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Chromosome Abnormalities Identified in 457 Spontaneous Abortions and Their Histopathological Findings

457 Spontan Abortus Materyalinde Tespit Edilen Kromozomal Anomaliler ve Histopatolojik Bulguları

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ABSTRACT

Objective: About 15% of clinically recognized pregnancies result in spontaneous abortion in the first trimester and the vast majority of these are the result of chromosome abnormalities. Studies of chromosomal constitutions of first trimester spontaneous abortions have revealed that at least 50% of the abortions have an abnormal karyotype. In this study we aimed to report the single centre experience of anomalies detected in spontaneous abortions.

Material and Method: We present rare numerical and structural cytogenetic abnormalities detected in spontaneous abortion materials and the histopathological findings of rest material of abortion specimens in our study population.

Results: Among 457 cases, 382 were successfully karyotyped while cell culture of 75 cases failed. Cytogenetic abnormalities were detected in 127 of 382 cases (33.24%). Autosomal trisomies were the predominant chromosomal abnormalities with a frequency of 48.8%. Structural chromosomal abnormalities were infrequent in conception materials. The mean age of the mothers was highest in trisomy group, the difference being significantly important (ANOVA p< 0.001). The most frequent chromosomal abnormalities were Turner syndrome, triploidy and trisomy of chromosome 16 followed by trisomy of chromosomes 22 and 21 and tetraploidy. Double trisomies and structural chromosomal abnormalities were rare. Trisomies were more frequent in advanced maternal age.

Conclusion: Detection of chromosomal abnormalities in spontaneous abortion materials is very important to clarify the causes of loss of pregnancy. Detection of structural chromosomal abnormalities in the cases and their carrier parents can provide proper genetic counseling to these families. These families can be directed towards pre-implantation genetic diagnosis to prevent further pregnancies with complications.

Key Words: Chromosomal abnormalities, Cytogenetic abnormalities, Pathology, Spontaneous abortion

ÖZ

Amaç: Klinik olarak gebeliklerin yaklaşık %15'i ilk trimesterde abortus ile sonuçlanmakta olup büyük kısmında ise neden kromozom anormallikleridir. Çalışmalar göstermiştir ki ilk trimesterda abortusla sonuçlanan gebeliklerin %50'sinde kromozomal olarak karyotip anomalileri görülmüştür. Çalışmada tek merkeze ait spontan abortus olgularındaki anomalileri sunmak amaçlandı.

Gereç ve Yöntem: Çalışmada tıbbi biyoloji ve genetik bölümümüze gelen spontan abortus materyallerinde tespit edilen sayısal ve yapısal sitogenetik anomalileri ve bu olguların histopatolojik bulguları sunuldu.

Bulgular: Karyotipleme için gelen 457 spontan abortus materyalinin 382 tanesinde başarılı karyotipleme yapılabilmiştir, 75 olguda hücre kültürü başarısız olmuştur. Sitogenetik anomaliler 382 olgunun 127'sinde görülmüştür (%33.24). Otozomal trizomiler %48,8 oranı ile en baskın görülen anomalidir. Yapısal anomaliler abortus materyallerinde pek sık değildir. Ortalama anne yaşının en yüksek olduğu anomali grubu trizomi grubudur ve fark istatistiksel olarak anlamlıdır (ANOVA p< 0.001). En sık görülen kromozomal anomaliler Turner sendromu, triploidi ve trizomi 16'dır. Bunları trizomi 22, 21 ve tetraploidi takip eder. Çalışmada çift trizomiler ve yapısal kromozom anomaliler nadirdir. Anne yaşı ileri olursa trizomiler daha sık görülmektedir.

