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Original Research

# Investigating Cytogenetic Profiles in Couples Experiencing Recurrent Implantation Failure Post *in vitro* Fertilization

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**Abstract**

This study evaluates how chromosomal factors affect assisted reproduction techniques (ART) challenges among infertile couples, impacting their chances of conception. Chromosomal abnormalities, a leading cause of pregnancy failure and miscarriages, were investigated in a four-year retrospective study involving 100 patients with a history of infertility and unsuccessful IVF treatment. Among these cases, nine (9%) displayed aberrant chromosomal patterns, including balanced translocations (5%), sex chromosome deletions (3%), and one case of a small supernumerary marker chromosome (sSMC) (1%). The results of the present study highlight the importance of integrating comprehensive cytogenetic analysis as a routine diagnostic tool for individuals dealing with infertility, particularly before assisted

reproduction techniques, to avert recurrent implantation failure and to enhance their chances of success.

**Keywords**
Infertility; chromosomal abnormalities; karyotyping; IVF; miscarriages

## 1. Introduction

Infertility, as defined by the World Health Organization (WHO), is the inability to achieve a clinical pregnancy following 12 months or more of regular unprotected sexual intercourse [1]. Globally, it affects approximately 25% of couples [2, 3]. This condition has a multifaceted origin, stemming from diverse factors such as genetic alterations, hormonal imbalances, genital infections, exposure to chemical and physical agents, reproductive organ anomalies, and testicular dysfunction [4]. Although the genetic reasons for infertility remain incompletely explored, chromosomal aberrations are recognized as a common causative factor for this condition [5].

Assisted reproduction techniques have significantly contributed to enabling conception for many infertile couples. However, despite advancements in ovarian stimulation, culture mediums, and laboratory conditions, the success rates for pregnancy and live births per transfer stand at approximately 35%-45% and 25%-36%, respectively [6, 7].

Recurrent implantation failure (RIF) poses a profound challenge for both couples and medical professionals, signifying the absence of pregnancy despite the use of high-quality embryos and without discernible causes. Chromosomal aberrations constitute a leading cause of pregnancy failure, miscarriage, and congenital anomalies in both natural conception and pregnancies resulting from *in vitro* fertilization (IVF) [6].

Couples often undergo ART without thorough genetic analysis, where genetic causes, including chromosomal aberrations, might contribute significantly to their infertility. Studies have reported chromosomal aberrations in 2-7% of infertile couples [8], with some data suggesting even higher percentages, notably in cases of male infertility [9, 10].

Our research aims to elucidate the cytogenetic basis underlying the failure of assisted fertilization in infertile couples.

## 2. Materials and Methods

This retrospective study spans four years (2019-2022). One hundred patients (50 couples) with a documented history of infertility and unsuccessful IVF treatment were referred for cytogenetic analysis at the Cytogenetics Department of the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia. The men in our study averaged 38.3 years (±4.1), while women averaged 36.6 years (±4.1). All participating couples had undergone one or more ART but remained unsuccessful in achieving pregnancy, even post-transfer of embryos estimated to be of high quality. Notably, individuals (couples) who experienced both primary infertility and a history of miscarriages after IVF treatment were excluded from this study.

### *2.1 Cytogenetic Analysis*

Approximately 5 ml of peripheral blood was taken from each patient using a heparinized syringe. Cytogenetic analysis was performed according to standard laboratory protocols. Peripheral blood lymphocyte cultures in PB-MAX (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) medium were treated with 0.1 μg/ml of colcemid (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) after a 72-hour incubation period. Subsequently, metaphase chromosomes were spread and stained using the G-banding technique [11, 12]. For each case, 22 metaphase spreads were examined, and in cases where mosaicism was suspected, 100 metaphases were analyzed. The International System for Human Cytogenetic Nomenclature (ISCN, 2020) was used to describe the karyotypes [13].

### *2.2 Statistical Analyses*

Statistical analysis of the gathered data involved the application of non-parametric tests to compare the frequency of chromosomal aberrations in the studied patients with literature-reported frequencies of these aberrations in the general population. In addition to the standard Chi-square test for frequency data analysis, the binomial test method was utilized. This method compares observed distributions with expected distributions of variables. In this study, the binomial test was instrumental in assessing the statistical significance of variations in the occurrence frequency of chromosomal aberrations between couples experiencing unsuccessful assisted fertilization and the general population. Statistical analysis was conducted using SPSS software version 22.0 (IBM SPSS Inc, Chicago, IL, USA). P values < 0.05 were considered statistically significant.

