CHROMOSOMAL ABERRATIONS IN INDIVIDUALS WITH INFERTILITY. A RETROSPECTIVE ROMANIAN STUDY.

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ABSTRACT:

Aim of the study: Chromosome abnormalities have an important role in reproductive failure. The presence of numerical or structural aberrations can induce primary infertility or recurrent pregnancy loss. The main purpose of our study was to determine the chromosomal constitution of infertile individuals.

Methods: The study was a retrospective analysis based on the results of the constitutional karyotypes in peripheral blood in 380 infertile individuals. The samples consisted of infertile patients of both sexes from Romania, who were studied in the Cytogenetics Laboratory of the Medical Genetic Center Personal Genetics, from 2022 to 2023.

Results: From the total patients, a percentage of 53% were men, respectively 47% women.

In total, 18 karyograms with structural or numerical anomalies were identified, i.e. a percentage of 5%. Sex chromosomes were involved in 7 cases and autosomes in 11. Thus, chromosomal abnormalities involving autosomal chromosomes represent a percentage of 61% of cases.

Of the total chromosomal abnormalities identified in patients, the largest percentage is represented by the pericentric inversion of chromosome 9, representing 44% of the abnormal karyograms.

Robertsonian translocations were found in only one case, representing 9% of the cases with autosomal abnormalities analysed for fertility problems.

Among sex chromosome abnormalities, the highest percentage was represented by men with 46,XX, respectively 43% of the total, identified in 3 cases. Tuner Syndrome was identified in 2 cases, i.e. 29% in total.

Conclusions: In summary, the results suggest that chromosomal aberrations are a major cause of infertility in humans and cytogenetic analysis should be strongly recommended for infertile individuals. Karyotyping is an essential study in infertility. The detailed clinical examination of this type of patients would facilitate early diagnosis and adequate management.

KEYWORDS: Cytogenetic studies; Infertility; Chromosomal aberrations; Reproductive issues; Karyotype; Klinefelter Syndrome; Turner Syndrome; Pericentric inversion of chromosome 9.

1. INTRODUCTION:

Infertility is a medical condition characterized by the failure to establish a pregnancy despite 12 months of regular, unprotected sexual intercourse.[1] The presence of two or more consecutive pregnancy miscarriages is also a characteristic that describes infertility and needs medical attention.[2]

There are several causes that lead to infertility: sperm abnormality in men and ovulation dysfunction or tubal pathology in women. Furthermore, infertility can also be due to hormonal, immunological, genetical, psychological and other causes. Also, infertility can be related to age, exercise, obesity or infectious disease; it can also result from surgery or blockage.[3]

In up to 30% of the cases, infertility remains without a specific diagnose, making it difficult for couples to receive proper medical guidance.[4]

According to an analysis study organized by the Association of Human Reproduction in Romania, 16.8% of the fertile population studied face problems related to reproduction and about 1 in 4 couples are facing difficulties related to spontaneous, medically undirected reproduction.[5]

For a long time, women were considered to be the main reason for fertility problems, but recent studies show that 40-60% of infertility is caused by male pathology.[6] It is already known that advanced age in male cases increases the risk of alteration of genetic material in sperm and men who delay reproduction have an increased risk in producing embryos with various pathologies.[7]

Chromosomal abnormalities play an important role in reproductive failure. These can be numerical or structural and can affect sex chromosomes or autosomes. The most common structural changes are translocations, inversions, deletions and duplications. Chromosomal aberrations are one of the principal genetic factors in infertility; therefore, constitutional karyotype analysis is essential in the diagnostic evaluation for identification of the underlying cause of reproductive failure.[8]

The objective of this investigation is to determine the chromosomal constitution of 380 infertile individuals, analysing the incidence and the type of karyotype abnormalities found both in males and females. Chromosome studies were performed to elucidate infertility causes, spontaneous abortions and foetal wastage.

The study population included patients with different forms of infertility: primary, secondary and recurrent miscarriage. In practice, the evaluation of chromosomal abnormalities in individuals with reproductive failure directs the doctors for risk evaluation and in selecting the most appropriate management and treatment options for infertile patients.

2. MATERIALS AND METHODS:

In this retrospective study, we analysed the cytogenetic results of 380 patients, from whom 200 infertile men (ages: 30-56) and 180 infertile women (ages: 18-41). The sample consisted of infertile patients of both sexes, from Romania, who were studied in the Cytogenetics Laboratory of the Medical Genetic Center, from 2022 to 2023. We analysed the chromosome formulas obtained and the age of the subjects at the time of diagnosis.