Sonuç: Sonuç olarak spontan abortus materyallerinde kromozom anomalilerinin değerlendirilmesi gebelik kayıplarının sebeplerini açığa çıkarmak için önemlidir. Yapısal kromozom anomalilerinin tespit edilmesi aileye sonraki gebeliklerde daha iyi genetik danışmanlık verilmesine yardımcı olur. Bu ailelere bir sonraki gebeliklerinde komplikasyonları önlemek için preimplantasyon döneminde genetik tanı ile rehberlik edilebilir.

Anahtar Sözcükler: Kromozomal anomaliler, Sitogenetik anomaliler, Patoloji, Spontan düşük

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INTRODUCTION

About 15% of clinically recognized pregnancies result in spontaneous abortion (SAB) in the first trimester and the vast majority of these are the result of chromosome abnormalities (1-3). Studies of chromosomal constitutions of first trimester spontaneous abortions have revealed that at least 50% of abortions have an abnormal karyotype (4-6). There are several etiologies that might be associated with pregnancy losses including endocrine, immunological, environmental factors, infections, anatomic malformations and genetic abnormalities (7). The most common chromosomal abnormality observed within first trimester spontaneous abortions is single trisomies (8). Most clinically recognizable SABs occur between 7 and 11 weeks of gestation. Around 50% of spontaneous abortions are caused by *de novo* aneuploidy or polyploidy due to meiotic or post zygotic mitotic error, *de novo* unbalanced rearrangements, and unbalanced segregation products of the parental balanced translocations. Unbalanced chromosome constitution could affect placental development resulting in pregnancy failure (9,10). Carriers of balanced reciprocal translocations have a high reproductive risk of conceiving chromosomally abnormal embryos as a result of imbalances during meiosis, leading to recurrent abortions or birth of affected children (3,11). Chromosomal abnormalities can be detected by using conventional cytogenetic analysis. Evaluation of chromosomal abnormalities in pregnancy losses is important to understand the associations between chromosomal abnormalities and pregnancy losses and to provide proper genetic counseling to the parents. Histopathological evaluation of abortion material is also important because it may not be possible or reasonable to undertake complex cytogenetic studies of spontaneous abortion on a routine basis because of the expense and as it adds little to management.

We present here rare numerical and structural cytogenetic abnormalities detected in spontaneous abortion materials and the histopathological findings of rest material of abortion specimens in our study population.

MATERIAL and METHODS

In our eleven-year experience, we had a total number of 457 miscarriage cases. Conception products were provided to Department and Medical Biology and Genetics by the department of the Obstetrics and Gynecology of the Akdeniz University Hospital to perform conventional cytogenetic analysis and the rest material of miscarriage samples were sent to pathology department for histopathological evaluation. Gestational ages varied from 7 to 36 weeks. Detailed reproductive histories were obtained from the families including gestational age, maternal age and outcome of previous pregnancies. To avoid maternal blood contamination, miscarriage samples containing chorionic villi were washed three times in physiological serum saline solution. Fetal or fetus-derived extra-embryonic tissues were identified and dissected from surrounding maternal deciduas. Selected tissue samples were minced and cultivated in T-25 tissue culture flasks including 5 ml Amniopan and Amniogrow complete mediums (Biotech, Cytogen), 0.05 ml penicillin-streptomycin solution (Biological Industries) and 0.05 ml L-Glutamine (Biological Industries). Metaphase chromosomes were harvested and G banded by GTG banding following standard procedures. In each case, at least twenty metaphase plates were evaluated by light microscopy.