All participants in the study provided signed consent. The study was conducted in agreement with the Helsinki Declaration and has approval from the Ethics Committee of the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia, No. 1039/7.

## 3. Results

Out of the 100 samples analyzed, 88/100 (88%) showed a normal karyotype, while chromosomal abnormalities were detected in 12 participants (12%), specifically in 5 males and 7 females. Among them, five (5%) patients exhibited balanced translocations, four (4%) had reciprocal translocations (two women and two men), and one (1%) female patient had a Robertsonian translocation. In all cases, the karyotype of their partners was normal. The abnormal karyotypes and the number of IVF attempts for these couples are presented in Table 1. Karyotypes of two patients with reciprocal translocations and one with sex chromosome deletion are shown in Figure 1 and Figure 2, respectively.

**Table 1** Chromosomal aberrations identified in 100 couples and the number of IVF attempts in couples with abnormalities.

| Chromosome aberrations | Karyotype | Number of IVF procedures |
|---|---|---|
| Numerical aberrations | | |
| | mos46, X, del(X) (q22q24)[46]/46, XX[54] | 3xIVF |

| | | |
|---|---|---|
| | 47, XY + mar | 2xIVF |
| Structural aberrations | | |
| Translocations | 46, XY, t(1; 2) (p34; p21) | 3xIVF |
| | 45, XX, der(13; 14) (q10; q10) | 2xIVF |
| | 46, XX, t(1; 6) (p24; p25) | 2xIVF |
| | 46, XX, t(2; 6) (q21; q21) | 2xIVF |
| | 46, XY, t(5; 14) (q31.1; q32.1), | 9xIVF |
| Deletions | 46, X, del(Y) (q11.2) | 3xIVF |
| | 46, X, del(X) (q26) | 2xIVF |
| Inversions | 46, XY, inv(9) (p11; q13) | 3xIVF |
| | 46, XY, inv(9) (p11; q13) | 2xIVF |
| | 46, XX, inv(9) (p11; q13) | 2xIVF |

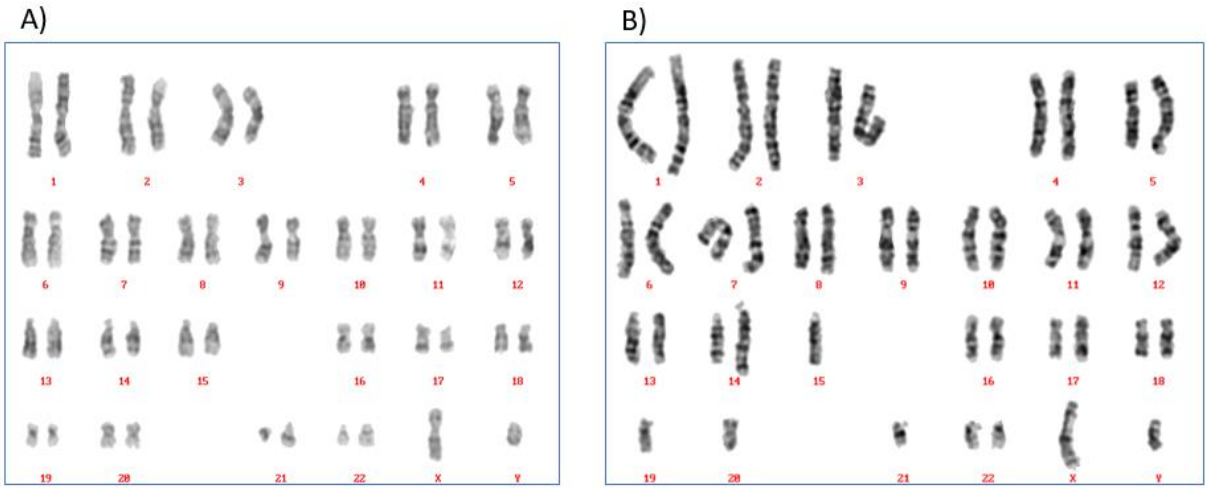


**Figure 1** Karyotype of patients with balanced translocations A) 46, XY, t(1; 2) (p34; q21) B) 46, XY, t(5; 14) (q31.1; q32.1).

