

A Study on Balanced Chromosomal Translocations in Couples with Recurrent Pregnancy Loss

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ABSTRACT

Background: Recurrent pregnancy loss (RPL) is an obstetric complication that affects couples in their reproductive age. Chromosomal abnormalities, mainly balanced rearrangements, could commonly be present in couples with RPL. **Aim:** The purpose of this study is to evaluate the contribution of chromosomal abnormalities and balanced reciprocal translocations, in particular occurring in either of the partners, resulting in RPL. **Materials and Methods:** A retrospective cytogenetic study was carried out on 152 individuals (76 couples) having a history of RPL. The cases were analyzed using G-banding and fluorescence *in situ* hybridization, wherever necessary. **Results:** Chromosomal abnormalities were observed in 3.2% of the total RPL cases, of which balanced translocations were observed in 4 (80%) individuals and marker chromosome was detected in 1 (20%) individual. All balanced translocations comprised reciprocal translocations, and no cases of Robertsonian translocations were detected in our study. Among reciprocal translocation carriers, three were male and one was female. Polymorphic variants were noted in 8 (5.3%) individuals. **Conclusions:** Chromosomal analysis is an important etiological investigation in couples with RPL. Balanced translocations are the most commonly detected chromosomal abnormalities in such couples. Thus, these couples are the best candidates for offering prenatal genetic diagnosis, thereby ensuring a better reproductive outcome.

KEYWORDS: Chromosomal abnormalities, reciprocal translocation, recurrent miscarriage

INTRODUCTION

Clinically recognized pregnancy loss is common, occurring in approximately 15%–25% of pregnancies. The majority of sporadic losses before 10 weeks' gestation result from random numeric chromosome errors, specifically trisomy, monosomy, and polyploidy.^[1] In contrast, recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies, involuntarily ending before 20 weeks of gestation.^[2] It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more.^[3] In approximately 2%–5% of couples with recurrent miscarriages, one of the partners carries a balanced structural chromosomal anomaly, most commonly a balanced reciprocal or a Robertsonian translocation.^[4–6] Although carriers of a

balanced translocation are usually phenotypically normal, their pregnancies are at increased risk of miscarriage and may result in a live birth with multiple congenital malformation and/or intellectual disability secondary to an unbalanced chromosomal arrangement. The risk of miscarriage is influenced by the size and the genetic content of the rearranged chromosomal segments.^[7–9]

Determining the presence of such a rearrangement in a parent is useful because it provides (1) an explanation

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for the miscarriages; (2) information about the risk for a live-born child with potentially serious anomalies, as well as the risk for future miscarriages; (3) availability of prenatal diagnosis in a future pregnancy; and (4) information for members of the extended family who may be at risk and may wish to undergo chromosome testing.

Appropriate evaluation of RPL should include parental karyotyping.^[10,11] In this study, we aim to identify the types of microscopically visible structural abnormalities and their frequencies in the parents with RPL.

MATERIALS AND METHODS

A 3-year, 4-month retrospective study from January 2014 to April 2017 was carried out in couples with a clinical diagnosis of RPL at our center. The institutional ethics committee approval was obtained. A total of 152 individuals (76 couples) were investigated for chromosomal abnormalities, who had two or more consecutive pregnancy losses before 20 weeks of gestation. In all the cases, detailed reproductive case histories were taken and karyotypes were generated.

Informed consent was obtained from the couples before performing the investigation. They were referred to the infertility center for detailed history and examination before performing the investigations. None of the couples had any significant medical or surgical history. The couples were phenotypically normal. Hormonal and anatomical factors of the uterus and ovaries were found to be normal. The male partners had normal semen analysis. Therefore, they were referred to our cytogenetic laboratory for chromosomal analysis. Chromosomal studies were performed on the basis of G-banding technique at high resolution.

