# CHROMOSOMAL ANOMALIES IN COUPLES WITH RECURRENT PREGNANCY LOSS

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## SUMMARY

This study explores the landscape of chromosomal anomalies in couples with recurrent pregnancy loss (RPL) who have not previously delivered abnormal fetuses. From 2014 to 2021, we analyzed 122 couples who had experienced more than two first-trimester miscarriages. After excluding common causes of RPL, we conducted a cytogenetic analysis using G-banding. The results revealed chromosomal anomalies in 8.2% of cases, including balanced reciprocal translocations in 4 men and two women, Robertsonian translocations in 2 men, and subfertility in 3 men. Additionally, one woman had a pericentric inversion of chromosome 9, and another had a mosaic karyotype 46, XX/47, XXX. The introduction of genetic counseling led to two successful pregnancies with normal karyotypes. These findings underscore the potential of karyotyping to identify genetic causes and inform reproductive planning, empowering couples to make informed decisions about their future pregnancies.

**Keywords:** Recurrent pregnancy loss, chromosomal anomalies, balanced translocation, Robertsonian translocation, cytogenetic analysis, genetic counseling, karyotyping

## INTRODUCTION

Genetic factors are the most frequent causes of spontaneous abortions (SA). Numerical chromosomal anomalies, such as aneuploidy or polyploidy, are detected in 50-80% of first-trimester miscarriages. The detection rate depends on the investigation methods used (e.g., FISH, CGH microarray), the composition of the groups studied (such as women of advanced age), and the specifics of family or obstetric history.[1,2] Most chromosomal abnormalities that cause miscarriage have random character. First-trimester SA expresses most (90%). However, these abnormalities might be associated with RPL.[3,4] According to different data, the frequency of chromosomal ab-

normalities in couples with RPL is 2-6%. [1,5,6] Translocation in one of the partners is a common and confirmed cause of recurrent miscarriage[7,8]. Prevalence of balanced translocations is higher in females than in males and higher in couples with a family history of stillborn or abnormal liveborn and, according to some authors, in subfertile men.[1,3,9,10]

Based on a meta-analysis of 79 studies, Tharapel A.T. et al. revealed that among couples with RPL, the structure of identified chromosomal abnormalities is as follows: either partner of couples with RPL has balanced reciprocal translocation in 50%, Robertsonian translocation in 24%, sex chromosome mosaicism in 12%, and in other cases, inversions and different sporadic chromosomal abnormalities were observed.[11]

The presence of a balanced chromosomal rearrangement in one partner can result in an unbalanced translocation in offspring. Phenotypic consequences (abort uses or abnormal liveborn) depend on the specific duplicated or deficient chromosomal segments. [1,2,5]

Translocations do not correlate with the age of mothers and the number of previous miscarriages. [1,6,12]

The theoretical risk of transmission of balanced translocations to offspring in unbalanced form is considerably higher than the empirical risk, which might be explained by the lethality of many segregant products.[1,5,6,8]

Different chromosomal aneuploidies may be expressed in translocation cases due to interchromosomal effects.[1,13] In first-trimester abortions, recurrent aneuploidy occurs more often than expected by chance, which might be tied to the mother's age and also to germ cell mosaicism.[1]

According to the last period data, in cases of structural abnormalities of chromosomes, IVF accompanied by PGD decreases the risk of spontaneous abortions but also decreases the chance of live birth compared to spontaneous pregnancy. In spontaneous pregnancies, considering concomitant factors, the live birth chance is up to 70%.[2,5,12]

There are no standard views on the necessity of karyotyping concepts or whether the karyotyping of couples with RPL (RCOG, ASRM, ECHRE protocols) is economically justified.[14,15]

Some experts recommend karyotyping couples with RPL if there is no information on the Karyotype of conceptuses.[15, 16]

Detection of frequency and types of chromosomal anomalies in couples with I trimester RPL without the history of delivery with the abnormal fetus.

## METHODS

One hundred twenty-two couples with > 2 first trimester miscarriages were involved in a prospective observational study in 2014-21 based on the Center for Reproductive Medicine "Universe" and the Georgian Centre of Prenatal Diagnostics.

The mean age of women was 30,3+2, and the mean age of men – was 32.1+3.

In all cases, family history and obstetric anamnesis were collected and analyzed.

Common causes of RPL—anatomic (congenital and/or acquired), hormonal (luteal insufficiency, diabetes, thyroid dysfunction, PCOS, hyperprolactinemia, etc.), and immunological (APS)—were excluded for all couples;

All couples have undergone cytogenetic investigation. The Karyotype was detected in peripheral blood lymphocyte cultures (G-banding).

*Ethical considerations:* Written informed consent was obtained from all participants before their inclusion in the study.

## RESULTS

Personal or family history of pregnancy and delivery of a fetus with congenital anomalies or child with mental retardation was not detected in any of the cases;

The Karyotype of previous concepts was not investigated in any of the cases;

The mean number of previous miscarriages in the standard group of RPL was 3,15, and in the couples with chromosomal anomalies – 2,9; Chromosomal anomalies in one partner were revealed in 10 cases (8.2%) (Table 1) Balanced reciprocal translocations were detected in 4 men and two women (Fig. 1), Robertsonian translocation – in 2 men, and three from 6 men with translocations (2 Robertsonian and one reciprocal) were subfertile (oligozoospermia); The total frequency of balanced translocations was 6,6%[8]; One woman had a pericentric inversion of chromosome 9, and one woman – had mosaic karyotype 46, XX/47, XXX.