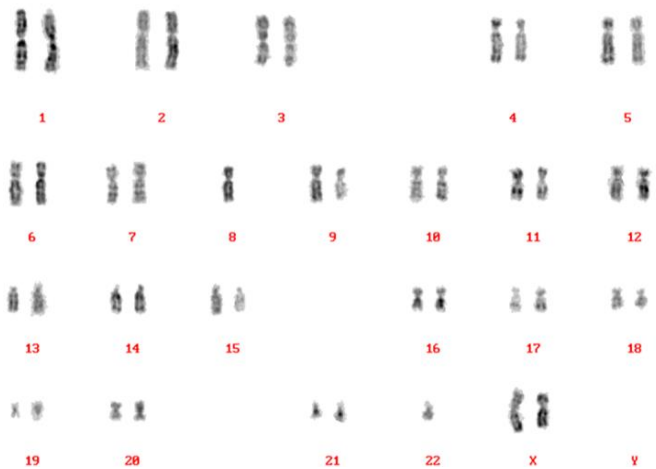

**Figure 2** Karyotype of a patient with sex chromosome deletions- 46, X, del(X) (q26).

Furthermore, a pericentric inversion of chromosome 9 was detected in three patients (3%) (two men and one woman). Among these cases, one couple encountered three unsuccessful assisted fertilization attempts, while the other two experienced two failed attempts each. The Karyotype of a male patient with an inversion on chromosome 9 is presented in Figure 3.

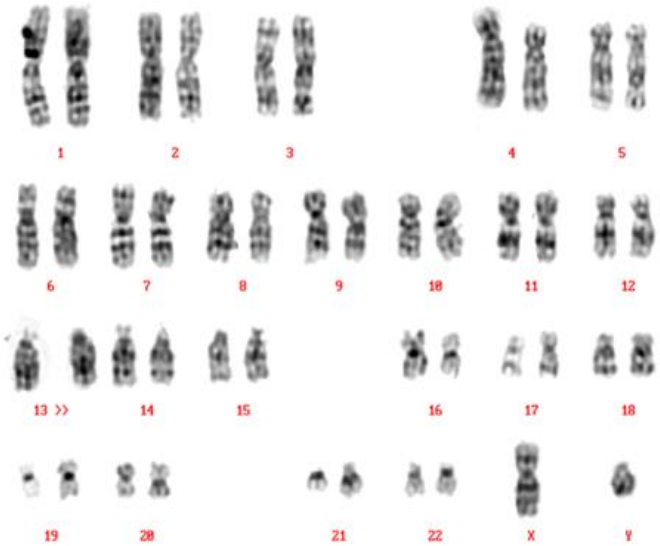


**Figure 3** Karyotype of a patient with an inversion on chromosome 9 (46, XY, inv(9) (p11; q13)).

A normal karyotype was observed between the remaining patients (n = 88) examined in this study, either in males or females. Notably, no pair was identified in which both individuals exhibited aberrant karyotypes. Overall, the frequency of chromosomal aberrations among the analyzed couples with unsuccessful assisted fertilization significantly exceeds that of the general population (9% vs. 1%) ($p < 0.001$). Moreover, compared to the frequency of aberrations in live-born children (0.625%), a notable distinction was observed in the frequency of chromosomal aberrations within the analyzed group.

Each specific chromosomal aberration, including unbalanced structural aberrations and balanced translocations, demonstrates a significantly higher frequency compared to the general population ($p < 0.001$). The only exception among these comparisons is the frequency of inversion of chromosome no. 9, which does not exhibit significant differences compared to the general population (3% vs. 1%) ($p = 0.079$).

Considering an expected frequency of 7% of chromosomal aberrations in patients with some form of infertility, this study did not reveal any deviations from this hypothesis ($\chi^2 = 0.614$, DF = 1, $p = 0.433$). This finding suggests a correlation with the anticipated involvement of chromosomal aberrations in the onset of infertility.

## 4. Discussion

Among the 100 patients examined, five individuals (5%) were identified to have autosomal balanced translocations, among which one female case involved a Robertson translocation 13; 14. Literature data indicated a frequency range of 0.16%-0.2% for balanced translocations within the general population [14]. Notably, our study revealed a considerably higher rate, approximately ten

times greater, of these translocations within the examined patient group. Previous research suggests that the occurrence of balanced translocations in men experiencing infertility is significantly elevated, ranging from five to ten times higher compared to the general population. In our study group, two males, constituting 4% of all males, were carriers of balanced translocations. Generally, this frequency tends to vary by about 0.7%, consistently matching the occurrence seen in female patients [10]. The findings from our study are not in alignment with the data above, as the frequency of female participants with balanced translocations is two, which accounts for 4% of all women.

