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ORIGINAL PAPER

Incidence and Types of Chromosomal Abnormalities in First Trimester Spontaneous Miscarriages: a Greek Single-Center Prospective Study

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ABSTRACT

Background: *Chromosomal abnormalities are the main cause of early miscarriages.*

Objective: *The aim of this cross-sectional cohort study was to investigate the chromosomal abnormalities in first trimester spontaneous miscarriages in a Greek population.*

Methods: *Spontaneous abortion samples from a single genetic center in Greece were analyzed* via *conventional karyotype analysis and quantitative fluorescent polymerase chain reaction (QF-PCR). All samples were accompanied by maternal blood samples to exclude contamination.*

Results: *The results of the present study showed that 83 out of the 198 available samples (41.9%) had*

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an abnormal karyotype. The majority of embryos suffered from numerical chromosomal abnormalities (90.4%). Autosomal trisomy (54.2%) was the most frequent chromosomal abnormality, while trisomies 16 and 22 (seven cases) were the commonest karyotype anomalies. Nine fetuses (10.8%) suffered numerical abnormalities of sex chromosomes (all cases with 45, X), while 12 of fetuses (14.5%) were diagnosed with triploidy (five males with 69, XXY and seven females with 69, XXX). All miscarriages following IVF and presenting with abnormal karyotype were diagnosed with numerical abnormalities. Finally, a fetus with double trisomy (14 and 21) and a rare case of coexistence of Klinefelter (XXY) and Edwards (trisomy 18) syndromes were observed.

Conclusion: *Cytogenetic analysis of products of conception is an important step involved in investigating the causes of miscarriages. In this study of spontaneous miscarriages, the incidence and types of chromosome aberrations are presented for the first time in a Greek population.*

Keywords: miscarriages, spontaneous abortions, chromosomal abnormalities, cytogenetics, pregnancy, Greece.

INTRODUCTION

Spontaneous miscarriage, defined as the loss of a fetus before the completion of the 20th week of gestation, which is considered the limit of viability, is the commonest pregnancy complication (1, 2). Although there is no general agreement, most researchers consider that, with regard to clinical pregnancies (those with ultrasonographic documentation of clinical signs of pregnancy), the frequency of spontaneous abortions is around 15%. More than 80% of miscarriages occur before the completion of 12 weeks of gestation and approximately 50% of cases are attributed to chromosomal abnormalities of the fetus (3, 4).

The role of chromosomal abnormalities as important causes of miscarriages has been revealed *via* systematic cytogenetic studies during the last decades (5, 6). Numerical chromosome abnormalities accounted for more than 80% of these abnormalities, while structural chromosome abnormalities and chromosome mosaicism for the remaining cases (3, 7-11).

Cytogenetic analysis of products of conception is an important step involved in investigating the causes of miscarriages (3, 11). The aim of this study was to examine chromosomal abnormalities in embryos detected after first trimester miscarriages. We report the results of the cytogenetic analysis of spontaneous abortions products from a single center in Greece. ❑

MATERIAL AND METHODS

Fetuses from spontaneous abortion were prospectively collected from a single genetic center in Greece. Cytogenetic analysis was performed in the private laboratory of genetics "Access to Genome" Athens, Greece. This study was approved by the Institutional Review Board of Aretaieio University Hospital, Greece. Samples were submitted for classical cytogenetic analysis and, in cases of culture failure, QF-PCR (Quantitative Fluorescence-Polymerase Chain Reaction) was performed. In all cases, both parents were of Greek origin.

Results were available for a total of 198 samples of abortions (79.2%) which were included in this analysis. For the 83 embryos found with chromosomal abnormalities, the following data were analyzed: karyotype, gestational age of spontaneous abortions (in completed weeks), maternal age (in completed years), and type of conception [natural conception or *in vitro* fertilization (IVF)].