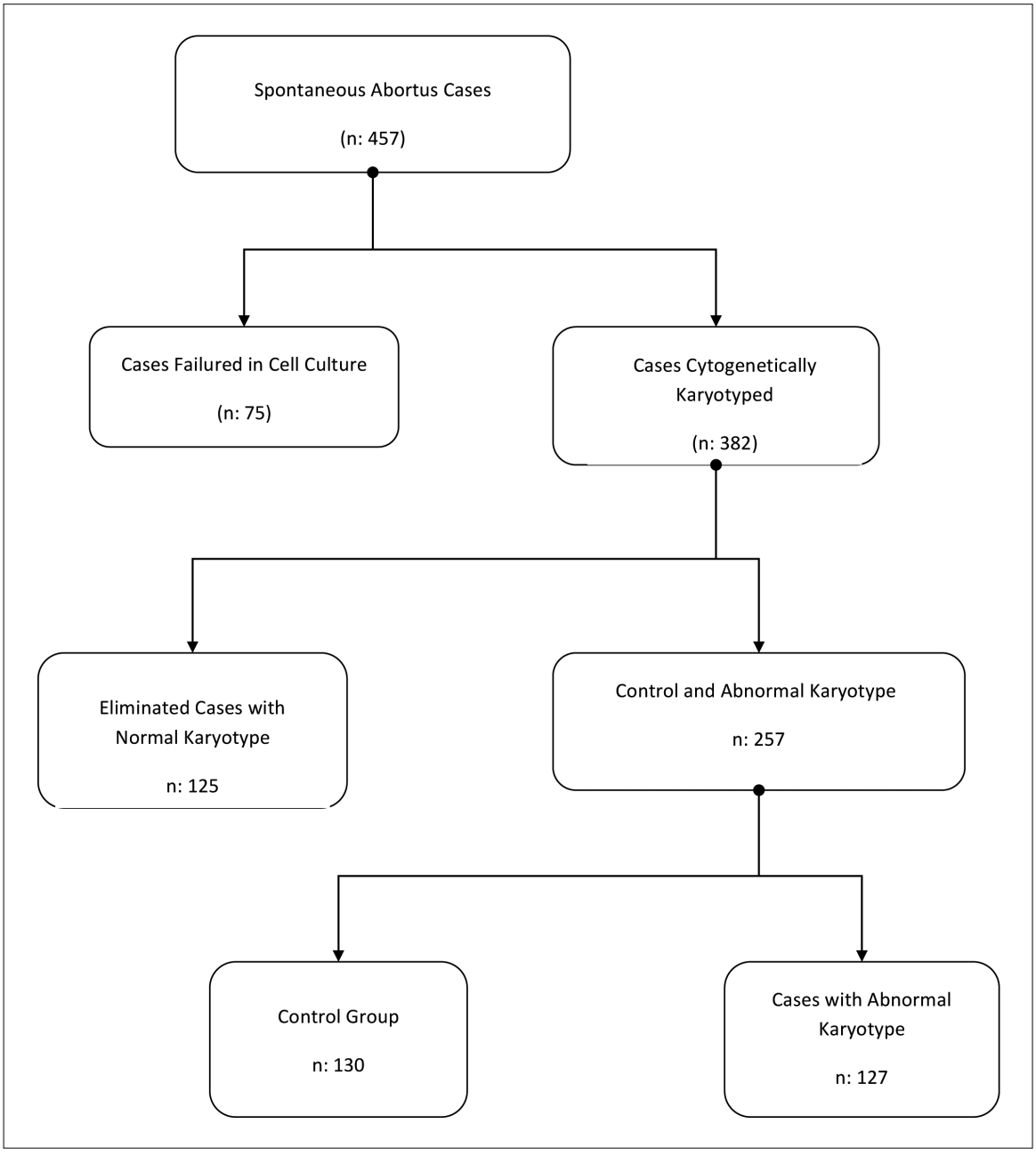
The rest miscarriage material of 76 of 457 cases was sent to the pathology department. Formalin-fixed and paraffin-embedded blocks were sectioned in 3μ thickness and stained with hematoxylin eosin. These hematoxylin eosin-stained sections were examined under the light microscope by an experienced pathologist.

Descriptive analyses were given as frequency, percentage, mean and Standard Deviation (SD). The Pearson Chi-square test was used for analysis of categorical data. For comparing the age difference between the chromosomal abnormality groups, the ANOVA (Analysis of Variance) test was used and after finding a significant difference the Bonferroni test was used for pair-wise comparison. ROC (Receiver Operating Characteristic) analysis was used for differentiating the chromosomally abnormal group from the normal group according to age. For statistical analyses, the SPSS 18.0 package software was used. $p < 0.05$ was accepted as statistically significant.

