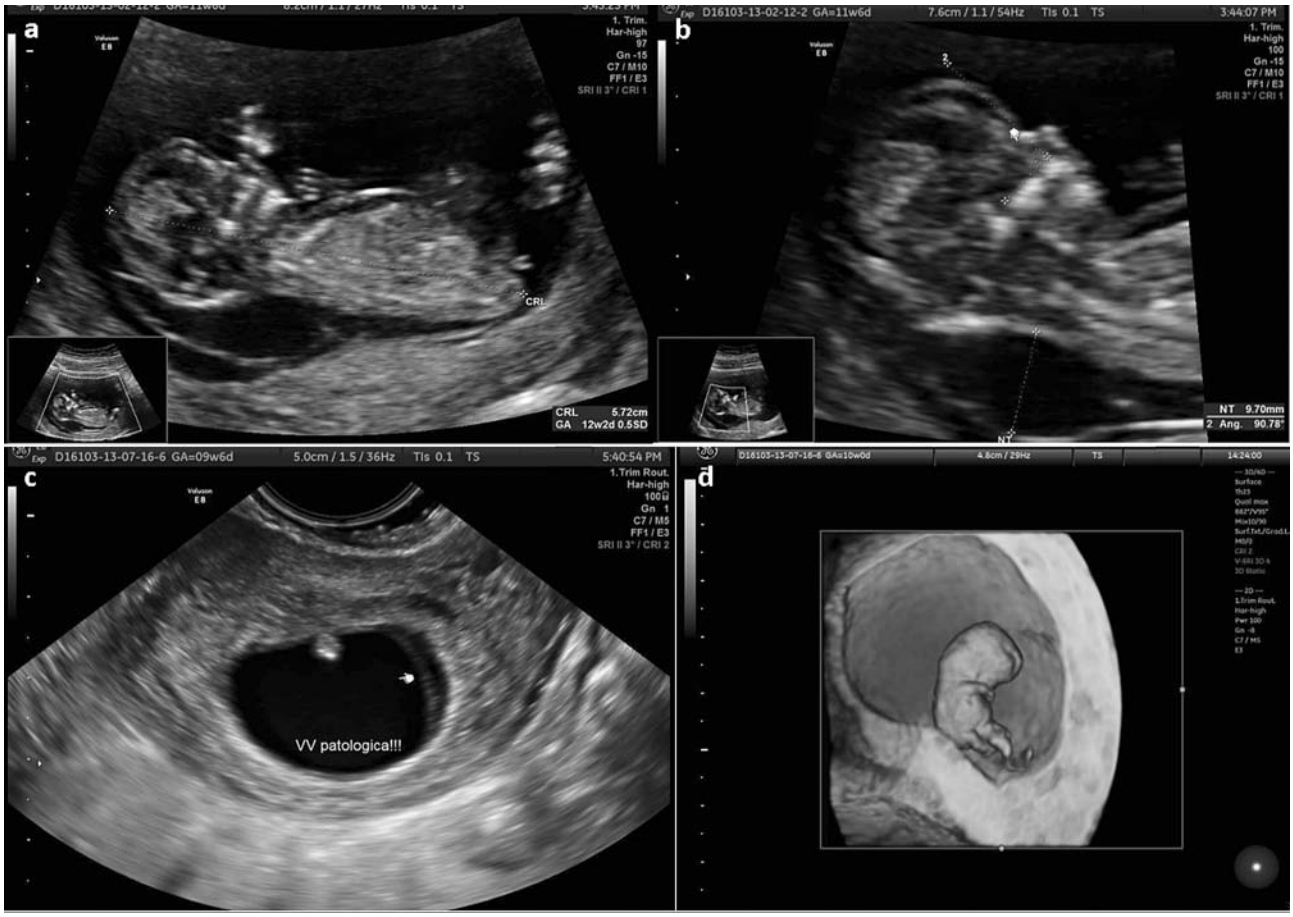

Figure 1. — a) Sagittal section of the fetus, crown-rump length measurement. Generalized subcutaneous edema. b) Fetal profile: absent nasal bone, large nuchal translucency, and abnormal facial angle. c) Missed abortion: small gestational sac, opaque yolk sac, and no visible embryo. d) Recent embryonic demise (9+5 WA), three-dimensional surface rendering of the gestational sac, amniotic cavity and embryo, normal cephalic/trunk differentiation, and normal limbs. No heart motion was present.

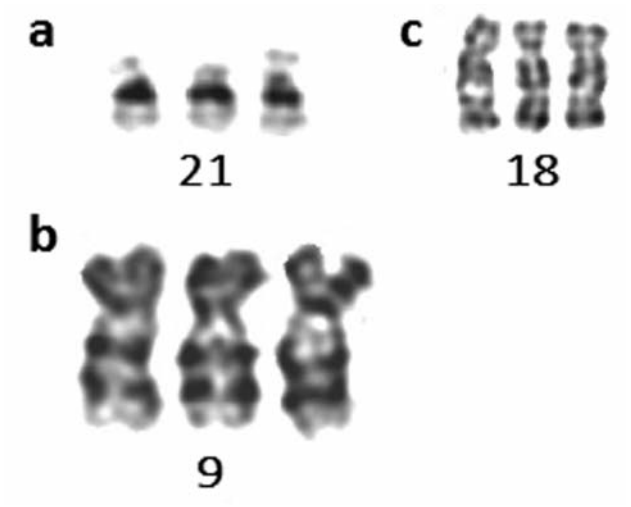

Figure 2. — Partial karyotypes: a) Trisomy 21, b) Trisomy 9, and c) Trisomy 18.

cephalic/trunk differentiation, the limbs were normal, a normal looking extraembryonic coelomic and amniotic cavity were found (Figure 1c). The GS had a normal aspect and tonus, the medium diameter was slightly smaller than expected (52.1 mm), the YS had normal ultrasound features (spherical, anechoic, diameter 5.6 mm). The normal topography (fundal) of the trophoblastic tissue and the normal (central) insertion of the umbilical cord was noted. The cervical length and the uterine arteries velocities were also normal.