Robertsonian translocations are detected in 0.9%-3.4% of infertile men experiencing severe spermatogenic dysfunction [5]; however, in our study group, none of the men were found to have Robertsonian translocations. In cases of balanced translocations, male carriers exhibit varying fertility levels, ranging from azoospermia to a normal spermogram. Consequently, comprehending the mechanism by which this translocation impacts fertility remains elusive. Contrarily, in female patients, the influence of Robertsonian translocations on gametogenesis appears minimal, yet it poses a more significant risk of transmitting an unbalanced rearrangement to offspring [10]. In our study, only one female had Robertsonian translocation, which is in accordance with the data from the literature.

Offspring of translocation carriers risk experiencing uniparental disomy or functional loss of genes at the breakpoints. The factors dictating the success of assisted reproduction techniques among couples with balanced translocations remain unclear. Segregation events that lead to unbalanced chromosomal complements, potentially resulting in infertility or early embryonic/fetal demise, often remain unidentified [15]. Individuals carrying balanced translocations are ideal candidates for Preimplantation Genetic Diagnosis (PGD) or mandatory invasive prenatal diagnostics. It is important to note that carriers of balanced translocations involving identical chromosomes might face challenges in producing healthy offspring. In some cases, an unbalanced rearrangement can be viable and lead to the birth of a child with a severe clinical condition [16, 17].

In our study, cytogenetic analysis revealed the presence of an sSMC of unknown origin in one male patient who underwent two unsuccessful assisted fertilization attempts. Utilizing multicolor fluorescent in situ hybridization (mFISH), it was determined that the sSMC contained heterochromatic material originating from chromosome 15 in this particular patient. Research indicates that in nearly 50% of cases, such markers originate from this chromosome. Conversely, patients with exclusively heterochromatic material have shown no observable phenotypic abnormalities, though a notably higher frequency of such markers has been observed in infertile men [18]. Individuals carrying the marker chromosome typically display typical physical traits and maintain fertility. However, several studies have highlighted a higher occurrence of these chromosomes among individuals struggling with infertility, accounting for about 0.125% of cases, approximately three times more prevalent than in the general population [19]. The precise impact of sSMCs on spermatogenesis remains unclear, but it is hypothesized that they disrupt "chromosomal movements" during meiosis [18]. In cases where patients have an sSMC karyotype, invasive prenatal diagnosis becomes necessary, alongside determining the origin of the sSMC, owing to the potential risk of uniparental disomy in the offspring.

Premature Ovarian Insufficiency (POI), occurring in approximately 1% of women [20], has been noted in patients with X-autosomal balanced translocations or deletions involving the X

chromosome. These deletions commonly exhibit breakpoints in the Xq24-Xq27 region, while translocation breakpoints predominantly occur from Xq13 to Xq21. Based on these findings, the Xq24-q27 and Xq13.1-q21.33 regions have been identified as POI critical regions 1 and 2, respectively. Several studies have highlighted Xq13-q27 as the critical region responsible for ovarian dysfunction, primary and secondary amenorrhea, as well as gonadal dysgenesis [21]. Through karyotyping analysis, we have identified deletions on the long arm of the X chromosome in two female patients. One patient displayed a terminal deletion on the long arm of the X chromosome, del(X) (q26). At the same time, the other exhibited an interstitial deletion-del(X) (q22-q24) - observed in a mosaic with a normal female karyotype. The first patient was referred for analysis after two unsuccessful attempts at assisted fertilization, while the second was referred after three unsuccessful attempts.

The thirty-three-year-old patient with the X(q26) deletion was referred after two failed assisted fertilization attempts due to decreased ovarian function and a lower anti-Mullerian hormone level. Family history revealed significant information: her grandmother experienced premature menopause after giving birth to the patient's mother at 19, who, in turn, also faced premature menopause a few years after having the patient and her sister before the age of 25. Additionally, the patient's forty-year-old sister faced infertility issues and entered premature menopause at thirty-eight. Among genes linked to premature ovarian failure, the *FMR1* gene on Xq27.3 is noteworthy, responsible for Fragile X Syndrome. A complete deletion of this region includes the *FMR1* gene, typically resulting in a normal female phenotype due to X-linked inheritance, barring rare cases of healthy X chromosome inactivation and dosage compensation. Considering the patient's aberrant karyotype, PGD becomes crucial, at least for selecting the embryo's sex. Male offspring would have a 50% chance of inheriting Fragile X Syndrome, and assessing whether such an embryo would be viable depends on the size of the deleted segment.