The patients were referred to the laboratory from the department of endocrinology, obstetrics and gynaecology, urology and clinical genetics specialties because of infertility or sterility and the suspicion of chromosomal aberration.

Conventional chromosome analysis (metaphase chromosome preparation) was performed according to standard cytogenetic protocol. A heparinized peripheral blood sample was collected from the patients, and chromosomal analysis was carried out on phytohemagglutinin (PHA) stimulated lymphocyte cultures. Twenty metaphases were analysed through GenAsis Cytogenetics Suite system for each patient, and, in case of abnormalities and mosaicism, the study was extended up to 30 metaphases. The karyotypes were recorded according to the actual version of the International System for Human Cytogenomic Nomenclature (ISCN 2020).

Limits of method: The method detects numerical chromosomal abnormalities and gross structural rearrangements with a resolution level above 5 MB; smaller structural chromosomal aberrations and low-level mosaicism for either numerical or structural changes cannot be detected.

All participants gave informed consent to genetic testing according to national regulations.

Records from the laboratory were analysed in order to obtain chromosome formulas, the gender and the age of the subjects at the time of karyotyping.

3. RESULTS:

From the total number of 380 patients with an indication of chromosomal analysis for infertility, a percentage of 53% were men (200), respectively 47% women (180) in our study. In total, 18 karyograms with structural or numerical anomalies were identified, i.e. a percentage of 5%. Of these abnormal karyograms, 11 were identified in males and 7 in female patients.

The average age of the patients investigated was 35 years old for men and 32 for women, with a median value of 33 years for men (30-56), respectively 32 for women (18-41).

Considering the representation on autosomes and sex chromosomes, chromosomal abnormalities involving autosomal chromosomes represent a percentage of 61% of cases. Of the 18 cases with abnormal karyograms, autosomes were involved in 11 cases and sex chromosomes in 7 cases.

Of the total chromosomal abnormalities identified in our patients, the largest percentage is represented by the pericentric inversion of chromosome 9, representing 44% of the abnormal karyograms. This anomaly is found in 5 cases of the male patients and 3 cases of the female patients.

The next most common anomaly involves sex chromosomes, with a total percentage of 40% of the cases. This finding also affects more men than women, with 4 cases found in male patients and 3 cases in female patients.

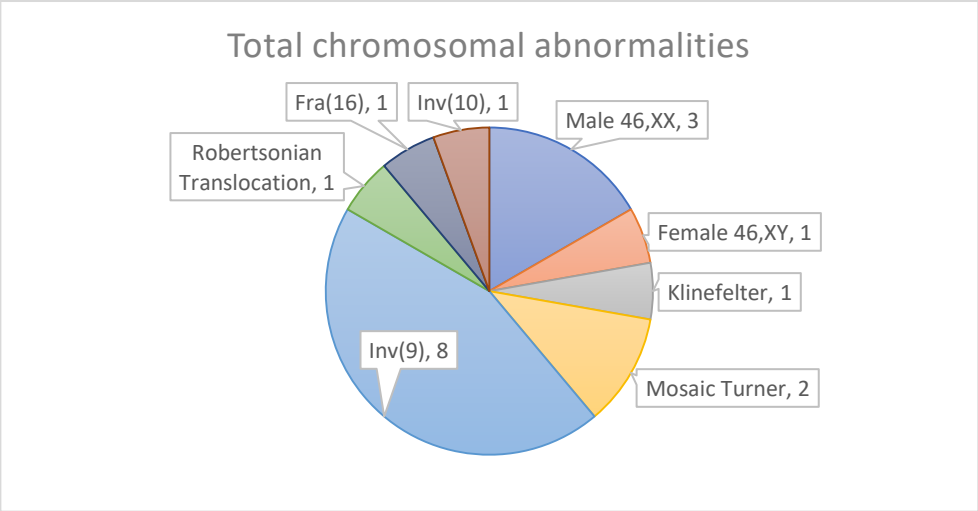

Fig. 1

	Male 46,XX	Female 46,XY	Klinefelter 47,XXY	Mosaic Turner	Inv (9)	Robertsonian translocation	Fra(16)	Inv(10)
Number	3	1	1	2	8	1	1	1
Percent	17%	6%	6%	11%	44%	6%	6%	6%

Table. 1

Taking in consideration only autosomal abnormalities, they were represented in the highest percentage by the pericentric inversion of chromosome 9, i.e. 73%. Robertsonian translocations were found in only one case, representing 9% of the cases analysed for fertility problems, the same as 16 chromosome fragile site and inversion of chromosome 10.