After nine days, the patient requested re-examination in the PDU, due to decreased pregnancy subjective symptoms (nausea and engorgement). The scan showed recent embryonic demise (CRL 28.6 mm, corresponding at 9+5WA). TOP was again performed. The conventional G banding analysis from product of conception revealed trisomy 18 in all cells (Figure 2c).

Discussion

The authors report a rare case with three different consecutive trisomic pregnancies. All pregnancies resulted from the same relationship. The couple was healthy and no consanguinity was present. Standard clinical cytogenetic analysis

indicated that both parents had normal peripheral blood karyotype, with no evidence of mosaicism in either patient or her partner.

At the first trisomy (47,XY,+21), the father was 31-years-old, and the mother 40-years-old. Eight and 11 months later, they had two pregnancies that ended spontaneously at nine to ten weeks of gestation: 47,XX,+9 and 47,XX,+18.

Despite the high frequency of human aneuploidy and advances in genetic analysis, less is known about the factors that modulate the recurrence risk. It was stated that trisomy recurrence can occur through three possible mechanisms: chance alone due mainly to maternal age, parental mosaicism or meiotic errors that increase rates of chromosome nondisjunction.

In the present case, the first pregnancy was affected by trisomy 21 and occurred in a 40-year-old mother. The risk of a subsequent trisomy 21 after a previous pregnancy with trisomy 21 is known to be increased, but is still unclear whether the risk of other trisomies runs in a similar way. The recurrence risk is dependent by the maternal age at the first affected pregnancy, and appears to be greater in younger women than older women [4, 5]. The recurrence risk for 21 is more increased than the age-related for a future pregnancy if the previous trisomy 21 pregnancy occurs in more than 30-year-old mothers. Robinson *et al.* investigated 54 couples with recurrent aneuploidy generally involving different chromosomes and found that the mean maternal age at the time of spontaneous abortion with chromosomal abnormality was 38 years, suggesting that increased maternal age was the major predisposing factor [6].

Also, the risk for the same trisomy subsequent to trisomy 13 or 18 appears to be increased [5, 7]. Warburton *et al.* reported a significantly increased risk of different trisomies following a trisomy 21 diagnosis. The standard morbidity ratio (SMR) was 2.3 for heterotrisomy, after an index trisomy 21, regardless of maternal age at the first trisomy. After a non-viable trisomy diagnosed in a spontaneous abortion, the SMR for a viable trisomy at prenatal diagnosis in a subsequent pregnancy was 1.8. Furthermore, they also found that following any of trisomy 13, 18, or 21, XXX or XXY, the risk of a different trisomy was significantly increased, supporting the hypothesis that some women have a higher risk for nondisjunction than others of the same age [7].

Parental gonadal mosaicism is a condition in which the precursors to gametes contain a mixture of two or more genetically different populations, one population of cells containing the normal genetic material, while the other contains a DNA mutation or chromosome anomaly.

Parental gonadal mosaicism could explain an increased risk of subsequent pregnancies of the same chromosome (homotrisomy), although it cannot explain an increased recurrence risk for a different trisomy (heterotrisomy) [8, 9].

In the present case the subsequent next two pregnancies were affected by autosomal heterotrisomy: trisomy 9 and trisomy 18, and parental gonadal mosaicism for trisomy could be ruled out. Mosaicism may be difficult to diagnose due to its low level or tissue-specific distribution: the trisomic cell line is sometimes documented only in ovary biopsies or germ cells, while other tissues (blood lymphocytes and skin) appear diploid [10, 11]. A father with elevated frequencies of correspondingly aneuploid sperm was identified in a family with four consecutive trisomic pregnancies: 47,XXY and 47,XYY were live births; 47,XX,+15 and 47,XX,+22, that were spontaneously aborted over a three-year period [12]. The parental origin of extrachromosome was determined only in the XXY child, by molecular methods. The extra Y was presumably derived from a paternal meiotic error, and for both autosomal trisomies the origin has not been established. Aneuploid sperm are present in low frequencies in most healthy men [13] and an increased risk associated with high frequencies of aneuploid sperm was found in some recurrent trisomies [12, 14, 15]. These findings suggest that in some rare cases recurrent trisomic pregnancies may have a paternal basis.

Meiotic nondisjunction is the mechanism leading to the majority of trisomy and in most cases occurs by chance. Autosomal trisomies are predominantly of maternal origin, while sex chromosomal trisomies have substantial paternal origins [16]. The risk to nondisjunction increases with advancing maternal age and seems to be more frequent in women over the age of 35. Mutations in genes that control oocyte maintenance and meiosis, variations in recombination frequency, genetic changes such as mitochondrial deletions, and aging processes in the ovary may increase predisposition to meiotic errors [1, 9].

In the present case, the authors suggest that factors associated with an increased risk of meiotic errors are involved in recurrence of different trisomies and the supplementary chromosome in all three pregnancies arose in maternal meiosis. Their hypothesis is supported by two studies, which found in almost all trisomies of recurrent pregnancies the error was of maternal origin, whereas paternal errors account for 7% of meiotic origin trisomies among spontaneous abortions [6, 17].

In conclusion, the present report supports the hypothesis that some women have a higher risk for nondisjunction than others of the same age. A closer supervision of women who have had one trisomic pregnancy is necessary based on their history alone. Counseling a couple with recurrent trisomies is difficult and future research on genetics regarding meioisis is required to assist them.

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