TRIPLOIDIES IN FIRST AND SECOND TRIMESTERS OF PREGNANCIES IN TURKEY

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ABSTRACT

Triploidy is the most common chromosomal abnormality in human conceptions that cause fetal loss before 20 weeks of gestation and has an incidence of 1 in 10,000 live births. Placental changes, fetal malformations and intrauterine growth retardation (IUGR) occur in triploid pregnancies. We performed karyotype analyses of 75 spontaneous abortions and 1,114 amniotic fluid cultures by conventional methods between 2002 and 2005 at our cytogenetics laboratory. Triploidy was detected in five spontaneous abortions and four amniotic fluid samples. Abortions were between the 9th and 13th weeks of pregnancy, and cytogenetic analyses revealed a 69,XXY karyotype in four of the aborted fetuses and a 69,XXX karyotype in one. Amniotic fluid cell cultures revealed a 69,XXX karyotype in three cases and 69,XXY in one. Amniocentesis was performed in four patients because of an increased trisomy 18 risk detected in maternal serum screening. In pregnant women undergoing second trimester amniocentesis, increased risk for trisomy 18 may be due to triploidy and should be taken into account during genetic counseling.

Key words: Triploidy, Maternal serum screening, Cytogenetics, Pregnancy

INTRODUCTION

Triploidy occurs in 1% of all conceptions and is one of the most common chromosome abnormalities in humans [1]. The cells of fetuses contain 69 chromosomes which originate from three haploid gametes or one diploid and one haploid gamete. Two types of phenotypic presentations can be seen according to the origin of the diploid gamete; diandry (type I) if double contribution is paternal and digyny (type II) if it is maternal [2]. Phenotypic features associated with fetal triploidy have been shown to occur in a broad spectrum including placental changes and fetal structural and growth anomalies [3]. Paternally-derived cases predominate among "typical" spontaneous abortions, whereas maternally-derived cases are associated with either early embryonic demise or with relatively late demise involving a well-formed fetus. When termination of the pregnancy is regarded, the condition carries medical risks for the mother. Therefore, prenatal diagnosis and decision on termination of pregnancy should be made as early as possible. For this purpose, first and second trimester maternal serum screening tests and ultrasonographic (USG) examinations are performed during routine practice [4,5].

First and second trimester maternal serum screening tests are performed at weeks 11-14 and 15-22 of gestation. First trimester screening includes fetal nuchal translucency measurements by ultrasonography combined with maternal serum free β -human

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chorionic gonadotrophin (f β -hCG) and pregnancy-associated plasma protein A (PAPP-A) levels as well as trisomy 21 risk (6). Second trimester screening includes maternal serum levels of human chorionic gonadotrophin (hCG), unconjugated estriol (uE3) and alpha-fetoprotein (AFP) combined with maternal age. Both tests have their own detection and false-positive rates regarding trisomy 21 risks. In triploid pregnancies, two patterns of maternal serum AFP, hCG and uE3 levels have been reported in the second trimester. The first is elevated AFP, elevated hCG and low or normal uE3. The second is low or normal AFP, low hCG and low uE3 [4].

Detection of triploidy based on increased translucency of nuchal thickness (NT) is effective in up to 66% of triploid fetuses in first trimester without combining maternal age. Furthermore, crown rump length (CRL) based on first trimester fetal biometry charts has been reported to be useful in the detection of triploidy [1].

In the current study, we performed cytogenetic analysis for prenatal diagnosis and spontaneous abortion materials and detected triploidy in a total of nine cases. Our findings are discussed on the basis of routine prenatal diagnosis risks.

MATERIALS AND METHODS

A total of 1,114 amniotic fluid samples and 75 abortion samples that were karyotyped between January 2002 and December 2005 were included. Amniocentesis was made between 15 and 22 weeks of gestation due to an increased risk of chromosomal abnormalities in maternal serum screening tests that were performed in the second trimester. Cytogenetic analysis was suggested whenever the combined risk was above 1/250 for Down's syndrome and/or combined risk above 1/100 for trisomy 18 [7].