For the karyotype analysis, all samples were cultured and harvested by standard techniques and conventional karyotype analysis by GTG banding was performed. Genomic DNA was extracted using the Maxwell 16 Cell LEV DNA Purification kit (Promega, USA). QF-PCR was performed using a set of short tandem repeat (STR) markers for chromosomes 13, 18, 21, X, and Y. Four STRs for X and Y chromosomes, six for chromosome 21, four for chromosome 18, and four for chromosome 13 were selected. Furthermore, the non-polymorphic sequence of the amelogenin (AMXY) gene and SRY (Sex-determining Region Y) were included for fetal sex determination. The PCR reactions were set in three different multiplex PCR assays of 25 μL total volume by using genomic DNA, PCR buffer (Invitro-

gen, USA), 1.5 mM $MgCl_2$, 5-10 pmol of each primer, 0.06 U/μL Taq polymerase (Invitrogen, USA) and carried out for 26 cycles. The fluorescent QF-PCR products were analyzed by capillary electrophoresis on an automated DNA sequencer (ABI 3100, Applied Biosystems).

Quantitative variables were expressed as mean ± standard deviation (SD) and were compared with the two independent samples Student's t-test, Qualitative variables were presented as numbers and percentages (%), and statistical differences between proportions were evaluated using Pearson's chi-squared or Fisher exact test. A two-tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using MedCalc Statistical Software version 12.7.7 (2013 MedCalc Software bvba, Ostend, Belgium). ❑

RESULTS

Among the 198 samples of abortions included in this analysis, chromosomal abnormalities were detected in 83 embryos (41.9%). The majority of embryos suffered numerical chromosomal abnormalities (75 embryos, 90.4%), whereas structural chromosomal abnormalities were detected in eight embryos (9.6%). The results of the cytogenetic analysis of all studied embryos are summarised in Table 1.

Four of the eight embryos with structural chromosomal abnormalities were diagnosed with derivative chromosome and three with Robertson translocation, while the remaining one was found to have ring chromosome.

Overall, autosomal trisomy was the most frequent chromosomal abnormality (45 cases, 54.2%). The commonest autosomal trisomies were found in chromosomes 16 and 22 (seven cases each, 15.6%). Furthermore, five embryos with trisomy 18 (Edwards syndrome) (11.1%) and five embryos with trisomy 13 (Patau syndrome) (11.1%) were identified, followed by trisomies 7, 14, 15, 20 and 21 (Down syndrome) (three cases each, 6.7%) and trisomy 3 (two cases, 4.4%). Finally, four embryos were found to have trisomies 4, 5, 8 and 12, respectively.

TABLE 1. Results of the cytogenetic analysis of miscarriage products

Karyotype	Cases	(%)
Structural chromosomal abnormalities	**8**	**9.6**
Derivative chromosome	**4**	**4.8**
46, XX,der(2)t(2;3)(p21.3;q35)	1	1.2
46, XX,der(8)t(2;8)(p21.3;q23)	1	1.2
46, XX,der(12)t(12;13)(p22.3;q14)	1	1.2
46, XY,der(13)t(8;13)(p21;q32)	1	1.2
Ring chromosome	**1**	**1.2**
46,XY,ring(15)	1	1.2
Robertson translocation	**3**	**3.6**
46,XX,rob(22;22)(q10;q10)	1	1.2
46,XY,rob(21;21)(q10;q10)	1	1.2
46,XY,rob(13;13)(q10;q10)	1	1.2
Numerical chromosomal abnormalities	**75**	**90.4**
Autosomal trisomy	**45**	**54.2**
47, XX, +3	2	2.4
47, XX, +4	1	1.2
47, XY, +5	1	1.2
47, XY, +7	3	3.6
47, XY, +8	1	1.2
47, XY, +12	1	1.2
47, XY, +13	5	6.0
47, XY, +14	3	3.6
47, XY, +15	3	3.6
47, XY, +16	7	8.4
47, XX, +18	5	6.0
47, XY, +20	3	3.6
47, XY, +21	3	3.6
47, XY, +22	7	8.4
Sex chromosome aneuploidy	**9**	**10.8**
45, X	9	10,8
Double aneuploidy	**2**	**2.4**
48, XY, +14 +21	1	1.2
48, XXY, +18	1	1.2
Mosaic	**7**	**8.4**
45, X/46, XX	5	6.0
46, XY/46, XX	2	2.4
Triploidy	**12**	**14.5**
69, XXY	5	6.0
69, XXX	7	8.4
Total	**83**	**100**