Metaphase chromosome preparations from the peripheral blood cultures were made according to the standard cytogenetic protocols. Peripheral blood was put for 72-h culturing where peripheral blood lymphocytes were induced with phytohemagglutinin. Cytogenetic analysis was performed by GTG-banding at approximately 550-band level. For Case 4, fluorescence *in situ* hybridization (FISH) was performed using whole-chromosome painting probes for chromosome 1, 3, and 4; a bacterial artificial chromosome probe RP11-95E11 in 3p26.3 (homemade probes); and a subtelomeric probe for 3pter (Abbott Molecular, VYSIS, Mannheim, Germany). Chromosome analysis was performed using Applied Spectral Imaging (ASI), Israel software. Karyotypes were described according to the International System for Cytogenetic Nomenclature (2013).^[12] Along with the structural rearrangements and aneuploidies, common chromosomal

variants were also studied. The variants were further verified using different methods such as C-banding and NOR-banding.

RESULTS

This study included 152 individuals (76 couples) with a history of RPL. The most common age group for female partners was 23–26 years followed by 27–30 years, and in male partners, it was 27–30 years followed by 35–38 years [Table 1]. Most of the couples had three spontaneous abortions following which they were referred to us for genetic evaluation [Table 2]. Most of the women aborted between 6 and 8 weeks followed by pregnancy losses between 8 and 10 weeks [Table 3].

Chromosomal abnormalities were found in 5 (3.2%) individuals. Balanced chromosomal translocations were detected in 4 (80%) individuals whereas marker chromosome was observed in 1 (20%) individual. Among the individuals with an abnormal karyotype, 2 (40%) were female and 3 (60%) were male, producing male-to-female ratio of 1.5:1 [Table 4]. Among variants, in the male partners, invY, Yqh+, and 1qh+ were noted in two cases each, and 15cenh+ and 22pstk+ were observed in one case each. Only one marker chromosome was noted in a female partner [Table 5].

Table 1: Age-wise distribution of the individuals

Age (in years)	Female Partner	Male Partner
18-22	2	0
23-26	22	3
27-30	19	24
31-34	18	19
35-38	9	20
39-42	6	7
>43 years	0	3
Total	76	76

Table 2: Distribution based on number of abortions

No. of Abortion	Total (n)
2	23
3	35
4	11
5	5
6	2

Table 3: Distribution based on occurrence at Weeks of Abortion

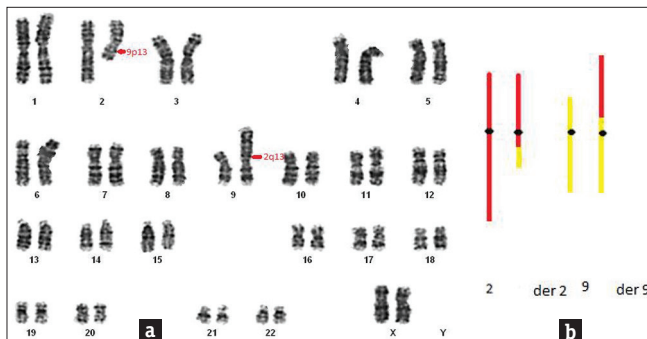
Weeks of Abortion	Total (n)
6-8	28
8-10	31
10-12	12
12-14	5

Table 4: Gender-wise distribution of chromosomal abnormalities

Aberrations	Female Partner		Male Partner	
	Karyotype	n	Karyotype	n
Reciprocal Translocation	46, XX, t(2;9)(q13;p13)	1	46, XY, t(15;20)(q22.3;q13.1) 46, XY, t(2;7)(p21;p15) 46, XY, der(1)(pter->q24.3::q32.1->qter), der(3)(4qter->4q12::1q24.3->1q31.1::3p26.2->3qter), der(4)t(3;4)(p26.2;q12)	1 1 1
Marker Chromosome	47, XX,+mar	1	-	-

Table 5: Distribution of polymorphic chromosomal variants

Variants	Female Partner	Male Partner
15cenh+	1	0
22pstk+	1	0
Inv Y	0	2
Yqh+	0	2
1qh+	0	2

**Figure 1:** (a) Karyotype showing balanced translocation in female: 46,XX,t(2;9)(q13;p13). (b) Schematic diagram of partial karyogram

CASE DETAILS

Case 1

In the first case, the couple had a history of RPL with an unknown cause. The male and the female partner were of 27 years of age. A reproductive history of the female partner revealed two missed abortions during 8th–10th week of pregnancy. Genetic analysis of the product of conception was not done. The karyotype of the female partner revealed balanced chromosomal translocations between the long arm of chromosome 2 and the short arm of chromosome 9 [46,XX,t(2;9)(q13;p13)] [Figure 1a and b] with clinically normal phenotype. The male partner had a normal karyotype [46,XY]. The parent's karyotype of the female partner was normal.