Both extra embryonic tissue and amniotic fluid tissue cultures were set up in two separate tissue culture flasks (Greiner, Frickenhausen, Germany) with Amniomed culture medium (Biochrom, Berlin, Germany). On the 7th day of culture, the medium was changed, and when an appropriate number of mitoses was observed, the cells were harvested [8]. Chromosomes were Giemsa-trypsin (GTG) banded and at least 20 metaphases were analyzed from each sample.

Genetic counseling was given in two sessions

to couples. During the first session, couples were informed about the suspicious genetic abnormality and genetic diagnosis methods after pedigree analysis. When karyotype analyses were completed and triploidy was detected, the parents were informed about the triploidy and the recurrence risks for individual karyotype findings during the second genetic counseling session. Detailed USG examination was performed in every pregnancy at 18 or 19 weeks of gestation. Pathological examination was performed in all aborted or terminated fetuses.

RESULTS

The clinical features of nine triploidy cases are shown in Table 1. Four of these were detected during cytogenetic analysis of amniotic fluid samples and five were detected during analysis of spontaneous abortions.

Among the 75 spontaneous abortion cases, we observed five triploidies and 11 other chromosome abnormalities consisting of seven autosomal trisomies (18, 21 and 22) and one sex chromosome trisomy (XXY) as numerical abnormalities, and two balanced and one unbalanced reciprocal translocation as structural abnormalities. The triploid abortions were between 9 and 13 weeks of gestation and maternal ages ranged between 24 and 45 years. Two cases had a history of a previous pregnancy loss (cases 1 and 2) which did not have any cytogenetic abnormalities. Cytogenetic analyses revealed a 69,XXY karyotype in four of the aborted fetuses and a 69,XXX karyotype in one. Except for case 5, all placenta samples from aborted fetuses were non molar, according to the pathological examination (Table 1).

Of the 1,114 amniocentesis cases, 1,067 had increased risk for Down's syndrome in second trimester triple test screenings. No triploidies were detected in this group. Instead, we detected trisomy 21 in 10 cases, trisomy 18 in six cases, trisomy 13 in three cases, XXY in two cases, XXX in one case, monosomy X in two cases and balanced reciprocal translocation in four cases. The remaining 47 cases from the 1,114 amniocentesis cases had increased risk for trisomy 18 and four triploidy cases were detected in this group. These patients were aged between 19 and 35 years of age. Trisomy 18 risk at triple screening was 1/50 in cases 6 and 8, 1/10 in case 7 and 1/20 in

Table 1. Clinical and laboratory findings for patients 1 through 9.

Case #	Maternal Age	Pregnancy Week	Pregnancy Outcome	Trisomy 18 ^a	USG Findings	Autopsy Findings	Pathological Examination of Placenta	Karyotype
1	26	9	Aborted	—	—	—	Non molar	69,XXY
2	24	9	Aborted	—	—	—	Non molar	69,XXY
3	31	13	Aborted	—	—	—	Non molar	69,XXY
4	45	9	Aborted	—	—	—	Non molar	69,XXY
5	28	9	Aborted	—	—	—	Partial mole	69,XXX
6	19	18	Termination after D _x	1/50	Median cleft lip hypertelorism, clinodactyly, oligohydramnios; normal placenta	220 g fetus with median cleft lip and palate, hypertelorism, exophthalmia, clinodactyly, syndactyly of third and fourth fingers and club foot	Non molar	69,XXX
7	25	17	Termination after D _x	1/10	IUGR with strawberry shaped head, clindactyly, hyperechogenic and oligohydramnios; normal placenta	79 g fetus with relative macrocephaly, low-set ears, exophthalmia, cleft palate, clinodactyly, adrenal hypoplasia	Non molar	69,XXX
8	35	19	Termination after D _x	1/50	Moderate, oligohydramnios, clinodactyly, club foot; normal placenta	Hypertelorism, clinodactyly, club foot	Non molar	69,XXX
9	24	19	Termination after D _x	1/20	IUGR, moderate, oligohydramnios, ventricular septal defect, vermian agenesis, club foot; normal placenta	Hypertelorism, club foot	Non molar	69,XXY

Figure 1. Karyotype obtained from amniotic fluid cell cultures of patient 9 has been reported as 69,XXY.

