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Structural chromosomal abnormalities in couples with recurrent abortion in Egypt

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Background/aim: To evaluate the incidence of chromosomal abnormalities in couples who experience recurrent abortion and identify additional factors that may be predictive of abortion, such as parental age and unfavorable obstetric or abnormal semen analysis.

Materials and methods: The present study examined 125 couples who had experienced recurrent abortion. All subjects provided a detailed personal medical history and ancestral history and underwent a physical examination. Women in the study group underwent biochemical testing and pelvic ultrasound examinations, and men underwent a semen analysis.

Results: Among the 125 couples tested, 8 couples (6.4%) displayed a balanced translocation, among which 7 (5.6%) showed a reciprocal translocation and 1 (0.8%) showed a Robertsonian translocation. All carriers of these translocations were aged <35 years. A significant proportion of carriers reported a poor obstetric history and a past fetal malformation. All male carriers had a normal semen analysis.

Conclusion: Couples who experience ≥2 pregnancy losses of unknown origin should undergo a cytogenetic analysis, and findings showing a chromosomal abnormality in either parent must be followed by genetic counseling.

Key words: Recurrent abortion, chromosomal abnormality, balanced carrier

1. Introduction

Abortion is the most common complication of pregnancy and affects ~15% of all clinically recognized pregnancies (1). Abortion is defined as the spontaneous loss of pregnancy before the fetus reaches viability, and therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation (2). Among all factors causing abortion, the only undisputed causes of recurrent pregnancy loss are genetic, anatomic, and immunologic factors (3). Although alloimmune pathologies, inherited thrombophilias, endocrinopathies, infections, and environmental exposure have been implicated in pregnancy loss, they are not established causes of recurrent abortion (3).

Most women with a history of recurrent abortion receive care from a gynecologist, who may have detected gynecological causes and excluded most serious maternal disorders (4).

In 50%–70% of miscarriages, a chromosome abnormality is identified in the products of conception (POC). This abnormality may derive from a balanced carrier parent or may result from a recurrent numerical abnormality, which is usually not inherited, but may cause recurrent abortion (5,6). Although many structural rearrangements occur de novo, the majority appear to be familial; thus, a cytogenetic analysis of the couple is important to exclude the possibility of structural rearrangements. Additionally, genetic counseling is indicated for couples who have experienced ≥2 losses. Because most balanced rearrangement carriers produce both balanced and unbalanced gametes, a combination of normal and abnormal conceptions is frequently seen in such couples. Rearrangements are more likely to be found in couples who have experienced both miscarriages and live births rather than in those who have only experienced a miscarriage (7). Chromosomal rearrangements may not only be lethal to the developing embryo or fetus, but may also cause significant congenital anomalies and mental retardation in an infant, if the pregnancy continues to term (8).

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2. Materials and methods

2.1. Subjects

This descriptive study enrolled 125 Egyptian couples who had experienced recurrent abortion and had visited the outpatient clinic of the Medical Genetic Center, Ain-Shams University, Cairo. Patients either visited the clinic on their own accord or were referred by an obstetrician or family practitioner for diagnosis, management, and counseling.

2.2. Methods

Written informed consent was obtained from each subject prior to enrollment in this study. Following enrollment, a detailed medical history was obtained from each subject, which included a perinatal history, a history of close relatives who had recurrent miscarriages or had experienced a stillbirth/neonatal death, and a history of children born with birth defects, dysmorphic features, or inherited disorders. The medical history also included birth of a child who later showed failure to thrive. A family pedigree was constructed for each subject and genetic testing showed that all subjects had a conventional karyotype. Female subjects underwent biochemical testing for prothrombin time, partial thromboplastin time, and thyroid evaluation, and also underwent a pelvic-abdominal ultrasound. Males underwent a complete semen analysis.

2.3. Statistical analysis

Computerized statistical analysis of data was performed using SPSS 16. The chi-square and Student t-test were used when appropriate. $P < 0.05$ was considered significant, and $P < 0.01$ was considered highly significant.

3. Results

A total of 125 couples (250 subjects) with a history of recurrent abortion were enrolled and examined in this study. The age range of women was 18–42 years (mean: 26 ± 4.9 SD) and the age range of men was 22–54 years (mean: 32.5 ± 5.8 SD). Conventional cytogenetic analysis of at least 20 metaphases showed that among the 125 couples (250 subjects), 8 couples (8 subjects, 6.4%; 5 women and 3 men) displayed a balanced structural chromosomal abnormality, as shown in Table 1. These abnormalities included 7 (5.6%) reciprocal translocations and 1 (0.8%) Robertsonian translocation, as shown in Table 2. While abortions occurred more frequently among couples with a carrier (Table 3), the mean number of abortions in carrier and noncarrier couples was not significantly different (Table 4). All carriers of translocations (women

Table 1. Sex distribution of abnormal karyotype.