Case 2

In the second case, a reproductive history of the female partner revealed six missed abortions during 8th–10th week of pregnancy. The age of the male partner was 45 years and of the female partner was 42 years. The karyotype of the male partner showed a balanced chromosomal translocation between the long arm of

chromosome 20 and the long arm of chromosome 15 [46,XY,t(15;20)(q22.3;q13.1)] [Figure 2a and b] with clinically normal phenotype, whereas the female partner is of normal karyotype [46,XX]. The parents' karyotype of the male partner could not be studied due to unavailability of blood samples.

Case 3

In the third case, the female partner had two missed abortions during 6th–8th week of pregnancy. The age of the male partner was 39 years and female 37 years. The karyotype of the male partner showed a balanced chromosomal translocation between the short arm of chromosome 2 and the short arm of chromosome 7 [46,XY,t(2;7)(p21;p15)] [Figure 3a and b] with clinically normal phenotype, whereas the female partner again had a normal karyotype [46,XX]. The parents of the male partner were not available for karyotyping.

Case 4

In the fourth case, the female partner had two missed abortions during 8th–10th week of pregnancy. The age of the male partner was 32 years and female 26 years. The karyotype of the male partner showed an apparently complex balanced chromosomal translocation between chromosomes 1, 3, and 4 [46,XY,t(1;3;4)(1pter->1q24.3::1q31.1->1qter;4qter->4q12::1q24.3->1q31.1::3p26.2->3qter;4pter->4q12::3p26.2->3pter)] [Figure 4a and b] with clinically normal phenotype. To confirm the complex chromosomal rearrangements or subtle translocations, three-color FISH was performed, which revealed that a small segment of chromosome 1q was deleted and got inserted between chromosome 3 and translocated part of chromosome 4. The female partner had a normal karyotype [46,XX]. The parents of the male partner had died long back, so the parental karyotype could not be carried out. However, karyotyping of his two brothers and one sister was done, which was normal.

DISCUSSION

The loss of a wanted pregnancy is disheartening to any couple. Reproductive problems are estimated to be present in approximately one in six couples.^[13] Chromosomal abnormality comprises approximately 8% of the cases presenting with reproductive failure such

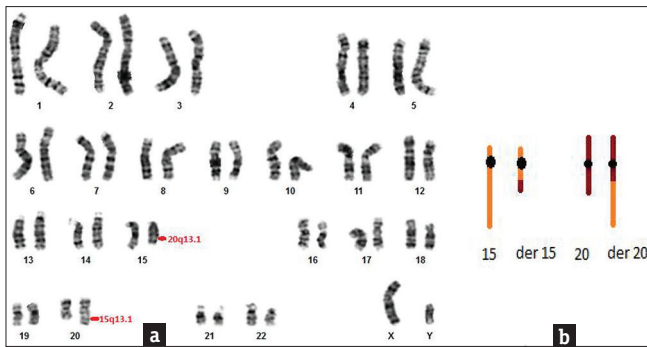


Figure 2: (a) Karyotype showing balanced translocation in male: 46,XY,t(15;20)(q22.3;q13.1). (b) Schematic diagram of partial karyogram

