Chromosomal Aberrations in 224 Couples with Recurrent Pregnancy Loss

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Background: Recurrent pregnancy loss (RPL) is a major reproductive health issue, affecting 2%–5% of couples. Genetic factors, mainly chromosomal abnormalities, are the most common cause of early miscarriage accounting for 50%–60% of first trimester abortion. Aim: To estimate the prevalence and nature of chromosomal anomalies in couples with recurrent miscarriage. Patients and Methods: This study included 224 couples with a history of 2 or more abortions. Both partners were karyotyped as part of the primary investigation. Cytogenetic analysis was carried out using the standard method. Results: A total of 224 couples with a history of two or more recurrent abortions were enrolled in this study. Chromosomal abnormalities were detected in 26 couples (11.6%) and 28 individuals (6.25%). We found a structural chromosome abnormality in 17/28 patients (60.7%); 12 patients had a reciprocal translocation (42.9%) including one patient with an additional inversion of the Y chromosome, 4 (14.3%) had a Robertsonian translocation, and one patient (3.6%) carried a paracentric inversion of chromosome 2. Numerical chromosome aberrations were detected in 5 patients; three patients (10.7%) with sex chromosome abnormalities and two (7.1%) with a marker chromosome. Six patients (21.4%) showed a heteromorphic variant involving chromosome 9. Conclusion: The prevalence of chromosomal abnormalities in couples with RPL is within the range reported worldwide. Cytogenetic analysis should become an integral part of the investigations of couples with at least two pregnancy losses of undetermined etiology.

Keywords: Chromosomal abnormalities, cytogenetic analysis, recurrent pregnancy loss

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most important cause of miscarriage before 10 weeks gestation. The majority of human aneuploidies arise from errors in the first meiotic division of the oocyte.

RPL may occur if one partner carries a balanced reciprocal translocation, a robertsonian translocation, or an inversion. A reciprocal translocation involves the exchange of two-terminal segments of nonhomologous chromosomes, a robertsonian translocation results from the centric fusion of two acrocentric chromosomes, while an inversion involves a change in the orientation of a DNA segment within a chromosome. Due to abnormal segregation at meiosis, carriers of balanced translocations are at an increased risk not only for RPL, but also for the birth of a disabled child. Inversions suppress recombination within the inverted sequence in heterozygotes, which can directly disrupt coding sequences or alter gene expression of adjacent genes or predispose to other rearrangements, mainly copy number alterations and translocations. Balanced inversion carriers experience decreased fertility, higher rates of miscarriage, and have children with multiple congenital anomalies.

Therefore, identifying couples with a chromosomal anomaly would help in providing proper genetic counseling, including prenatal and preimplantation genetic diagnosis (PGD). The study was carried out with the aim of estimating the prevalence and nature of chromosomal anomalies in couples with recurrent miscarriage.

**Patients and Methods**

The research was reviewed and approved by the Ethics Committee (IORG#: IORG0008812). The minimal sample size was calculated based on a study aimed to detect chromosome abnormalities in couples with RPL and to compare our results with those reported previously. Ghazaey et al. (2015) reported that about 11.7% of couples were carriers of chromosomal aberrations. Based on their study, and assuming that 400,000 couples had a history of RPL, 15% out of them had chromosomal aberrations, a minimum sample size of 196 couples with a history of RPL is the enough required sample for estimation of prevalence (cross-sectional) study (Killeen, 2005) (Daniel, 1991), with a significance level of 95% (accepted alpha error of 0.05) and ±5% confidence interval (5% Absolute precision). Sample size per group does not need to be increased to control for attrition bias (Pannucci & Wilkins, 2010). This study included 224 couples (448 individuals) with a history of 2 or more abortions, recruited from Human Genetics clinic from November 2015 to October 2019. Informed consents were obtained from all participants after explanation of the purpose of the study. Couples where the female partner reported history of systemic diseases or thromboembolic disorders were excluded from the study. Both partners were karyotyped as part of the primary investigation. Cytogenetic analysis was performed on peripheral blood lymphocytes incubated for 72 h in media enriched with fetal bovine serum and phytohemagglutinin. Twenty-five metaphases were analyzed following Giemsa trypsin banding at 550 band level. Mosaicism was confirmed if a second cell line was present in more than 5% of cells scored. C-banding was used to confirm the presence of inversion or additional heterochromatin in cases of suspected chromosomal heteromorph.