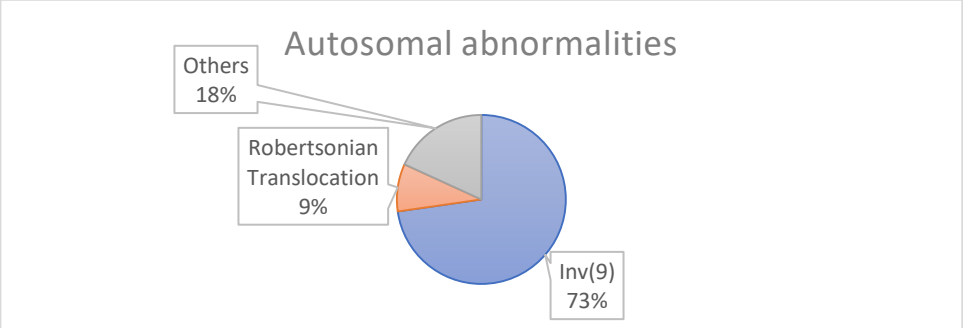

Fig. 2

Among sex chromosome abnormalities, the highest percentage was represented by men with 46,XX, respectively 43% of the total, being identified in 3 cases. Tuner Syndrome in mosaic was identified in 2 cases, i.e. 29% in total. Only one case of Klinefelter Syndrome (47,XXY) and one woman with 46,XY were found.

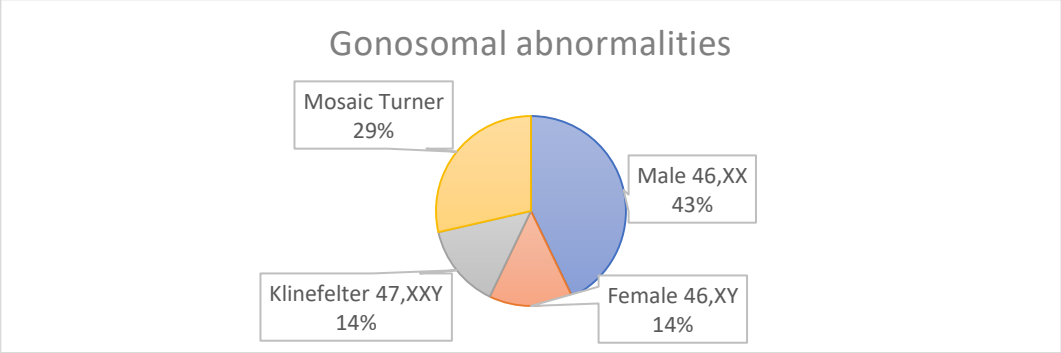

Fig. 3

4. DISCUSSIONS:

There are multiple genetic factors involved in infertility and chromosomal studies have an important role in deciphering the complexity of the causes[9]. Our study investigated numerical and structural chromosomal abnormalities both at autosomal and gonosomal chromosomes. Like Yan Liu et. al study[10], we analysed the incidence and the type of chromosome abnormalities. In their study, the rate of chromosome abnormalities is 3.84% in 14965 infertile couples. We found an incidence of 5% karyotype anomalies, but the cases we analysed are divided into 380 patients, with 200 males and 180 females investigated separately.

An important role is attributed to the sex chromosomes which explain fertility disorders. Also, large structural alterations, over 5 megabases, are possible to be diagnosed by karyotyping and may explain infertility or the result of genetically unbalanced foetuses.

Women with **Turner syndrome** can have several physical and developmental characteristics. Partial or complete absence of an X chromosome can lead to reduced ovarian development and a compromised ovarian function.

Mosaic Turner syndrome is a rare form of TS in which some of the body's cells have a normal 46.XX karyotype, while others have a 45.X karyotype. Around 15-25% of women with TS have mosaicism[11]. Infertility remains a major concern for women with mosaic Turner syndrome, but its severity and frequency may vary depending on the proportion of mosaic cells and overall reproductive health.

Ovarian function in mosaic Turner syndrome can be variable. Some women may show normal or mildly impaired ovarian function in cells with karyotype 46,XX, while cells with karyotype 45,X may show reduced or absent ovarian function. This discrepancy can influence fertility and cause variability in the presentation of infertility.[12]

The evaluation and management of infertility in mosaic Turner syndrome can be complex and require an individualized approach. Assisted reproductive techniques, such as in vitro fertilization (IVF) and the use of donated oocytes, may be options for some women with mosaic TS who wish to have children.

