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Balanced Chromosomal Translocations of Parents in Relation to Spontaneous Abortions

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Abstract

The most significant complication of pregnancy is recurrent miscarriage. Numerous factors have been described as associations with recurrent wastage such as: uterine abnormalities, immunological factors, endocrinologic imbalance and chromosomal defects. Cytogenetic evaluation of couples with recurrent pregnancy losses is performed on the basis of G-banding technique only after other possible etiologic factors have been excluded. The purpose of this study was to determine the frequency of balanced translocation in 153 couples who were introduced to the medical genetic laboratory by gynecologists. The prevalence of balanced chromosomal translocation was 9.8% among which 3.3% appeared with Robertsonian translocation and the remaining (6.5%) was evident with different type of balanced chromosomal rearrangement. The yield of positive results for balanced chromosomal translocation carrier was lower than that expected. With regard to the low incidence of balanced translocation in normal population and high cost and time-consumption of chromosomal analysis cytogenetic investigation should be suggested only in couples with recurrent spontaneous abortions when clinical data fail to clarify the cause

Keywords: Recurrent Spontaneous Abortion (RSA); Karyotype; Balanced Translocation

Introduction

The most common complication of pregnancy is recurrent spontaneous abortion (RSA), which referred to termination of pregnancy prior to 20 weeks of gestational age, with a prevalence of 10% to 15% in all pregnancies [12,20]. After either two or three spontaneous pregnancy losses, couples are labeled as recurrent aborters [12,20,21]. Numerous factors have been described as associations with spontaneous abortions such as: uterine abnormalities, immunological factors, endocrinologic imbalance, genital infectious disease and specific genetic disorders [16].chromosomal defects such as aneuploidy account for approximately 50% of sporadic fetal losses prior to 15 weeks [21].

For several years, the question has been asked, "Why

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spontaneous abortion is so common in human?" not until 1960s when chromosome analysis became possible did the answer to this question become evident. Chromosome analysis of the products of conception revealed that as many as 50 to 60% of all spontaneous abortions are caused by lethal chromosomal abnormalities of the concepts [33].

This study was supported by other reports of chromosomal findings in the causation of abortion, all of which were consisted in identifying a large portion of chromosomally abnormal abortuses [3,33]. The most cases of aneuploidy arise from non-disjunction at meiosis in one parent leading to abnormal gametes. In some species of vertebrates and invertebrates, gametogenesis is the step during which selection occurs. In many species if there is a chromosomally abnormal egg or sperm, fertilization will not occur. Human reproduction is very inefficient in the selection process during gametogenesis, a chromosomally abnormal egg or sperm can still fertilize. On the other hand, the human reproductive process is exceedingly efficient in selecting out the chromosomal abnormalities after fertilization, with that selection process being spontaneous abortion. Clinicians should convey to patients that random abortion is a common human phenomenon and nothing more than natural selection process [21].

Studies of couples with RSA have demonstrated that in approximately 2-3% of these couples, one of the partners is a balanced translocation carrier who has experienced 2 or more pregnancy losses [21]. It is accepted that a balanced translocation carried by one of the partners can cause repeated spontaneous abortions [9-11,17,18,23,25,29,30].

The logical question that one might ask is, whether any couple who are going to get married should undergo chromosomal investigation in order to identify balanced translocations. The purpose of this study was to determine the frequency of balanced translocation in 153 couples who were introduced to the medical genetic laboratory by gynecologists, regarding the number of abortions, as well as maternal age, gestational age, consanguinity marriage. Other factors have been excluded.

Material and Method

One hundred and fifty three couples with the history of spontaneous abortions were assessed for cyto-genetic study, searching for chromosomally balanced translocations.

0.5 ml peripheral whole blood samples were collected into sterile heparinized tube and were cultured for 3 days in RPMI 1640 medium, supplemented with 20% of fetal calf serum, Penicillin and Streptomycin. The lymphocytes were stimulated by phytohemaglutinin. The cells were harvested by adding colchicine 2 h before the slide preparation.

The cells were exposed to hypotonic solution (0.05 M KCl) and then treated with trypsin-giemsa banding following fixation with three part ethanol and one part glacial acetic acid. 30-40 metaphase cells were analyzed microscopically for their chromosome constitution. Each chromosome was analysed for its presence and pairing 46 human chromosomes in well defined order, was performed based on characteristic band. The 23 pairs differ in the length of the arms and each show unique banding pattern (Plate 1).

Results

Maternal Age

Figure 1 shows that the youngest and the oldest women were 16 and 38 years of age, respectively. The median age was 25.3±4.63.

Consanguineous Marriage

In this study 73 couples (47.7%) had consanguinity marriage and the remaining (52.3%) was non-consanguineous mating. The results were outlined in Figure 2, and indicated that the consanguinity marriage was not an important etiologic factor in recurrent miscarriage.

The Number of Abortions

Four hundred and sixty three abortuses cases were emerged from the collected data. Among the 153 couples 3 mothers with 28, 38, 30 years of age had 11, 10, 9 miscarriage, respectively, but the higher rate of abortions were evident with the group of 3 pregnancy losses (Fig. 3).