**Statistical analysis of the data**

The sample size was calculated according to Charan and Biswas (2013). Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Chi-square test for categorical variables, to compare between different groups Fisher’s Exact correction for chi-square when more than 20% of the cells have expected count less than 5. Student t-test for normally distributed quantitative variables, to compare between two studied groups. F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups.

**Results**

A total of 224 couples with a history of two or more recurrent abortions were enrolled in this study. The mean age of female partners was 28.3 years (range: 16–49 years), whereas the mean age of male partners was 34 years (range: 23–65 years). The number of previous abortions varied from 2 to 16 abortions/couple with a mean of 3.9. We observed no increase in number of abortions with advanced maternal age (P = 0.477), as shown in Table 1. Consanguineous mating was observed in 123 couples (54.9%). The frequency was higher among couples with normal karyotypes (56.1%) compared to couples with chromosomal aberrations (46.2%), the difference was not statistically significant (P = 0.34). We detected chromosomal abnormalities in 26 couples (11.6%) and 28 individuals (6.25%). We found a structural chromosome abnormality in
17/28 patients (60.7%); 12 patients had a reciprocal translocation (42.9%) including one patient with an additional inversion of the Y chromosome, 4 (14.3%) had a Robertsonian translocation, and one patient (3.6%) carried a paracentric inversion of chromosome 2. Numerical chromosome aberrations...
Chromosomal aberrations were more frequent in females (16 patients [7.14%]) compared to males (12 patients [5.35%]), the difference was not statistically significant ($P = 0.435$).

RPL alone as a presenting feature was more common among couples with chromosomal abnormalities (65.4%) than among couples with a normal karyotype (51.5%), however, this difference was not statistically significant ($P = 0.183$). The frequency of the presence

| Number of abortion | Total studied couples ($n=224$), $n$ (%) | Couples with chromosomal aberrations ($n=26$), $n$ (%) | Couples with normal chromosome complement ($n=198$), $n$ (%) | $\chi^2$ | $P$ |
|-------------------|-------------------------------------------|-----------------------------------------------|-------------------------------------------------|--------|----|
| 2                 | 76 (33.9)                                  | 5 (19.2)                                      | 71 (35.9)                                        | 2.845  | 0.241|
| 3                 | 48 (21.4)                                  | 7 (26.9)                                      | 41 (20.7)                                        |        |     |
| $\geq$4           | 100 (44.6)                                 | 14 (53.8)                                     | 86 (43.4)                                        |        |     |

$\chi^2$=Chi square test, $P$=$P$ value for comparing between the studied groups

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were detected in five patients; three patients (10.7%) with sex chromosome abnormalities and two (7.1%) with a marker chromosome. Six patients (21.4%) showed a heteromorphic variant involving chromosome 9 [Table 2]. Identical chromosomal anomalies were present in both partners in 2 couples; one couple showed a balanced translocation between chromosomes 11 and 22 while the second carried an inversion of the heterochromatic region of chromosome 9. Both couples were consanguineous.