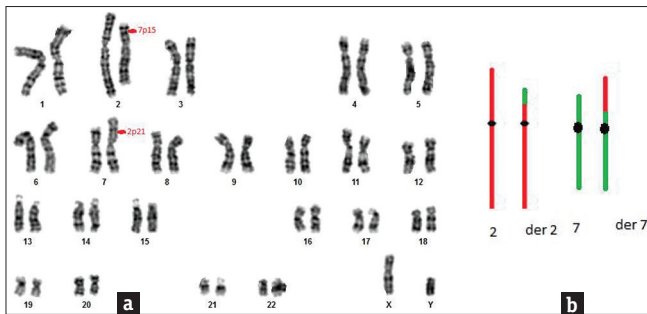


Figure 3: (a) Karyotype showing balanced translocation in male: 46,XY,t(15;20)(q22.3;q13.1). (b) Schematic diagram of partial karyogram

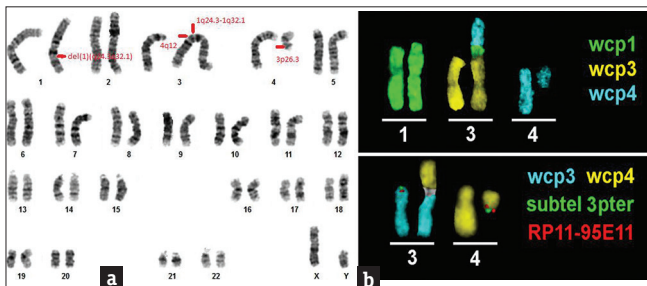


Figure 4: (a) Karyotype showing balanced translocation in male: 46,XY,der(1)(pter->q24.3::q32.1->qter),der(3)(4qter->4q12::1q24.3->1q31.1::3p26.2->3qter),der(4)t(3;4)(p26.2;q12). (b) FISH results with whole-chromosome painting (WCP) for chromosomes 1, 3, and 4, and subtelomeric probes 4pter and 3pter along with RP11-95E11 in 3p26.3

as infertility and RPL.^[14] Chromosomal aberrations, either numerical or structural, can have profound effects on pregnancy outcome. Couples with balanced translocations have a 50% chance of having RPL and a 20% risk of having children with unbalanced chromosomal aberrations.^[15]

At present, there exist only a small number of well-understood etiologies for RPL, which include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, and antiphospholipid antibody syndrome. Other probable or possible etiologies include additional endocrine disorders, heritable and/or

acquired thrombophilias, immunologic abnormalities, infections, and environmental factors. After evaluation for these causes, approximately half of all cases usually remain unexplained.^[16-18]

Approximately 2%–4% of RPL is associated with a parental balanced structural chromosome rearrangement, with the most common being balanced reciprocal or Robertsonian translocations.^[19] A reciprocal translocation is an interchange of chromosomal material between specific chromosomes, and it may be the result of fork stalling and template switching, microhomology-mediated break-induced repair, breakage–fusion–bridge cycles, or chromothripsis.^[20] These are balanced when the exchange does not result in loss of genetic material and unbalanced when genetic material is gained and/or lost.

In our study, we observed balanced chromosomal translocations in 4 (2.6%) individuals. In a study done previously by Sheth *et al.* on a larger population, balanced chromosomal translocations were detected in 3.5% of cases.^[6] Additional structural abnormalities associated with RPL include chromosomal inversions, insertions, and mosaicism. We observed eight cases of polymorphic variations. Chromosome 1 and Y most commonly showed polymorphic variations. Inversion Y (28.6%) and Yqh+ (28.6%) heteromorphism constituted a major part of polymorphic variants. Satellite polymorphic variants (pst+) and centromeric heteromorphisms were also noted in our study. Frequency of polymorphic variants was observed to be more in males than females, which was in concordance with other studies.^[21] Various other studies have also reported similar polymorphic variants in association with RPL.^[6] Several authors have also hypothesized that certain variant chromosomes are associated with congenital malformations, cancer, RPL, and infertility in their respective studies.^[22] However, a comparative number of studies have also reported the absence of any such association.^[23] Furthermore, Carothers *et al.* concluded that reproductive fitness of carriers of heterochromatic variants of the human karyotype is normal.^[24,25] Single-gene defects, such as those associated with cystic fibrosis or sickle cell anemia, are seldom associated with RPL.^[26] However, the specific information regarding the chromosomal status of the couple and if possible the abortus remains of paramount importance during the evaluation of such cases.