Gestational Age

Of the 463 abortus fetuses, 393 cases (85%) were evident at first trimester, 67 cases (14.5%) were seen at second trimester and third cases (0.5%) were accounted at third trimester (Fig. 4). These results strongly suggest higher incidence of spontaneous abortions in the less developed stage of gestation.

Frequency of Balanced Translocation Carriers

Parental karyotypes from 153 couples who were suffering from recurrent abortions were performed in order to confirm or exclude the presence of balanced chromosomal translocation carrier status. Carrier state of balanced translocation was found in only 15 partners (9.8%). Among them 5 individuals (3.3%) appeared with Robertsonian translocation and the remaining 10

Plate 1. GTG banding. Robertsonian balanced translocation 46XY,t(13q;14q).

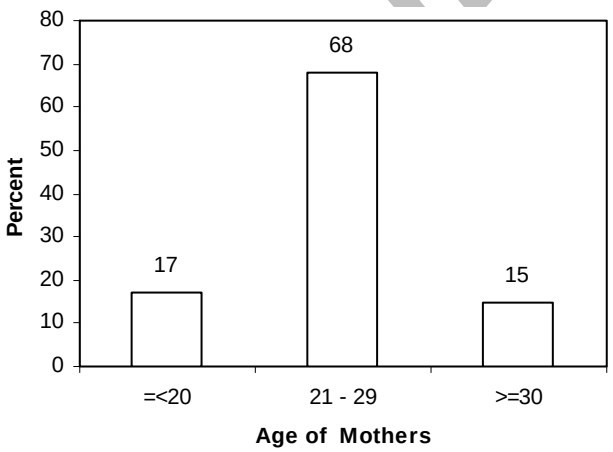

Figure 1. Distribution of Maternal age.

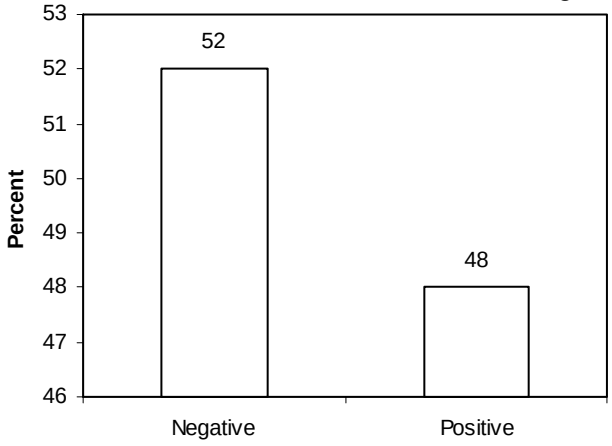

Figure 2. Prevalence of consanguinous marriage.

partners (6.5%) emerged with different type of balanced chromosomal rearrangement. The results were summarized in Table 1 and Figure 5. The distribution of carriers of balanced translocation were almost the same in either sex (8 men and 7 women) (Table 1).

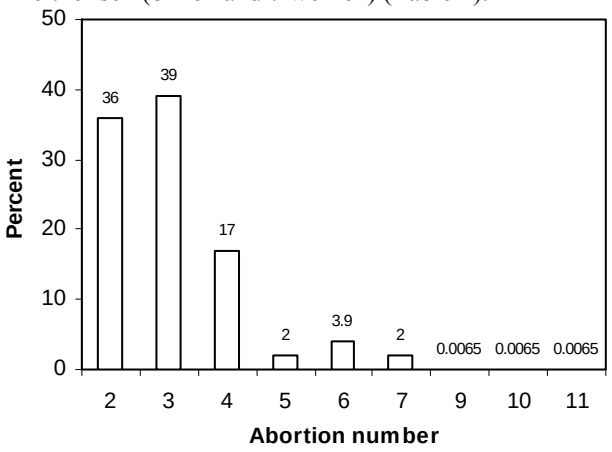

Figure 3. Distribution of abortion number.

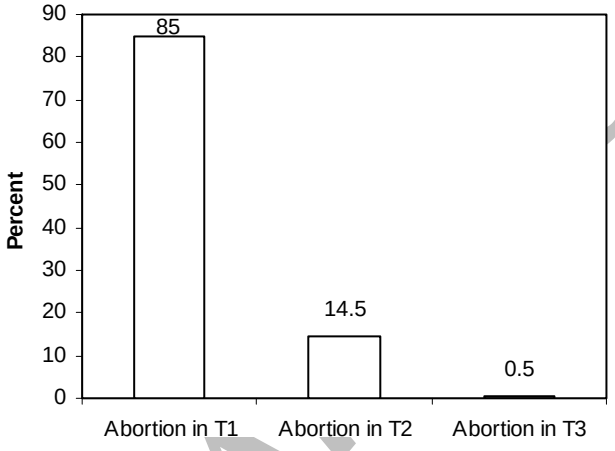

Figure 4. Distribution of abortion number in each Trimester.