| Karyotypes                        | Reproductive outcome | Age maternal/paternal (years) |
|-----------------------------------|----------------------|-------------------------------|
| mos 47,XXX[3]/46,XX [47]          | 3 abortions          | 26/32                         |
| mos 45,X [23]/46,XX[27]           | 4 abortions          | 27/28                         |
| 47,XX,+mar                        | 4 abortions          | 27/27                         |
| mos 47,XY,+mar[3]/46,XY[47]       | 3 abortions/2 normal children | 30/43                         |
| mos 47,XYY[4]/46,XY[46]           | 2 abortions          | 30/40                         |
| 46,XX,t(1;6)(q32.3; q26)          | 9 abortions          | 25/27                         |
| 46,XX,t(1;6)(q41; p24)            | 5 abortions          | 23/38                         |
| 46,XY,Y(t;15)(p35; q15)           | 4 abortions          | 36/39                         |
| 46,XX,t(3;7)(p26; p15)            | 2 abortions/dysmorphic infant with 46,XY,der(3)t(3;7)(p26; p15) mat karyotype | 33/65                         |
| 46,XY,Y(t;15)(p23; q26.2)         | 4 abortions/one normal child | 28/36                         |
| 46,XX,t(4;6)(q25; q26)            | 4 abortions          | 27/32                         |
| 46,XY,t(5;18)(13.1q; q12.2)       | 2 abortions/still birth due to skeletal dysplasia and chest hypoplasia | 21/32                         |
| 46,X,inv(Y)(p11q11), t(6;7)(q23; q13) | 5 abortions            | 18/25                         |
| 46,XX,t(7;11)(q22; q23)           | 8 abortions          | 49/54                         |
| 46,XX,t(9;11)(q34; q23)           | 4 abortions          | 33/36                         |
| 46,XX,t(11;22)(q23; q11.2)        | 5 abortions/a girl with 46,XX,t(11;22)(q23; q11.2) aged | 39/40                         |
| 46,XY,Y(t;11;22)(q23; q11.2)      | 1 day has polycystic kidney and polydactyly/a boy with 46,XY,Y(t;11;22)(q23; q11.2) apparently normal/3 NND | |
| 45,XX,der(13;14)(q10; q10)        | 4 abortions          | 27/30                         |
| 45,XY,der(13;14)(q10; q10)        | 3 abortions          | 29/39                         |
| 45,XX,der(14;15)(q10; q10)        | 3 abortions/one still birth/one NND with CHD/one infantile death/4 Normal children | 35/38                         |
| 45,XY,der(21;22)(q10; q10)        | 2 abortions/one NND/one normal child | 30/38                         |
| 46,XX,inv(2)(p11.2;p23)           | 8 abortions/male infant with MCA and 46,XY,rec(2)dup(2)(p15) inv(2)(p11.2;p23)mat/one child with normal karyotype | 30/32                         |
| 46,XX,inv(9)(p11q13)              | 3 abortions          | 33/49                         |
| 46,XX,inv(9)(p11q13)              | 2 abortions/one normal child | 20/29                         |
| 46,XX,inv(9)(p11q13) 46,XY,inv(9) (p11q13) | 3 abortions            | 35/33                         |
| 46,XY,inv(9)(p11q13)              | 8 abortions          | 26/30                         |
| 46,XY,9qh+                       | 3 abortions          | 28/28                         |
of a healthy child was higher among couples who had normal karyotypes (33.8%) compared to couples with chromosomal aberrations (23.1%), the difference did not reach statistical significance ($P = 0.271$). The reproductive outcome of the studied couples is presented in Tables 3 and 4. Figures 1-3 show the karyotypes of carriers of balanced rearrangements with chromosomally abnormal offspring.

In the present study, more than 50% of couples with a chromosomal anomaly experienced 4 or more abortions, however, this percentage did not reach a statistically significant level ($P = 0.241$) when compared to couples with normal chromosome complement [Table 5].

**Discussion**

RPL remains a reproductive challenge both for the clinician and the patient. Carriers of a balanced chromosomal abnormality are at higher risk of generating abnormal gametes leading to stillbirth, recurrent abortions, and the birth of dysmorphic/mentally handicapped infants.\(^{[11]}\) Hence, detecting a cytogenetic defect in case of miscarriage may play a significant

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**Figure 1:** (a): Karyotype of female with 46,XX, t(3;7)(p26;p15), (b): Karyotype of offspring with 46,XY, der(3)t(3;7)(p26;p15)mat, (c): Pachytene diagram of the t(3;7)(p26;p15)

**Figure 2:** (a): Karyotype of female with 46,XX, t(11;22)(q23;q11.2), (b) Karyotype of offspring with 46,XX, t(11;22)(q23;q11.2)mat/pat, (c) Pachytene diagram of the t(11;22)(q23;q11.2)
role in the management of couples with RPL. In the current study, the prevalence of chromosomal aberrations among couples with RPL was 11.6%, which goes in agreement with both international and national studies[19‑21] [Table 6]. The discrepancies between various studies may be attributed to differences in sample size, inclusion criteria, and techniques of cytogenetic studies.[22]

The incidence of chromosomal abnormalities was higher among females (7.14%) compared to males (5.35%); some studies reported such difference to be statistically significant[24,29] whereas others, including the current study, did not find the difference to be of statistical significance ($P = 0.435$).[30,31] This higher female frequency may be explained by the fact that chromosomal anomalies compatible with fertility in females may be combined with sterility in males.[21,32]