RESULTS

Among the 457 cases, 382 were successfully karyotyped (culture success rate: 83.58%) while the cell culture of 75 cases failed (culture failure rate: 16.42%). Cytogenetic abnormalities were detected in 127 of 382 cases (33.24%). We included 257 cases of 382 karyotyped cases in our study group. This study group consisted of 127 cases of the karyotypically abnormal group and 130 cases of the control group with normal karyotype (with ages and abortion rates similar to the karyotypically abnormal group). The design of our study is given in Table I. The mMean maternal age in the karyotypically abnormal cases was 31.11 years (Standard Deviation (SD) ± 5.49) and the mean gestational age was 9.44 weeks (SD ± 3.39).

Table I: Scheme of study design



Normal chromosomal constitution was detected in 255 cases (66.76%). The female/male sex ratio of the cases with a normal karyotype was 1.74 (162 females/93 males). The frequency of chromosomal abnormalities was higher in the group composed of cases with an age over 35 years than in younger cases (41.86% vs 30.67%). Chromosome abnormalities were more frequent in first trimester conceptions than second trimester conceptions (43.6% vs 7.77%). Turner syndrome and trisomy 16 were the most frequent abnormalities in the cases aged below 35 years of age, whereas trisomy 16 and trisomy 21 were the most frequent abnormalities in the cases aged over 35 years.

Autosomal trisomies were the predominant chromosomal abnormalities with a frequency of 48.8% of all chromosome abnormalities, followed by 45, X, (n: 21, 16.5%), triploidies including mosaics (n: 17, 13.38%), tetraploidies (n: 7 cases; 5.5%), double or triple trisomies of various chromosomes (n: 6 cases, 4.72%), and XY/XX/XXY mosaicism (n: 1 case,

0.78%). The most common trisomies were trisomy 16 (n: 16, 12.7%), 22 (n: 10, 7.8%), 21 (n: 7, 5.5%), 13 (n:4, 3.1%) and 10 (n:4, 3.1 %) (Table II). Among the triploid cases, 12 cases had 69, XXY (one of them had an associated anomaly) and 5 cases were 69, XXX karyotypes (3 of them had an associated anomaly). 4 cases with tetraploidy had the 92, XXYY karyotype whereas 3 cases had the 92, XXXX karyotype.

Karyotype descriptions of the cases with double trisomies were 48,XY,+7,+21, 48,XX,+16,+21, 48,XX,+13,+15, 48,XY,+2,+21. Trisomies of chromosomes 8, 16 and 21 were observed in one case. Also, trisomies of chromosomes 8, 12, 18, 20 were observed in another case.

Structural chromosomal abnormalities were infrequent in conception materials, and some rare structural abnormalities including *de novo* structural chromosome abnormalities such as derdic(13)(13;18)(p11.1;p11.1) leading to partial trisomy 18p11.1-pter, del(18)(p11.2-pter) and del(7)(q22q32) were found. Unbalanced products of the parental balanced Robertsonian translocations were observed in four cases. In case 10, a derivative chromosome from adjacent-1 segregation of the paternal balanced reciprocal translocation t (6; 13) (p23; q12) resulted in partial monosomy 6p23-pter and partial trisomy 13q12-qter regions. In case 11, *de novo* der (5) t(5;13) (p15; q12) resulted in partial monosomy 5p15-pter and partial trisomy 13q12-qter regions. Case 12 had interchange trisomy 7, resulting from 3:1 segregation of the familial reciprocal translocation t(5;7) (q13:p11.2). Co-existence of trisomy 16 and a familial transmitted balanced translocation t(1;5) (p22;q13) was observed in case 13 (Table III).

