Original Research Article

Chromosomal aberrations in couples with infertility

Abstract

Aims: : One of the most significant causes of infertility in men and women can be chromosomal abnormalities. The study aimed to investigate the age, frequency, and types of significant cytogenetic abnormalities among infertile couples.

Study design: Retrospective study.

Place and Duration of Study:142 couples (284 patients) were referred to the Center for Genetics of the Faculty of Medicine in Sarajevo between 2018 - 2022.

Methodology: The research included 284 respondents aged 20 to 54 with infertility. Karyotyping was performed on peripheral blood lymphocytes using the Giemsa trypsin banding (GTG) technique.

Results: The highest frequency of infertility was in the couples group from 30-39 years old. The chromosomal aberration in infertil~~ity~~ couples was 2.8%. Out of 160 cases of primary infertility, aberrant karyotypes were recorded in five patients, and three aberrant karyotypes were recorded in 124 patients diagnosed with secondary infertility. Compared to numerical aberration, the most common type of chromosome was a structural aberration. ~~The highest frequency of infertility was in the couples group from 30-39 years old.~~ In both types of infertility, a structural aberration of inversion of chromosome 9 was recorded.

Conclusion: The frequency of chromosomal abnormalities and the age of couples with infertility suggest that cytogenetic analysis is essential for the timely detection of the cause of infertility. It has special significance for couples who decide on assisted fertilization.

Keywords:Infertility, structural and numerical chromosomal aberration, age.

1. INTRODUCTION

According to the World Health Organization, sterility, or infertility, is one of the most significant health problems. Infertility is defined as the inability to achieve pregnancy within a year of regular sexual intercourse (without the use of contraceptives). Infertility can be primary or secondary. Primary infertility is when a person has never achieved a pregnancy, and secondary infertility is when at least one prior pregnancy has been achieved.The reason for infertility can be in both men and women, and sometimes it is impossible to explain the causes. Estimates show that 48 million couples and 186 million individuals live with infertility(1). In men, infertility is most often caused by problems in ejaculation (2), a lack or low level of sperm, or abnormal shape (morphology) and movement (motility) of sperm. In women, infertility can be caused by several abnormalities of the ovaries, uterus, fallopian tubes, and endocrine system, among others. Some of the reasons are genetic, endocrine, physiological, anatomical, and immunological abnormalities of the reproductive system, which can affect the likelihood that a woman will become pregnant and give birth to a live child (3). Genetic causes of infertility can be numerical and structural chromosomal aberrations affecting autosomal and sex chromosomes and monogenic and polygenic disorders. It is important to determine the exact cause of infertility because

chromosomal aberrations are responsible for 2-14% of male infertility (4) and as much as 10% of female infertility (5).Regardless of the cause of the problem, it is very important to detect the problem in time. Assessing the risk of transmission is essential in cases where genetic disorders are behind such problems. Detecting a change in a chromosome or gene allows the possibility of providing precise genetic information about inheritance risks (6). The study aimed to investigate the age, frequency, and types of significant cytogenetic abnormalities among infertile couples.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY

In this retrospective study, we analyzed the cytogenetic results of 142 couples (284 patients) referred to the Center for Genetics of the Faculty of Medicine in Sarajevo between 2018 - 2022. The research included 284 respondents aged 20 to 54 with infertility.

When arriving at the Center for Genetics at the Faculty of Medicine in Sarajevo, couples are informed about the goals and diagnostic potential of the analysis that will be performed. TheEthical standards and the Declaration of Helsinki were performed in the present study.

Short-term cultivation methods perform cultivation of peripheral blood samples at patients', and commercial media for peripheral blood were used for cultivation (*PB–MAX*^{TM}*Karyotyping*medium (*Gibco*)) (7). Instructions and rules given by the International System of Human Chromosomal Nomenclature (ISCN) were followed when the cytogenetic analysis was performed (8). With every karyotype analysis, 25 cells terms sample are used by the G-bending technique (9). The results were analyzed using SPSS 20 (*Statistical Package for the Social Sciences*, IBM, NY, USA) program. Data were expressed in frequency, such as the total number of cases and percentage of the total number. The average age of the subject was presented as the median with the minimum and maximum range of the variable.

3. RESULTS

In the framework of our study, 142 couples, or 284 patients referred to the Center for Genetics due to some reproductive issues, were examined. Reproductive problems concern infertility, primary and secondary. The lower age limit of our population was 20, and the upper age was 54. The mean value was 34.80, with a standard deviation of ± 5.94.

Most patients belong to the 30-39 age category (Figure 1). A total of them were 173 (61%). Within the group of patients aged 40-49, there are 56 patients (19%). 52 (18%) are in the 20-29 age group, and only three patients (1%) are in the 50 and over age group.