In the case of the second woman with an interstitial deletion of X (q22-q24) in mosaic with a normal female karyotype and three failed assisted fertilizations, cytogenetic analysis was sought, as infertility reasons were unclear. A milder clinical presentation was expected due to the mosaic karyotype, which was confirmed, showing no signs of gonadal dysfunction, yet pregnancy remained elusive. Should pregnancy occur, invasive prenatal diagnostics, combined with molecular-cytogenetic analysis and PGD, would be crucial for ensuring a healthy offspring, considering the possibility of inheriting an unbalanced karyotype. This becomes particularly significant for potential male offspring.

Furthermore, our study identified one couple experiencing three unsuccessful assisted fertilization attempts. The male patient was placed with a deletion on the long arm of the Y chromosome Yq11.2. Across various populations worldwide, Y chromosome microdeletions vary significantly, ranging from less than 2% to over 24%, depending on region and ethnicity [22]. These microdeletions are prevalent in as many as 5% of severely oligospermic men and up to 10% of azoospermic men [23, 24]. This aberration is directly inherited by male offspring, necessitating the Intracytoplasmic Sperm Injection (ICSI) technique in assisted fertilization for such cases. Following Klinefelter's syndrome (47, XXY), the primary genetic cause of male infertility arises from microdeletions within the AZF region of the Y chromosome [25, 26].

In the current study, we identified a pericentric inversion of chromosome 9 (p11; q13) in two male and one female patient. This inversion occurs at a 1-1.65% frequency in the general population and is typically regarded as a normal variant of chromosome 9, showing no associated

phenotypic expression [26]. However, specific reports indicate a higher occurrence of this inversion of chromosome 9 among individuals with azo- and oligospermia, suggesting reduced fertility in male carriers. Moreover, a slightly elevated frequency has been observed in women from couples undergoing the ICSI technique for assisted fertilization. Multiple studies suggest an increased likelihood of spontaneous abortions in couples where one or both partners carry this inversion [27-30].

The literature data highlights that chromosomal aberrations among examined patients are a known factor contributing to infertility [31]. However, cases where the cause of infertility was medically apparent were often overlooked, and the genetic basis of this issue was not promptly analyzed. A notably higher incidence of chromosomal abnormalities was observed among male partners in infertile couples, surpassing 10%. In female infertility cases, multiple studies have noted increased rates of chromosomal irregularities compared to the general population. Some authors have even reported discriminating frequencies among individuals with secondary infertility. However, except in cases such as Turner syndrome, the association between abnormal karyotypes in women and female infertility remains less explicitly understood compared to the link observed in infertile men [32]. While male infertility can stem from diverse factors like genital tract structural issues, infections, varicocele, hormonal imbalances, chronic ailments, and exposure to substances or radiation, around 40% of cases lack a clear medical cause, suggesting a potential role for genetic factors demanding further analysis.

Our study demonstrated a statistically significant difference in aberrations compared to the general population, expected given the patient pool referred for *in vitro* fertilization due to various medically defined reasons. Unfortunately, these patients were referred only after unsuccessful assisted fertilization attempts rather than before or during preparation for the procedure. Concerning known frequencies of chromosomal abnormalities in subfertile couples from existing literature, statistical analysis revealed no significant difference within the patient population of this study, indicating a high percentage of couples harboring such aberrations.

## 5. Conclusions

Our study underscores the importance of conducting karyotype and potential genetic analyses for patients undergoing assisted fertilization, considering that we found chromosomal abnormalities in 12% of study participants. It advocates for implementing these tests during the preparation phase for *in vitro* fertilization rather than waiting until after unsuccessful attempts or the birth of a child with chromosomal aberrations. Considering assisted fertilization's emotional, physical, and financial toll, timely and comprehensive preparation becomes imperative, potentially preventing multiple failed attempts. Therefore, our findings strongly advocate for including cytogenetic analysis as a standard diagnostic procedure for individuals facing infertility, particularly as part of the preparation process for assisted fertilization.

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## Author Contributions

Each author significantly contributed to the preparation, implementation, and writing of this study.

## Competing Interests

The authors have declared that no competing interests exist.

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