In cytogenetically abnormal groups; the mean age of the mothers was 28.57 (SD: ±4.79) years in the Turner group, 32.95 (SD: ± 5.01) in the trisomy group, 29, 29 (SD: ± 5.19) in the triploid and tetraploid group, and 28.42 (SD: ± 6.40) in the structural abnormalities group. The mean age of the mothers was highest in the trisomy group and the difference was significant (ANOVA $p< 0.001$). In the chromosomally abnormal group 8 of 21 Turner cases (38.1%), 37 of 70 trisomy cases (52.9%), 10 of triploidy-tetraploidy cases (41.7%), and 8 of 12 structural anomaly cases (66.7%) had a previous spontaneous abortion history. Statistically there was no significant difference between chromosomally abnormal cases (Chi-square, $p=0.332$) (Table IV). The mean age of the chromosomally normal 130 cases was 30.57 (SD: ± 5.31) years. The cut-off age for trisomies was 30 years (criterion values and coordinates of ROC curve are given in Figure 1).

Histopathological examination was performed for 72 cases and 53 cases (73.6%) had nonspecific changes (such as perivillous fibrin, hydropic villi), 11 cases (15.3%) were exaggerated placental site and 8 cases (11.1%) were incomplete mole hydatidiform. Exaggerated placental site cases cytogenetically consisted of 3 (27.3%) Turner syndrome, 1 (9.1%) trisomy 10, 1 (9.1%) trisomy 9, 2 (18.2%) tetraploidy and 2 (18.2%) rare trisomy cases. Partial mole hydatidiform cases cytogenetically consisted of 2 each of triploidy and structural anomaly, and one each of Turner syndrome, Trisomy 16, Trisomy 13 and double trisomy cases. There was no clinically significant relationship between histopathological diagnosis and cytogenetic anomaly.

Table II: Number and percentage of chromosomally abnormal group

Chromosomal abnormality	Number of the cases (n)	Percentage (%)
45,X	21	16.5
Trisomy 16	16	12.6
Trisomy 22	10	7.9
Trisomy 21	7	5.5
Trisomy 13	4	3.1
Trisomy 10	4	3.1
Other trisomies	22	17.4
Double/triple trisomy	7	5.5
Triploidy	17	13.4
Tetraploidy	7	5.5
Structural abnormalities	12	9.5
Total	**127**	**100**

Table III. Rare numerical and structural chromosomal abnormalities detected in spontaneous abortion materials

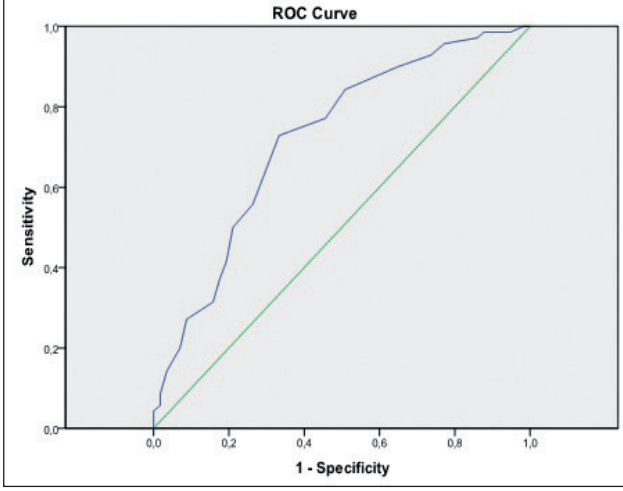
Case No	Karyotype	Maternal age (years)	Gestational age (weeks)	Obstetric history
1	47,XX,+15[14]/48,XX,+13,+15[4]/46,X,+5[2]	34	10	2 IE
2	48,XY,+2,+21[20]	33	8	-
3	48,XX,+16,+21[20]	37	6	-
4	48,XY,+7,+21[20]	38	7	-
5	48,XXY,+22[18]/46,XX[82]	36	8	-
6	46,XX [74]/49,XX,+8,+16,+21[24]	40	8	1 SA
7	50,XY,+8,+12,+18,+20[20]	31	7	-
8	45,XY,derdic(13)t(13;18)(p11.1;p11.1)dn[49]/ 46,XY,del(18)(p11.1p11.3),13p-[1]	32	22	-
9	46,XX,del(7)(q22q32)dn[20]/46,XX[20]	37	9	-
10	46, XX,der(6)t(6;13) (p23;q12)pat[20]	26	24	1 SA
11	46,XX,der(5)t(5;13)(p15;q12)dn[20]	28	8	2 IE
12	47,XY,+7,t(5;7)(q13;p11.2)[20]	25	8	-
13	47,XX,+16,t(1;5)(p22;q13)[20]	31	9	1 SA