Sex	Abnormal karyotype (n = 8)		Total (%)	P
	Rcp (%)	Rob (%)		
Male	3/7 (42.9%)	-	3 (37.5)	0.41
Females	4/7 (57.1%)	1/1 (100%)	5 (62.5)	
Total	7	1	8	

Rcp: reciprocal translocation, Rob: Robertsonian translocation, $P > 0.05$.

Table 2. Structural chromosomal abnormalities in affected couples.

Type	Couple no.	Karyotype	Age	Sex
	5	46,XY,t(3;8)(p25;p11)	30	M
	41	46,XX,t(4;6)(p24;q25)	22	F
	45	46,XX,der(9;17)(p24;q25.1)	24	F
Rcp 7	48	46,XY,t(11;22)(q23;q13)	27	M
	53	46,XY,t(9;21)(p21;q22)	31	M
	81	46,XX,t(7;21)(p11;p11)	22	F
	117	46,XX,t(6;12)(q21;q23)	31	F
Rob 1	19	45,XX,t(13;14)(q10;q10)	25	F

Rcp: reciprocal translocation, Rob: Robertsonian translocation.

Table 3. Number of abortions in couples.

Number of abortions	Couples (%)	Carriers
2	23 (18.4%)	1/23 (4.3%)
3	33 (26.4%)	2/33 (6%)
4	24 (19.2%)	2/24 (8.3%)
≥5	45 (36%)	3/45 (13%)

Table 4. Mean number of abortions in cases with normal and abnormal karyotype.

	Mean	SD	P
Noncarrier = 117	4.4	2.5	0.8
Carrier = 8	4.3	2.1	

P > 0.05 (not significant).

and men) were aged ≤35 years. A higher percentage of couples where one partner was a translocation carrier had poor obstetric history (37.5%) compared to couples where both partners had a normal karyotype (28.2%). Carrier couples also experienced a higher percentage of infant deaths (12.5% vs. 1.7%, P = 0.05). Additionally, as shown in Table 5, carrier couples experienced a higher rate of fetal malformation compared to couples with a normal karyotype (25% vs. 5.1%, P < 0.05). Semen analyses showed that 3 of 125 men had abnormal-appearing sperm or sperm with defective motility; however, all men had normal karyotypes.

Table 5. Comparison between carrier and noncarrier couples as regards poor obstetric history.

Obstetric history	Noncarrier n = 117 (%)	Carrier n = 8 (%)	P
ND	13 (11.1)	1 (12.5)	0.9
SB	15 (12.8)	-	0.2
FM	6 (5.1)	2 (25)	0.02*
ID	2(1.7)	1 (12.5)	0.05*
IUFD	5 (4.3)	-	0.5

ND: Neonatal death, SB: stillbirth, FM: fetal malformation, ID: infant death, IUFD: intrauterine fetal death, * significant at P ≤ 0.05.

Table 6. Worldwide studies of chromosomal rearrangements observed in couples with recurrent miscarriages (11–14).

	No. of studied couples	Structural aberration			Others	Total (%)
		Rob	Rcp	Inv		
Belgium (Ghent)	96	2	6	-	-	8 (8.3%)
France (Paris)	315	5	7	4	-	16 (5.1%)
Italy (Padua)	145	4	4	4	2	14 (9.6%)
Japan	639	9	19	1	-	29 (4.5%)
Netherlands (Leiden)	67	3	5	1	-	9 (13.4%)
Netherlands (Rotterdam)	148	3	6	3	2	14 (9.6%)
Saudi Arabia (Riyadh)	193	1	10	2	-	13 (6.7%)
Oman	380	3	18		7	28 (5.5%)

Rcp: reciprocal translocation, Rob: Robertsonian translocation, Inv: inversion.

4. Discussion

In 3%–6% of couples with recurrent pregnancy loss, one partner has a genetically balanced structural chromosome rearrangement. Such balanced translocations account for the largest percentage of karyotypic abnormalities (9). The clinical consequences of such abnormal gametes include repeated abortions, stillbirth, and birth of malformed children and mentally handicapped children (10).

The incidence of chromosomal abnormalities among the participant couples was 6.4% (3.2% of individuals), which was similar to the incidence reported in other studies conducted in the Middle East. These observed an incidence of 6.8% and 6.7% in Saudi Arabia and Oman, respectively (11,12). Studies conducted worldwide have shown considerable differences in the frequency of chromosomal aberrations, which have ranged from 2.76% to 18.75% (Table 6) (11–14). Variations in sample size, evaluation criteria for couples, and techniques of cytogenetic analysis have all contributed to these differences among studies (15). It is also possible that the incidence of chromosomal aberrations may vary across different populations (12).