Figure 2. One of the fetuses with triploidy, after termination of pregnancy.

case 9 (Table 1). Human chorionic gonadotropin values ranged between 0.16 and 0.23 multiples of median (MoM). Cytogenetic analyses revealed a 69,XXX karyotype in three cases and 69,XXY in one (Table 1, Figure 1). All of these pregnancies were terminated and pathological examinations revealed non molar placentas. Minor fetal anomalies were seen during USG examination in these cases (Table 1, Figure 2).

DISCUSSION

Triploid conceptions die early in development, and account for 10% of all spontaneous abortions [9]. Studies performed on spontaneous abortion tissues revealed that diandric triploidy usually arises as a result of dispermy. Triploid karyotypes may be XXX, XXY or XYY with a ratio of 1:2:1. When the abnormality is in paternal meiosis, first division errors result in the XXY karyotype, whereas second division errors result in XYY and XXX karyotypes, each at about the same frequency. As a result, karyotypes with at least one excess Y chromosome would be expected to occur more frequently. The XYY karyotypes are usually associated with early lethality and spontaneous abortion (4) but this was not observed

in spontaneous abortions in the current study, where four XXY karyotypes and one XXX karyotype were found instead.

Cases with low level hCG usually have non molar placentas and are likely to be primarily digynic. Digynic triploidy arises from errors in maternal meiosis and results in XXX and XXY karyotypes with an expected ratio of 1:1, although an excess of XXX cases has been reported [4]. Similarly, three of our second trimester patients had XXX karyotypes and one had a XXY karyotype.

The sex chromosome complement in triploid pregnancies determines the levels of maternal serum hormones and whether the placental phenotype would be molar or non molar. [4]. The XYY triploid karyotypes frequently result in early molar development, while XXY with an intermediate probability and XXX with lowest probability, results in cystic changes and eventually fetal death. The XXX triploids survive longer *in utero* as a result of a lower but still significant probability for cystic changes. An XXY karyotype could be an explanation for our first trimester spontaneous abortions.

There is no correlation between triploidy and advanced maternal age. In our triploidy cases, maternal

ages ranged between 19 and 45 years. Maternal ages were below 35 years in seven of nine triploid cases. Therefore, we concluded that, first and/or second trimester maternal serum screening tests may be more valuable than maternal age when triploidy is regarded.

Second trimester maternal serum hormone analysis has shown high or low levels of hCG, low levels of uE3 and high levels of AFP in triploid pregnancies [6,7,10,11]. Trisomy 18 was associated with a decrease in serum AFP, hCG and uE3 levels in the second trimester of pregnancy [12]. In triploidy, hCG and uE3 values were usually lower than in trisomy 18 [4]. Maternal hCG values as low as 0.01 MoM have been reported. In all our second trimester patients, high risk was observed for trisomy 18 and hCG values ranged between 0.16 and 0.23 MoM.

Triploidy should always be kept in mind in cases at risk according to maternal serum hormone levels. The diagnosis can be rapidly confirmed by molecular cytogenetics of interphase cells. Although cytogenetic analysis is essential in diagnosis of triploidy, parental origin may be detected by molecular genetics methods. Recurrence risk in diandric triploidy associated with partial hydatiform mole has been reported to be 1-1.5% [13]. Parents should be informed about detailed USG scans and prenatal cytogenetic diagnosis in future pregnancies.

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