Table IV: Mean age and abortus history of each karyotypically abnormal cases

Karyotype	Turner n (%)	Trisomy n (%)	Triploidy-Tetraploidy n (%)	Structural Abnormalities n (%)	p
Age*	28.57 (SD: ±4.79)	32.96 (SD: ±5.01)	29.29 (SD: ±5.19)	28.41 (SD: ±6.40	<0.001
Abortus history**					0.332
Absent	13 (61.9%)	33 (47.1%)	14 (58.3%)	4 (33.3%)	
Present	8 (38.1)	37 (52.9)	10 (41.7%)	8 (66.7%)	

* ANOVA, Bonferroni test; p_1(trisomy&turner) =0.005, p_2 (trisomy&triploidy-tetraploidy), p_3 (trisomy&structural abnormality)= 0.033,

** Pearson Chi-Square



ROC analysis for age	Performance Values
Cut off	age>30
Sensitivity	72.86%
Specificity	66.67%
PPV	72.9%
NPV	66.7%
OR (%95 CI)	5.37 (2.51-11.50)

Figure 1: ROC analysis of ages determining cut off age of trisomy
ROC: Receiver Operating Characteristic, **PPV:** Positive Predictive Value, **NPV:** Negative Predictive Value, **OR:** Odds Ratio, **CI:** Confidence Interval

DISCUSSION

The most frequent chromosomal abnormalities were Turner syndrome, triploidy and trisomy of chromosome 16 followed by trisomy of chromosomes 22 and 21 and tetraploidy in our study population while double trisomies and structural chromosomal abnormalities were rare. These findings were in concordance with the literature (7,12). We detected several rare double trisomies and structural chromosomal abnormalities in spontaneous abortion materials.

Double trisomy is a rare and could be detected in nearly 1.2% of the karyotyped spontaneous miscarriage materials with inter-institutional variability ranging between 0.80-2.64 percent (13,14). In our study, frequency of the double trisomy was 1.3% and in concordance with the literature. After the first report of a patient with Down-Klinefelter syndrome, more than 385 double trisomies have been reported (14). Double trisomies were more frequent in cases with advanced maternal age greater than 35 years. The mean age of our cases with double or multiple trisomies was 35.6 years. Autosomal chromosomes frequently observed in single trisomies such as chromosomes 8, 13,15,16,18 and 21 and sex chromosomes were also the most frequently involved chromosomes in double trisomies in spontaneous abortions. According to the recent reviews, double trisomy of chromosomes X&22 was the first while trisomy 2&21 and trisomy 7&21 were the second reported cases in the literature. Triple or multiple trisomies are also rare with a frequency of 0.05% in spontaneous abortion materials (15). This figure was 0.52% in our study population.