Males with chromosomal aberrations were suggested to have lower fertility rate due to poor spermatic motility, abnormal seminal profile with azoospermia or severe oligoasthenoteratozoospermia.[33]

In the present study, more than 50% of couples with a chromosomal abnormality reported 4 or more abortions; however, no significant difference was detected in the number of abortions experienced by couples with a chromosomal abnormality compared to those with normal karyotypes ($P = 0.241$), which goes in agreement with other published reports.[20,34]

Consanguineous coupling in Egypt is still high, representing 30% of all mating.[35] In the current study, nearly 55% of couples were consanguineous. The frequency of consanguineous mating in the present study was higher among couples with normal karyotype (56.1%) compared to couples

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**Table 6: Comparison of the frequency of chromosomal aberrations in the present study to the literature**

|                | Number of couples studied | Reciprocal translocation | Robertsonian translocation | inversion | Others | Total (%) |
|----------------|--------------------------|--------------------------|---------------------------|-----------|--------|-----------|
| Current study  | 224                      | 11                       | 4                         | 1         | 10     | 26 (11.6) |
| Iran[13]       | 728                      | 37                       | 7                         | 21        | 20     | 85 (11.7) |
| Saudi Arabia[23] | 1074                    | 36                       | 8                         | 11        | 22     | 77 (7.2)  |
| Oman[24]      | 290                      | -                        | -                         | 3         | 3      | 23 (8)    |
| Egypt[20]     | 125                      | 7                        | 1                         | -         | -      | 8 (6.7)   |
| Morocco[25]   | 238                      | 8                        | 1                         | 4         | -      | 13 (5.45) |
| Italy[26]     | 145                      | 4                        | 4                         | 4         | 2      | 14 (9.6)  |
| Canada[27]    | 100                      | 4                        | 3                         | 4         | 2      | 13 (13)   |
| Turkey[28]    | 1510                     | 30                       | 12                        | 9         | 11     | 62 (4.1)  |

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**Figure 3:** (a): Karyotype of female with 46,XX, inv(2)(p11.2p23), (b): Karyotype of offspring with 46,XY, rec(2)dup(2)(p15)inv(2)(p11.2p23)mat, (c): Schematic diagram of partial karyogram showing the paracentric inversion chromosome 2 with her offspring.
with chromosomal anomalies (46.2%), however the
difference was not statistically significant (P = 0.34).
Identical chromosomal abnormalities were detected in
both partners in 2 consanguineous couples; one with a
translocation involving chromosomes 11 and 22, and the
other couple had an inversion of the heterochromatin of
chromosome 9. This rare event where both partners carry
the same chromosomal anomaly has been reported in
consanguineous Indian couples. The consanguineous
couple where both partners carried the same 11; 22
translocation had two living children. Both children
were carriers of the familial translocation, one child
had polydactyly and polycystic kidney, and the other
was normal. The occurrence of clinical expressions in
a balanced translocation carrier may be due to physical
interruption of genes or a disturbance in their regulatory
environment.

In the present study, structural anomalies were 4 times
more frequent than numerical aberrations, which goes
in agreement with previous reports. Reciprocal
translocations were the most commonly identified
balanced chromosomal aberrations in couples with RPL,
in accord with previous studies. If one partner of
a couple carries a balanced chromosomal translocation,
the probability of miscarriage is nearly doubled.

Even though carriers of balanced chromosomal
rearrangements commonly have a normal phenotype,
the probability of generating unbalanced gametes is
significant due to complex segregation modes through
meiosis. In reciprocal translocation carriers, a
quadrivalent arrangement is created at meiosis I via
pairing of translocated chromosomes and the two
corresponding normal chromosomes. This structure
usually undertakes one of three modes of separation:
2:2 (segregation of two chromosomes to one cell
and two chromosomes to the other), 3:1 (segregation
of three chromosomes to one cell and one to the
other) or 4:0 (segregation of all chromosomes of the
quadrivalent to one cell and none to the other). Within
the 2:2 mode of segregation, chromosomal disjunctions
might be alternate, adjacent 1, or adjacent 2. Alternate
segregation represents the sole segregation pattern
producing gametes with balanced genetic counters:
one bearing normal chromosomes while the other
carries the balanced translocated chromosomes. Other
segregation models will create unbalanced gametes
leading to apparent infertility, recurrent abortion, or
birth of a phenotypically abnormal offspring with mental
retardation or other congenital defects.