In our study we found two patients with mosaic Turner syndrome. Both patients suffered with fertility problems and were sent by the gynaecologist. Thus, through the karyotype analysis their fertility issues were able to get an explanation and a diagnosis.

XXY gonosomal aneuploidy, most known as **Klinefelter syndrome**, is a numerical chromosomal disorder that targets the sex chromosomes and affects men. Hypogonadism, characterized by reduced testosterone production and functional impairment of Leydig cells, is a common feature of KS and contributes to infertility[13].

Men with mosaic Klinefelter syndrome can have a wide range of symptoms, which can vary depending on the proportion of mosaic cells and the level of tissue damage. Infertility may be less severe in mosaic KS than in the complete form, but it remains a significant problem for many affected men.

Although rare, structural abnormalities involving the X chromosome or autosomes may also be associated with Klinefelter syndrome. These abnormalities may include deletions, duplications, inversions or translocations of genetic material, which can affect gene expression and contribute to the clinical features seen in KS.

Klinefelter Syndrome is found in the majority of cases as 47,XXY karyotype, which is consistent with our finding[14]. From our cohort of 380 patients, we had one man with complete Klinefelter syndrome: 47,XXY karyotype.

The **XX Male Syndrome**, also called De La Chapelle, represents a sexual developmental disorder characterised by a male phenotype and a female 46,XX karyotype. Phenotypically individuals can present in various forms from congenital ambiguous genitalia to normal males,

usually diagnosed after puberty or later at reproductive age, when the infertility is detected[15]. It is a rare syndrome with an incidence of 1 in 20 000–25 000 males[16].

In our 380 cases analysed for fertility issues, we found 46,XX karyotype in 3 male patients, representing 17% of the total chromosomal abnormalities. It is the most common sex chromosome finding in our study, with a percentage of 43%. This finding is biased, considering there are more male patients than female. Nevertheless, it is still a surprise, comparing with Klinefelter and Turner Syndrome which are the most frequent sex chromosome abnormalities[17]. We found only 1 case of Klinefelter Syndrome and 2 cases of Turner Syndrome in mosaic.

Individuals with **Swyer Syndrome**-complete or pure gonadal dysgenesis are phenotypically female, with external female genitalia and primary amenorrhea, and a 46,XY karyotype. Most of these patients have a uterus and fallopian tubes, but the internal reproductive structures (could be ovaries or testes) can be underdeveloped and not functional. They are named „streak gonads", because consist of fibrous tissue and are at high risk of malignancy- gonad blastoma. Swyer Syndrome is usually diagnosed at puberty, when the menstrual period does not begin[18].

In the analysed cases, we had one patient with complete 46,XY karyotype which was present in all metaphases.

The **inversion of chromosome 9** is a common cytogenetic abnormality found in at least 1.5% of the general population[19]. The link between pericentric inversion of chromosome 9 and recurrent pregnancy loss or other fertility problems has been the subject of many studies in reproductive genetics. There are a lot of reports with conflicting findings about the clinical significance, but many studies show an association with reproductive problems[20]. For example, a retrospective study on 19,950 women found the incidence of chromosomal polymorphisms, including inv(9), to be higher in patients with fertility issues compared to controls[21].

In our study we found the pericentric inversion of chromosome 9 inv(9)(p12q13) in 44% of the abnormal karyograms, representing the most frequent chromosomal anomaly in patients with fertility issues. Many types of inversions involving various breakpoints have been studied[22]. Starke H. et al reported that the most common breakpoints involve bands p12 and q13[23], which is also consistent with our findings.

Many clinical studies show that chromosome 9 inversion is more common among women than men, but it is more frequently correlated with DNA abnormalities at the level of spermatozoa and with a high degree of sperm DNA fragmentation. Many research show that males are more prone to have an impairment with clinical findings related to reproduction failure, rather than female patients carrying this inversion[24].

Even though there is no consensus about the higher incidence in female patients, our study found 5 males and 3 women with chromosome 9 inversion, showing a higher percentage in male patients.