Trisomies are more frequent in advanced maternal age (16). The maternal age in the trisomy group was higher than the other chromosomally abnormal groups and the chromosomally normal group in our study as in the literature. The cut-off value for maternal age that increases the risk of trisomy was 30 years. The prenatal evaluation of a fetus where the maternal age is over 30 years should be more detailed because the estimated trisomy ratio is higher than the maternal age under 30 years. The most common trisomy is trisomy 21 in all pregnancy materials and live births (17,18). It is known that the most common trisomy in spontaneous abortion is trisomy 16 (19). In our study, trisomy 16 was the most common abnormality in the trisomy group. Our cases were in the missed abortion group and this may show that trisomy 21 usually does not cause missed abortion as much as trisomy 16 and 22, but we can not say the same thing for the other trisomy groups because they are actually rare in all pregnancy materials (13,18).

Reciprocal translocations are the most common structural chromosomal rearrangements in humans with an estimated incidence of 1:712 in newborns (20). In meiosis, the translocated chromosomes might be segregated in different segregation modes resulting in different chromosomal constitutions in gametes. Only alternate segregation results in normal or balanced gametes. Analysis of meiotic segregation modes by FISH in pre-implantation embryos from pre-implantation genetic diagnosis cycles showed that 2:2 segregation was the predominant segregation mode (59.1%) followed by, 3:1 segregation (22.0%), and 4:0 segregation (2.0%). In the 2:2 segregations, incidence of adjacent-1 (26.8%) was higher than that of alternate (22.4%) or adjacent-2 (6.1%) segregation (11). Most of the embryos with unbalanced genetic content were eliminated by spontaneous abortions and still births (21). In case 10, der (6) t (6;13) (p23;q12) had developed from adjacent-1 segregation of the paternal translocation and resulted in partial trisomy 13q13-qter region and concomitant monosomy of the 6p23-pter. However, in case 11, the der (5) t(5;13) (p15;q12) derivative chromosome was *de novo* and resulted in partial trisomy 13q12-qter and monosomy 5p15-pter, The rate of interchange trisomy resulting from 3:1 segregation was higher in balanced translocations with acrocentric chromosomes with a frequency of 9.5% than that without acrocentric chromosomes at 4.3% (11). To our knowledge, our case 12 is the first case with interchange trisomy of the chromosome 7 detected in spontaneous abortion material resulting from 3:1 segregation of the familial translocation t(5;7)(q13;p11.2).

The coexistence of a reciprocal translocation and chromosomal aneuploidy in an individual is also a rare event and several reciprocal translocation carrier Down syndrome patients have been reported (22-24). In some of the cases, an inter-chromosome effect between these two events has been suggested (25). To the best of our knowledge, this is the first report of the coexistence of trisomy 16 and familial transmitted balanced reciprocal translocation t(1;5) (p22; q13) detected in spontaneous abortion material.

Another rare case had interstitial deletion of the q22-q32 band interval of the chromosome 7 and was spontaneously aborted at 9 weeks gestation. Intermediate interstitial deletion of chromosome 7 spanning from q22 to q31 bands is rare and causes multiple congenital malformations in the affected children (26,27). Only a few rare prenatally detected cases presenting with fetal growth retardation and ultrasonographic findings such as cranial malformations, syndactyly in the lower extremities, renal pelvic dilatation,

elevated nuchal fold thickness and cardiac malformations have been reported (27-29).

The evaluation of spontaneously aborted specimens has changed greatly and histopathological evaluation is not enough for a better understanding of the pathogenesis of the defects in aborted specimens. It is well known that it is necessary to know the chromosomal constitution (19). In our study there was no significant relationship between histopathological diagnosis and chromosomal abnormality. The number of histopathologically evaluated cases are few and the literature and our findings suggest that histopathological evaluations provide limited data about the pathogenesis of the spontaneous abortions (19).

In conclusion, detection of chromosomal abnormalities in spontaneous abortion materials is very important to clarify the causes of pregnancy losses. Detection of structural chromosomal abnormalities in the cases and their carrier parents can provide proper genetic counseling to these families. These families can be directed towards pre-implantation genetic diagnosis to prevent further pregnancies with complications.

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