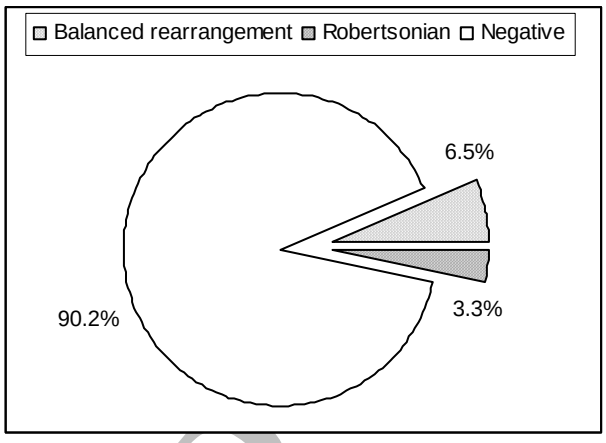

Figure 5. Prevalence of Balanced Translocations.

Discussion

The distribution of maternal age did not play an important role in the incidence of recurrent miscarriage (Fig. 1). This result is in disagreement with the results of Stephenson *et al.* and Cramer wise [5,28] who claimed that women under 36 years of age have higher frequency of recurrent euploid miscarriage. On the other hand Smiths and colleagues suggested that no increased odds ratios were found for young or advanced maternal age, or for short preceding birth interval [27], such discrepancy results might be related to different distribution of maternal age in other countries.

No significant correlation was found in the rate of spontaneous abortions between consanguineous and non-consanguineous couples (Fig. 2). These results are comparable with the results of study of al Husain and al Bunyan and also khoury and Massad who have shown that, total parental losses were essentially the same among consanguineous (8.3%) and non consanguineous couples (8.9%), as well as the rate of neonatal death. Total postnatal fatality rate was 2.7% for consanguineous and 2.2% for non consanguineous group [1,14].Therefore consanguineous marriage is not an important etiologic factor in relation to recurrent miscarriage.

Among the 153 couples 3 mothers with 28, 38, 30 years of age had 11, 10, 9 miscarriage respectively. These data indicate that the rate of pregnancy losses increases with the increaseed risk of subsequent abortion. These results were in favor of the results of Leridon who concluded that if there has been no previous abortion, the risk is generally less than 150/1000 but if there has been even one previous abortion it becomes practically double [15]. Such results were supported by Cramer & Wise who concluded that

even a single pregnancy loss, increases the risk for subsequent abortion [5].

The frequency of abortion was more prominent in first trimester. These results are comparable with the results of Zhou and colleagues who claimed that, a history of one or more first trimester abortion was related to an increased risk of abortion for the following pregnancy [34]. These results were also confirmed by the study of Simpson who observed that most clinically recognized pregnancy losses occur prior to 8-9 weeks of gestational age [24].

Cytogenetic evaluation is performed only after exclusion of other possible etiologic factors. The presence of balanced chromosomal translocations was evident in only 15 partners (9.8%) of 153 couples who studied. These results were comparable with the results of Makino *et al.* who observed that among the 639 couples, 8.6% of partners showed chromosomal balanced carrier [17]. Similar work by Mameli and colleagues indicated an incidence of 8% for balanced translocation in 100 examined individuals, which is near to the mode (about 9%) observed in previous studies [18]. Tsui *et al.* claimed that the overall incidence of chromosomal anomaly was 51 (9.92%) out of 514 individuals [31].

Table 1. The frequencies of balanced rearrangements and Robertsonian translocations

Balanced Rearrangements (n=10) (6.5%)		**Robertsonian Translocations (n=5) (3.3%)**	
Paternal (n=5)	Maternal (n=5)	Paternal (n=3)	Maternal (n=2)
46XY,t(17;21)(p13.3;p13)	46XX,t(2;3)(p25.3;q29)	45XY,−13,+t(13q,14q)	45XX,−13,+t(13q,21q)
46XY,t(7;9)(q36.3;q34.3)	46XX,t(16;3)(q24.3;q29)	46XY/45XY,−21,+t(21q,21q)	45XX,−21,+t(21q,21q)
46XY,t(6;22)(q27;p13)	46XX,t(17;9)(p13.3;q34.3)	46XY/45xy,−14,+t(14q,21q)	
46XY,t(18;21)(p11.32;q22.3)	46XX,t(5;7)(q35.3;q36.3)		
46XY/46XY,t(2;17)(q37.3;p13.3)	46XX,t(6;19)(q27;p13.3)		

In this investigation the karyotype alterations (balanced translocation) were significantly more common in women with 4 or more spontaneous abortions, therefore balanced translocation carriers have a higher risk of recurrent miscarriage in contrast to the general population. These findings are in agreement with the results of similar works which had been done by other investigators who stated that couples who have had multiple miscarriages are at risk for carrying a balanced translocation, since these carriers may produce unbalanced gametes [31,22].

Although it is believed that the detection of chromosomal translocation carrier state may be a prognostic value for couples who are suffering from recurrent miscarriage, nevertheless most of the time spontaneous abortion is a random event and represents the natural selection process [21].

However, with regard to the low incidence of balanced translocation in normal population and high cost and time-consumption of chromosomal analysis cytogenetic investigation should be suggested only in couples with recurrent spontaneous abortions when clinical data fail to clarify the cause [18].

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