In general, the incidence of chromosomal abnormalities is higher in women than in men (11,16), possibly because abnormalities compatible with fertility in females may be associated with sterility in males (9,16,17).

In our study (8 cases), 5 of 8 women (62.5%) and 3 of 8 men (37.5%) had a chromosomal abnormality. However, there was no significant difference between men and women regarding who carried the abnormality ($P > 0.05$). This finding was similar to results from other studies, which noted that a paternal chromosomal abnormality may contribute not only to infertility but also to the pathogenesis of miscarriages (12,18,19).

Among the structural chromosomal abnormalities found in the present study, the largest group consisted of reciprocal translocations in 7 of 8 cases (87.5%; 4 females and 3 males), involving chromosomes 6, 7, 8, 9, 11, 12, 17, 21, and 22 (Table 2). The Robertsonian translocation was found in only 1 of 8 cases (12.5%), and that was in a woman with t(13q;14q). This finding was in accordance with other studies in which reciprocal translocations were the most common type of mutation, followed by the Robertsonian translocation, which was present only in females (11,16).

In our study, all translocation carriers (men and women) were aged <35 years. In accordance with our study, Franssen et al. reported that the expecting carrier status decreased when recurrent abortion occurred at an advanced maternal age, whereas sporadic miscarriage rates increased dramatically in women in their late thirties and over (9). Recurrent miscarriages that occur in older age groups (maternal age of ≥35 years and paternal age of >40 years) are likely due to age-related chromosome abnormalities (nondisjunctions), mainly trisomies, rather than to structural translocation (20–23).

The percentage of abortions among the participant couples increased with the percentage of individuals who carried a chromosomal abnormality. The highest percentage of individuals with a translocation (13%) was found in the group which had experienced ≥5 abortions. However, a comparison of the mean number of abortions in healthy couples and couples who carried a translocation failed to show a statistically significant difference (Table 4), which was consistent with the results of other studies that reported no increase in the rate of chromosomal anomalies relative to the number of abortions (16,24).

In this study, couples where one partner carried a translocation had a significantly ($P < 0.05$) higher rate of child malformation (25%) compared to healthy couples (5.1%) (Table 5). Pedigree analysis may help us to predict the probability of carrier couples. When a parent carries a balanced chromosome rearrangement, the chance of having a malformed live birth with an unbalanced chromosome complement is about 1% to 15% (8).

In men, somatic chromosomal abnormalities often lead to low sperm concentration, abnormal sperm, and male infertility, resulting in a reduced likelihood of pregnancy and increased likelihood of miscarriage (25). In this study, semen abnormalities were detected in 2.4% of men, all of whom had a normal karyotype. Additionally, all carrier men had normal semen parameters regarding sperm numbers, motility, and morphology. This was in agreement with other studies that showed that reciprocal translocations may cause rheumatoid arthritis but do not affect sperm production and activity/fertility parameters. Yet, Robertsonian translocations, which are compatible with fertility in women, may be associated with sterility in men (26–28). Sperm quality is often associated with the embryo's ability to progress to implantation. Paternally expressed genes modulate the proliferation and invasiveness of trophoblast cells and subsequent placental proliferation (29,30). Furthermore, evidence suggests that abnormalities in sperm DNA may affect embryo development and possibly increase the risk of miscarriage (31).

In conclusion, chromosomal rearrangements in carrier parents are among the most common causes of recurrent miscarriage. The present study showed that the incidence and distribution of chromosomal abnormalities among Egyptian couples with repeated fetal loss is comparable to that reported worldwide, especially in the Middle East. Physicians in charge of reproductive clinics should be aware of cases of cytogenetically abnormal pregnancies with repeated prior pregnancy loss. There was no apparent increase in the rate of chromosomal abnormalities in relation to the number of miscarriages and maternal age. A higher incidence of balanced translocation carriers was observed among younger parents, while in older parents recurrent abortion was usually due to meiotic

nondisjunction events. Couples where one partner carried a translocation usually had a poor obstetric history with a high rate of fetal malformations; therefore, the construction of a family ancestral and medical history was important to help them form realistic expectations concerning pregnancy outcome. A normal semen analysis does not rule out the possibility of a man having chromosomal abnormality; additionally, an abnormal semen test does not necessarily indicate an abnormal karyotype. A POC analysis conducted on tissue from an aborted fetus allows an informed prognosis of a future pregnancy. Additionally, cytogenetic analysis should be part of the evaluation of couples who have experienced ≥2 pregnancy losses due to unknown causes. Detection of a structural chromosomal abnormality in either parent must be followed by genetic counseling to allow parents to make an informed reproductive decision regarding subsequent pregnancies.

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