In the present study, both adjacent 1 and alternate
segregation were observed in the offspring of the
carriers of the t(3;7) and t(11;22) respectively. Couples
with balanced reciprocal translocation have a 50% risk of RPL and a 20% possibility of having offspring
with unbalanced chromosomal rearrangements. The
production of unbalanced, balanced, and normal gametes
depends on the breakpoints and the chromosomes
implicated. The greater imbalance will most probably
result in miscarriages, while the slight or less significant
imbalance will raise the possibility of having children
with unbalanced karyotype. Balanced chromosomal
translocations might additionally result in sequence
rearrangements of the functional genes that could cause
reproductive errors accompanied by RPL.

Robertsonian translocations were less frequently
encountered than reciprocal translocations, which agrees with published reports. Robertsonian
translocations carry reproductive risks that are dependent
on the chromosomes involved and the sex of the
carrier. For carriers of the most common Robertsonian
translocation der(13;14), the risk for miscarriage is
approximately 15%. At meiosis, segregation of
trivalent structure may result in nullisomic or disomic
gametes for one of the chromosomes involved in the
rearrangement and consequently to a zygote with
trisomy or monosomy in addition to zygotes with
normal chromosome complement or carrying the
balanced rearranged. Zygotes with monosomy are
not compatible with life, and most translocation trisomy
conceptuses are expected to result in first trimester loss
or earlier; however, some survive beyond the second
trimester and to term. The risk for trisomy 13 in a
carrier of der (13;14) does not exceed 0.4%.

Inversions, both pericentric and paracentric, have been
reported in cases with RPL with a frequency lower than
Robertsonian translocations, as observed in the
present study. The risk of pregnancy loss in carriers of
a chromosome inversion is not known. The couple
with a paracentric inversion of chromosome 2, had
8 abortions, a child with a recombinant karyotype
exhibiting multiple congenital anomalies as well
as a child with normal chromosome constitution.
Hypothetically, heterozygous carriers of paracentric
inversions do not generate viable unbalanced offspring.
During meiosis, the occurrence of crossing-over
event(s), within the inversion loop of affected segments,
yields one dicentric and one acentric recombinant
chromosome, which are both lethal. However, numerous
examples of viable recombinant progeny have been
reported. A number of mechanisms explaining the
meiotic creation of recombinant stable chromosomes
with duplication and/or deletion have been proposed,
including unequal crossover, breakage and reunion
of sister chromatids, the abnormal process of
U-loop recombination\cite{47} and breakage of dicentric recombinants.\cite{48} We propose an unusual mechanism, involving breakage and unequal reunion of sister chromatids within the inversion loop, to explain the structure of our patient’s recombinant chromosome.

Polymorphic variants including inversion of chromosome 9 and 9qh+, have been observed in the current study in agreement with previous reports.\cite{25,29} Heterochromatic polymorphisms, have been implicated in mitotic instability and a tendency towards an increased risk for aneuploidy.\cite{8}

Genetic counseling is preferably offered before subsequent pregnancy; hence, all choices ought to be discussed, and optimum planning assumed. When a couple presents with RPL, detailed family history should be acquired, as this may present clues about familial chromosomal rearrangement. History of congenital anomalies, infertility, mental retardation, spontaneous miscarriage, or perinatal mortality is substantial since each is characteristic of chromosomal anomalies.

Genetic counseling is vital when a structural genetic factor is recognized as there is a risk of having a child with an unbalanced karyotype. When one of the partners carries a structural genetic abnormality, prenatal diagnosis (through amniocentesis, or chorionic villus sampling)/PGD are possible tools to detect the genetic anomaly in the offspring.\cite{49}

**Conclusion**

The prevalence of chromosomal abnormalities in Egyptian couples with RPL is within the range reported worldwide. Cytogenetic analysis should become an integral part of the investigations of couples with at least two pregnancy losses of undetermined etiology. Genetic counseling is crucial in the management of couples with RPL. Chromosome abnormalities in couples with repeated abortions are a strong indication for prenatal/PGD, helping a precise reproductive decision considering future pregnancies.

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**Conflicts of interest**

There are no conflicts of interest.

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