***Table 1.*** ***Type of Chromosomal Anomalies and Reproductive disorders in couples with RPL***

| N | Karyotype | Numbers of first trimester miscarriages | Other reproductive disorders |
|---|---|---|---|
| 1 | 46, XX, t (2;13) (p14;q32) | 2 | |
| 2 | 46, XX, t (5;16) (p12;q22) | 2 | |
| 3 | 46, XY, t (2;9) (p22;p24) | 2 | |
| 4 | 46, XY, t (18;21) (q22;q21) | 3 | |
| 5 | 46, XY, t (10;18) (q11,2; q2,1) | 3 | subfertility (olygozoospermia) |
| 6 | 46, XY, t (6;22) (p21.3;q13.3) | 4 | |
| 7 | 45, XY, rob (13;15) (q10;q10) | 4 | subfertility (olygozoospermia) |
| 8 | 45, XY, rob (13;14) (q10;q10) | 3 | subfertility (olygozoospermia) |
| 9 | 46, XX, inv (9) (p11;q12) | 3 | |
| 10 | 46, XX / 47XXX (18/32) | 3 | |

***Figure 1.***

***Couple with 2 SA Woman 21y old, Karyotype 46, XX, t (2;13) (p14;q32)***

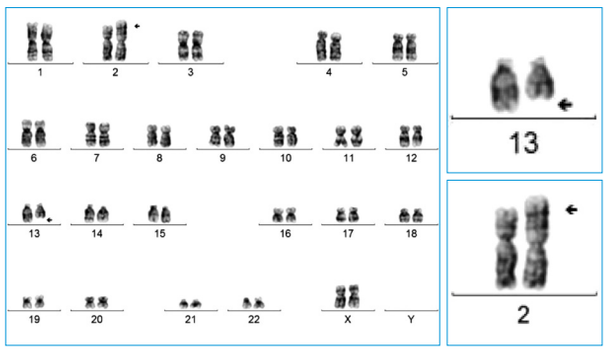
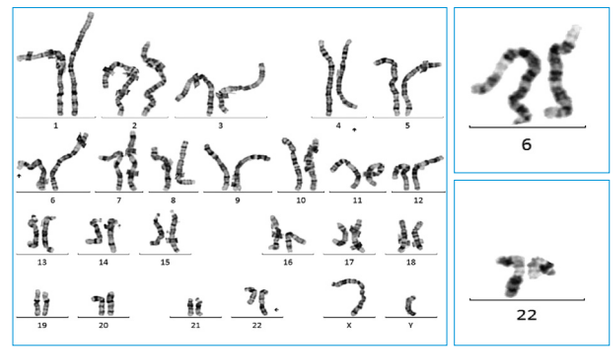



***Figure 2.***

***Couple with 4 SA Male partner 30 y old, Karyotype 46, XY, t (6;22) ( p21.3;q13.3)***



Pericentric inversion of chromosome 9 was revealed in 1 woman with a history of 3 previous I trimester spontaneous abortions, karyotype – 46, XX, inv$^{9}$(p11; q12); Pericentric inversion of chromosome 9 is considered as a variant of normal Karyotype with incidence 1-3% of the general population.[17] This inversion does not correlate with abnormal phenotypes, but in the literature exist, conflicting views regarding the association of this variant with such clinical conditions as infertility, RPL, and stillbirth.[17,18,19]

A mosaic karyotype 46, XX/47, XXX (37/63) was found in 1 woman with a history of 3 previous I-trimester spontaneous abortions. It is important to note that sex chromosome polysomy is a scary condition, occurring in only 0.05% of spontaneous abortuses, and it is not incompatible with life.[1]

## DISCUSSION

The causative relationship of pericentric inversion of chromosome 9 and X chromosome polysomy with RPL needs further investigation. Genetic counseling was conducted for all couples with detected chromosomal anomalies, informing them of their risks and reproductive opportunities, including IVF with PGD, spontaneous pregnancy with or without CVS or amniocentesis, gamete donation, and child adoption.

Following genetic counseling, two women achieved spontaneous pregnancies. One 24-year-old woman, whose 26-year-old husband had a reciprocal translocation 46, XY,t$^{6;22}$(p21.3;q13.3) and a history of four previous first-trimester spontaneous abortions, became pregnant and received intensive prenatal care and psychological support. Noninvasive prenatal genetic screening results were expected, and the pregnancy ended with the timely physiological delivery of a phenotypically usual girl with a karyotype of 46, XX. Another 39-year-old woman with a history of two previous first-trimester spontaneous abortions, who had a reciprocal translocation 46, XX-,t$^{5;16}$(p12;q22), also achieved spontaneous pregnancy. At 18 weeks, fetal balanced translocation (similar to the maternal) was detected by amniocentesis. The pregnancy was maintained and ended with the physiological delivery of a phenotypically normal fetus.

Revealing the natural causes of RPL by karyotyping couples might benefit these couples and the experts managing their cases. Our results indicate that karyotyping couples with RPL without a history of delivering abnormal fetuses is reasonable, as chromosomal anomalies among them are not rare.[8,2] Balanced chromosomal rearrangement in one partner can result in an unbalanced translocation in offspring, and phenotypic consequences (abortions or abnormal live births) depend on the specific duplicated or deficient chromosomal segments.[1,2] These chromosomal disorders can often be clinically revealed mainly by spontaneous abortions.[3,13]

## CONCLUSION

In couples with RPL and without a history of delivery with the abnormal fetus, when the chromosomal status of previous miscarriages is unknown, considerable frequency of balanced structural chromosomal anomalies (with prevalence in male partners- 6/2) indicates on the reasonability of karyotyping of such couples, especially when the male partner is subfertile.

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