Robertsonian translocations are structural rearrangements between the acrocentric chromosomes and are among the most common balanced chromosomal abnormalities[25]. With

a total prevalence estimated to be 1/800 individuals, rob(13;14) and rob(14;21) constitute the majority of findings[26]. In our study we identified only one case out of 18 abnormal karyograms, a male patient with rob(13;15), which is considered a rare Robertsonian translocation. Robertsonian carriers are usually healthy individuals but are known to have fertility issues, spontaneous miscarriages, offsprings with unbalanced rearrangements or even imprinting disorders if chromosomes 14 and 15 are involved[27], as in our case.

Other findings that were present in our cohort of patients with reproductive problems were a fragile situs on the long arm of chromosome 16 in a male patient which was present in 4 metaphases out of a total of 20 that were analysed, and an inversion on chromosome 10 at a female patient which was present in all the analysed metaphases. Carriers of pericentric inversions on chromosome 10 may experience recurrent miscarriages due to unbalanced gamete production. Also, this structural rearrangement may interfere with normal chromosomal pairing and segregation during meiosis, being a possible case of fertility disorders[28].

The maximum reproductive potential is found to be between 20-25 years for women, decreasing afterwards as they get older. If, for a healthy woman between the ages of 20 and 30, the monthly chances of conceiving are approximately 25%, they drop below 10% for women over 35[29]. Although men do not have a fixed supply of sperm and can theoretically procreate without an age limit, both the quality and quantity of semen decreases over time. In our patients, the average age for presentation is 33 years old (35 in males and 32 in females).

These results in our study show that genetic evaluation is crucial both for diagnosis but also for discovering possible personalised treatment options in couples with reproductive issues. Karyotyping is only the initial step in a full genetic investigation. For patients facing infertility, there are additional tests that can help in the diagnosis and prevention of genetic abnormalities.

Genetic counsellors and medical genetics doctors can help patients with a complete reproductive health investigation. They can direct the patients with the testing odyssey, depending on the clinical symptoms and testing results. Moreover, they also help with the emotional and psychological consequences of the couples.[30]

For example, in male infertility, Y-chromosome analysis and CFTR gene mutation analysis are additional tests that can complete a genetic investigation when karyotype results are normal[31]. In women with premature ovarian insufficiency, CGG repetition expansion of the FMR1 gene to detect Fragile-X is also another recommendation[32]. Primary ovarian failure can be caused by pathogenic variants in FSHR gene which lead to the absence of oocytes, so identifying a variant can lead to treatment options such as donor oocytes[33]. Also, for people who opt for assisted reproduction and have a history of recurrent spontaneous abortions, preimplantation genetic testing can be opted for in order to select the euploid embryos and increase the live birth rate[34]. IVF using preimplantation genetic testing has faced significant progress in treating reproductive and fertility issues. Especially for couples with structural chromosomal rearrangements, PGT is is a gold standard method in order to achieve a successful pregnancy.[35]

In conclusion, karyotyping couples with reproductive problems is an essential first step for discovering the causes of infertility in both males and females facing reproductive health issues.

Our study carried out on the 380 patients with reproductive problems, in the period 2022-2023, revealed that the rate of chromosomal abnormalities was 5%. This shows that more attention and studies are needed for the genetic causes of infertility. Depending on the diagnosis, clinical recommendations can be made in order to have a better reproductive outcome.

The most frequent anomaly found is the pericentric inversion of chromosome 9. Other genetic changes found in this study are sex chromosome abnormalities, Robertsonian translocation and pericentric inversion of chromosome 10. All these genetic anomalies explain the reason for testing and can be diagnostic for fertility disorders.

This study was carried out in the Personal Genetics laboratory in Bucharest, Romania. The obtained data demonstrate that cytogenetic analysis remains an important tool in the diagnosis of patients with fertility disorders.

1. DATA AVAILABILITY STATEMENT:

The data presented in this study are available on request from the corresponding author.

2. AUTHOR CONTRIBUTIONS:

Conceptualization: A.B, M.T, M.S.; methodology: C.G, C.I.; reporting cytogenetic results: G.P., D.I., I.B., A.B.; formal analysis: C.I.; investigation: A.B., M.T., M.S.; data curation: A.B; writing: A.B, M.T.; original draft preparation: A.B., M.T., M.S., C.G.; writing—review and editing: A.B., M.T., M.S.; visualization: M.T., C.I. All authors have read and agreed to the published version of the manuscript.

3. INFORMED CONSENT STATEMENT:

Informed consent was obtained from all subjects involved in the study.

4. EXTERNAL FUNDING:

This research received no external funding.

5. CONFLICTS OF INTERESTS:

The authors declare no conflicts of interest.

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