In the evaluation of RPL, parents should undergo peripheral karyotyping to detect any balanced structural chromosomal abnormalities. Reciprocal translocations are one of the most common human chromosomal aberrations, occurring in about 1 in 600 individuals in the general population, whereas they have a frequency of about 7%

in couples with RPL.^[3] These rearrangements are twice more common in females than males. On the contrary, in our study, we have found that the male-to-female ratio is 2.25:1. In a study done by Mozdarani *et al.*, male partners had significantly higher chromosomal abnormalities (5.88%) than females (3.61%).^[14]

In most cases, carriers of balanced reciprocal translocations have a normal phenotype, but may experience reproductive issues such as infertility or multiple miscarriages. Nearly 6% of apparently balanced *de novo* translocations are associated with clinical abnormalities. In our study, the female partners had no endocrinological and uterine abnormalities. The male carriers had normal semen study. They can often be infertile as the chromosomal aberration may lead to spermatogenic arrest and are often detected while getting investigated for azoospermia. The semen profiles of translocation carriers may not always predict fertility outcomes. The female carriers remain fertile, and the only effect could be pregnancy loss.^[27-29]

Couples with balanced reciprocal translocation have a 50% chance of having RPL and a 20% risk of having children with unbalanced chromosomal rearrangements.^[30] The formation of balanced, unbalanced, and normal gametes is dependent on the basis of the breakpoints and the chromosomes involved. The larger imbalance will most likely lead to miscarriages whereas the subtle or smaller imbalance will increase the risk of having offspring with unbalanced karyotype. Balanced chromosomal translocations may also lead to sequence rearrangements of the functional genes that may result in the reproductive errors accompanied by repeated pregnancy loss.^[31]

Genetic counseling is best provided before the next pregnancy; hence, all options should be explored and appropriate planning instituted. When a patient presents with RPL, a detailed family history should be obtained, including information about the partner's family. The family history may provide a clue to the presence of a familial chromosomal rearrangement. A history of any congenital anomaly, mental retardation, infertility, spontaneous abortion, or perinatal death is significant because each is characteristic of chromosomal anomaly. Most of the balanced reciprocal translocations are *de novo*, but familial cases have been reported frequently. In our study, Case 1 and Case 2 appear to be *de novo*. In Case 3 and Case 4, there was no significant family history, which again goes in favor of *de novo* inheritance, although familial inheritance cannot be ruled out.

Genetic counseling is very crucial when a structural genetic factor is identified as there is a risk of having

a child with an unbalanced karyotype. The likelihood of a subsequent healthy live birth depends on the chromosome(s) involved and the type of rearrangement. When one of the partners has a structural genetic abnormality, prenatal diagnosis through amniocentesis, or chorionic villus sampling are options to detect the genetic abnormality in the offspring. Couples could also opt for preimplantation genetic diagnosis (PGD) for specific translocations, with transfer of unaffected embryos or the use of donor gametes.^[32] The use of donor gametes may be recommended in cases involving genetic anomalies that always result in embryonic aneuploidy (i.e., Robertsonian translocations involving homologous chromosomes).^[33] Implications for the extended family should also be discussed, and assistance should be provided in informing relatives. Although our study is carried out over a short period and in a small cohort, we wish to emphasize that a balanced translocation, as a genetic cause, is the most common occurrence among couples with RPL.^[6,34,35]

CONCLUSIONS

To help aid couples struggling with RPL, limited and focused genetic testing is recommended as part of the diagnostic workup. Parental karyotyping should be advised to all the couples undergoing evaluation for RPL. The carriers of a balanced translocation should be informed regarding the risk of congenital anomalies in their offspring. Hence, genetic counseling is indicated in all cases of RPL associated with parental chromosomal abnormalities. Depending on the diagnosis, directed therapy may include prenatal diagnosis or *in vitro* fertilization with PGD.

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Conflicts of interest

There are no conflicts of interest.

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