There were 48 (59.3%) male embryos and 33 (40.7%) female embryos, with a sex ratio (males/females) of 1.45 (Table 2); two embryos (2.4%) had a mosaic 46, XY/46, XX genotype. Structural abnormalities were found in four (50%) male embryos and four (50%) female ones, whereas numerical abnormalities were identified in 44 (60.3%) male embryos and 29 (39.7%) female ones, resulting in sex ratios of 1 and 1.52, respectively. The proportion of female embryos was 21% lower among embryos with numerical anomalies, by comparison with those with structural chromosomal abnormalities (39.7% *versus* 50%, respectively), although the difference did not reach statistical significance (p = 0.260)

Among samples with autosomal trisomy there were 37 (82.2%) male embryos and eight (17.8%) female embryos, with a sex ratio of 4.63. All fetuses with autosomal trisomies 5, 7, 8, 12, 13, 14, 15, 16, 20, 21 and 22 were male, whereas those with trisomy 3, 4, and 18 were female. The proportion of male fetuses was 2.7 fold significantly higher (82.3% *versus* 30.6%, respectively; 95% CI 1.7–4.3, p < 0.001) among miscarriages with autosomal trisomies than the other types of chromosomal abnormalities. Nine embryos (10.8%) suffered sex chromosome aneuploidy, and all of them had Turner syndrome (45, X). Furthermore, five abortion products were female mosaics (45, X/46, XX).

There were 12 (14.5%) triploid embryos, and this was the only category where females overmatched males (five male products with 69, XXX karyotype and seven female products with 69, XXX karyotype, sex ratio: 0.71). Finally, one male fetus with double trisomy (in chromosomes 14 and 21, karyotype 48, XY, +14 +21) and one case of combined autosomal and sex trisomy (male fetus with Klinefelter and Edwards syndromes, karyotype 48, XXY, +18) were identified.

In our sample, spontaneous miscarriages occurred between 7 and 12 weeks of pregnancy, with a mean duration of 7.8 (± 1.1) weeks (Table 2). Gestational age did not differ between miscarriages with structural and those with numerical chromosomal abnormalities (mean 8.0 *versus* 7.8 weeks, respectively; p = 0.605).

Maternal age ranged between 25 and 42 years (mean age 35.0 ± 4.6 years); 53.0% of mothers were older than 35 years and 21.7% were aged ≥40 years (Table 2). Women who miscarried embryos with numerical abnormalities were non-significantly older than those with structural abnormalities (mean age 35.3 *versus* 32.6 years, respectively; p=0.116). Moreover, women aged < 35 years were more likely to miscarry embryos with structural abnormalities than those aged 35 or older (17.6% *versus* 4.1%, respectively), although the difference was marginally statistically significant (p = 0.059).

Eleven (13.3%) aborted pregnancies occurred after IVF, and all of them were diagnosed with numerical abnormalities. The proportion of structural abnormalities in naturally conceived miscarriages did not differ from those after IVF (11.1% *versus* 0%, respectively; p = 0.589). Additionally, non-significant differences were found between IVF and spontaneously conceived abortions regarding the frequency of aneuploidy overall (81.8% *versus* 62.5%, respectively; p = 0.314), autosomal aneuploidy (63.6% *versus* 52,8%, respectively; p = 0.538), sex chromosome aneuploidy (18.2% *versus* 9.7%, respectively; p = 0.341), mosaic (9.1% *versus* 5.9%, respectively; p = 0.650) and triploidy (9.1% *versus* 15.3%, respectively; p = 0.593). ❑

DISCUSSION

It is well established that chromosomal abnormalities are responsible for nearly half of cases

Fetal sex	Cases	(%)
Male	48	59.3
Female	33	40.7
Duration of pregnancy (competed weeks)	**Cases**	**(%)**
7	41	49.4
8	29	34.9
9	6	7.2
10	3	3.6
11	3	3.6
12	1	1.2
Maternal age (completed years)	**Cases**	**(%)**
25-29	8	9.6
30-34	26	31.3
35-39	31	37.3
≥40	18	21.7
Conception	**Cases**	**(%)**
Natural	72	86.7
IVF	11	13.3

TABLE 2. Maternal and fetal characteristics of miscarriages with chromosomal abnormalities (IVF=*in vitro* fertilization)

of first trimester fetal loss. In this study, in a total of 198 samples from first trimester products of conception from spontaneous miscarriages an abnormal karyotype was found in 83 cases (frequency 41.9%).

Among chromosomal abnormalities identified in our sample of abortion products, the majority (90.4%) were numerical anomalies and mostly autosomal trisomies (54.2%). Numerical chromosomal abnormalities are the most common cause of premature pregnancy loss and account for 86% of first trimester miscarriages attributed to chromosomal abnormalities. Single chromosomal trisomies are the commonest chromosomal abnormalities observed in first trimester miscarriages (3). Numerical chromosome anomalies are classified into two basic types: polyploidy and aneuploidy. Aneuploidy usually occurs after the non-disjunction of homologous chromosomes in meiosis I or the failure of sister chromatids to separate during meiosis II. The probability of non-disjunction increases with maternal age. Mosaicism syndromes can be caused by mitotic non-disjunction in early fetal development resulting in an embryo containing both aneuploid and normal cells. Mosaicism appears in almost 8% of cases in cytogenetic analyses of miscarriages products (7).

Trisomies 13, 16, 18, 21 and 22 are the most common changes in autosomal number, constituting almost half of all cases of spontaneous miscarriages with genetic anomalies. Approximately one-fourth of sex chromosome aneuploidies are cases with Turner syndrome (45, X), while Klinefelter syndrome (47, XXX) is less common. Autosomal monosomy is practically always incompatible with life (3, 7). The commonest autosomal trisomies identified in our sample were trisomies 16 and 22 (15.6% each), followed by trisomies 18 and 13 (11.1% each). Trisomy 16 is the most common trisomy in products of conception from spontaneous abortions, with these embryos never surviving until birth. Trisomy 22 is the third most frequent trisomy in spontaneous abortions, representing 10-15% of cases (12, 13). Due to severe congenital malformations live births and postnatal survival of trisomy 22, neonates are very rare events. Among 23 children born with non-mosaic trisomy 22, Tinkle *et al* (14) found a median survival of four days, while Heinrich *et al* (15) reported the case of a male neonate with trisomy 22 surviving for 29 days. Additionally, in our study the frequency of trisomies 7, 14, 15, 20 and 21 was 6.7% and the proportion of cases with trisomy 3 was 4.4%. Finally, four embryos were diagnosed with trisomy 4, 5, 8 and 12, respectively. In the present study, the commonest sex chromosomal abnormality was monosomy 45, X (10.8%). Turner syndrome (45, X) is the only monosomy that is compatible with survival until birth. Furthermore, it is the commonest sex chromosome aneuploidy in miscarriages, being responsible for 20% of first trimester fetal loss. Mosaic embryos were found in seven (8.4%) cases: five with 45, X/46, XX, and two with 46, XX/46, XX. Twelve (14.5%) embryos (five male embryos 69, XXX and seven female embryos 69, XXX) were diagnosed with triploidy. Triploidy has been estimated to occur in 15% of all miscarriages attributed to chromosomal abnormalities, with only a minority of triploidic embryos surviving to term and those living very rarely more than a few days (16). The origin of the additional haploid set remains controversial, with early cytogenetic studies suggesting paternal origin (diandric triploidy) in the majority of cases, whereas later studies reported a large proportion of maternally-derived cases originated through errors in meiosis II (digynic triploidy) (17). In a review of data from 17 relevant studies, Jenderny (18) found a 61% frequency of pure trisomy among 3,749 aberrant karyotypes in conception products after spontaneous miscarriages. In agreement with previous research (13, 19), the incidence of structural anomalies in this study was not related to fetal sex, whereas among embryos with numerical chromosomal abnormalities, the sex ratio was statistically significantly 2.7 fold higher than among the other types of chromosomal abnormalities.

Finally, two male embryos with double trisomy (2.4%) were identified in this study: one with coexisting trisomy 14 and 21 (48, XY, +14 +21) and another one with double aneuploidy Edwards and Klinefelter (48, XXY, +18). The proportion of double trisomies in early fetal loss has been reported to range from 0.2% to 4.6%, and a total of only 444 cases have been reported in the literature (20). Additionally, while the occurrence of double aneuploidy in liveborn neonates is relatively rare, however, the combination of Edwards and Klinefelter syndromes is extremely rare, with only 15 cases reported in the literature (21). No case of Edwards and Klinefelter coexis-

tence in products of conception after spontaneous abortions has been reported in large studies (13, 20).

Structural chromosomal abnormalities were identified in eight (9.6%) embryos. Specifically, four embryos were diagnosed with derivative chromosome; we have also found three cases of Robertson translocation and one case with ring chromosome. Structural abnormalities account for 6% of fetal chromosomal abnormalities in first trimester pregnancy loss (3, 7). In the present study we observed no statistically significant difference in gestational age among miscarriages caused by structural *versus* numerical abnormalities, which was in accordance with recent studies (22).

Translocations are the most common structural chromosomal aberrations (about one in every 200 people carries a balanced translocation or inversion). Diagnosis of balanced abnormalities in one of the parents may predispose to an unbalanced karyotype leading to spontaneous abortions or seriously ill children (23). Although an increasing number of couples who carry translocations are referred to IVF centers for preimplantation genetic diagnosis (PGD) for carriers of translocations, evidence that PGD improves live birth rates in these couples remains insufficient (24).

In this study, the mean maternal age was 35 years, with > 20% of mothers being older than 40 years. Advanced maternal age is a well-established major risk factor for spontaneous miscarriages (25), mainly due to numerical chromosomal defects resulting from non-disjunction events. As expected, in the present study the frequency of structural chromosomal abnormalities was 4.3 times higher in products of conception after spontaneous abortion from women aged < 35 years compared with older women (≥ 35 years), which was in agreement with other researchers (22, 26).

Eleven (13.3%) pregnancies that ended in spontaneous miscarriages came after IVF. Research suggests that chromosomal disorders are common causes of first trimester spontaneous miscarriages after IVF or natural conception, without statistically significant differences in total frequency or type of chromosomal abnormalities (27, 28). Indeed, in the present study, spontaneous abortions of IVF and spontaneously conceived pregnancies did not differ regarding the frequency of autosomal or sex chromosome aneuploidy, triploidy or mosaicism. Of note, no case with structural chromosomal abnormalities was identified among miscarriages after IVF, all abortions being diagnosed with numerical disorders in our population. Although this finding could be partly attributed to the advanced maternal age in this study, it merits further evaluation. Bettio *et al* (29) also found no case of structural abnormalities in a sample of 18 miscarriages after IVF. Similarly, in the study of Pendina *et al* (28) structural abnormalities among miscarriages with chromosomal abnormalities after IVF had a prevalence of 0% (0/65) for those aged ≥ 35 years.

The strengths of this study include the cytogenetic analysis of a large sample from a homogeneous population, the reliability of results due to the homogeneous cytogenetic procedures performed in a single genetic laboratory, the high success rate of the diagnostic strategy, and the minimization of the possibility of false diagnosis due to maternal cell contamination. Study limitations were mainly related to the limitations of the laboratory diagnostic techniques which have been used. For example, although QF-PCR was used as a supplementary method to improve success rate in the detection of chromosome aberrations in the cases of culture failure, it could not detect changes outside the target sequence. ❑

CONCLUSION

To our knowledge, this is the first published study investigating chromosomal abnormalities in spontaneous miscarriages in a Greek population. Our results provide important data on the incidence and types of chromosomal aberrations in Greece, which generally seem to fall within the internationally reported range. Cytogenetic analysis of the products of conception is an important step involved in investigating the causes of miscarriages, while QF-PCR may play an important role as a rapid supplementary test. The results of the above-described cytogenetic analysis appear to be supportive of the conduct of pertinent parent counselling in order to avoid unnecessary or poorly documented as well as costly further examination and treatment. ❑

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