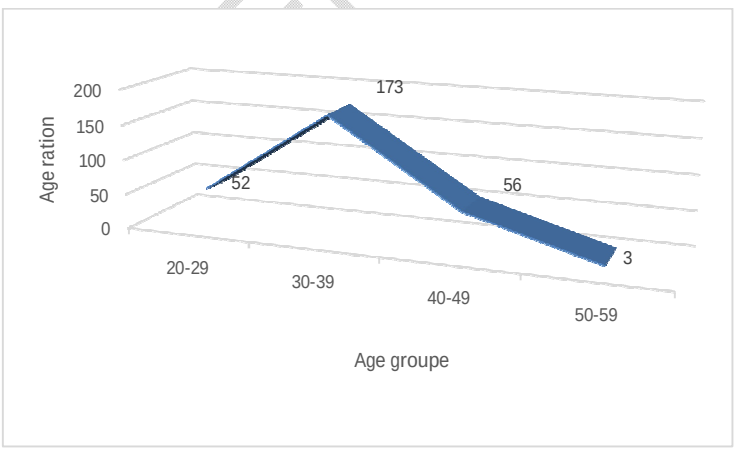

Figure 1. Age distribution of couples with infertility

Most men were in the 30-39 age range, 86 (60.5%) of them, followed by those in the 40-49 age group. There were 35 (24.6%) respondents in this group, and 18 (12.7%) men belonged to the group 20 to 29. The smallest number of respondents belongs to the 50-59 group, three (2.1%) of them.

Regarding women, there are also most of them in the age group of 30 to 39 years, 87 (61.3%) of them. Then, 34 (24%) belong to the 20-29 age group, and 21(14.7%) women belong to the 40-49 age group.

Of 284 patients, 160 were assigned to the primary infertility group (56,4%). One hundred twenty-four patients (43,6%) were diagnosed with secondary infertility. Of these patients, five women had three spontaneous abortions, while the other had one or two spontaneous abortions.

Eightcases with an aberrant karyotype were recorded in couples with infertility. Out of 160 cases of primary infertility, aberrant karyotypes were recorded in five patients (3.1%), and threeaberrant karyotypes were recorded in 124 patients diagnosed with secondary infertility (2.4%). Table 1. shows the karyotypes. Robertsonian translocation was found in women with two miscarriages. One woman's karyotype was mosaicism 46, XX/47, XXX. Two men with primary infertility had a rare translocation (46, XY, t(3;11)(q29;q14); 46, XY,t(4;21)(q12;q11.2)). While two women and one man had a pericentric inversion of chromosome 9.

Table 1. Type and frequency of chromosomal aberration in infertile couples

Karyotype	Type of infertility	Type of aberrations	Frequency (n)	Percentage (%)
46,XX, inv(9)(p11;q13)	Primary	Structural	2	25%
46,XY, inv(9)(p11;q13)	Primary	Structural	1	12.5%
46, XY, t(3;11)(q29;q14)	Primary	Structural	1	12.5%
46,XY,t(4;21)(q12;q11.2)	Primary	Structural	1	12.5%
46,XX, inv(9)(p11;q13)	Secoundary	Structural	1	12.5%
46,XX/47,XXX	Secoundary	Numerical	1	12.5%
45,XX,rob(13;14)(q10;q10)	Secoundary	Numerical	1	12.5%

Legend: Data are presented as absolute numbers and percentages of a total number of cases affected by a particular chromosome aberration. n-number of cases

The mean age for subjects with an aberrant karyotype was 31 years, with a standard deviation of ±7.57. For male respondents (three), the mean value was 29,-3 years, with a standard deviation of ± 5.68. The mean age of female respondents (five) was 32 years, with a standard deviation of ± 9.

A t-test was also performed for two groups of subjects (male and female part of the population with aberrations) to determine whether there was a statistically significant difference in age between the subjects of the two sexes. The *P*= 0.3868, so this data is taken as an argument that there is no statistically significant difference regarding the age of male and female subjects with present chromosomal aberrations.

DISCUSSION

Millions worldwide have infertility problems. Many causes affect infertility, one of them being genetic factors (10, 11). Chromosomal aberrations represent one of the most significant causes of infertility and spontaneous abortions. The frequency of aberrant karyotypes in the general population ranges from 0.5% to 1%, while this

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percentage is significantly higher in people with reproductive problems (12). In our research, the percentage with an aberrant karyotype is 3.1% in people with sterility, which is a large percentage compared to the number of subjects. Some pregnancies, unfortunately, end in spontaneous abortion.One of the causes of spontaneous abortions is chromosomal anomalies, mostly aneuploidy (13, 14). Interestingly, we recorded the exact structural change, inversion of chromosome 9, in women with primary infertility as well as in women with secondary infertility. A man also had this inversion. Regarding the pericentric inversion of chromosome 9 (inv(9)), we have divided opinions among scientists. According to some authors, this inv(9) is considered a normal variant, and according to others, this type of inversion affects infertility (15,16).

The frequency of chromosomal aberrations among couples with recurrent, repeated miscarriages (two or more) varies from 2-8% (17). In our research, cases with one, two, or three repeated abortions were recorded. It is interesting to point out that chromosomal aberrations were not recorded in couples with three habitual abortions. In the literature, there is data on the increased frequency of chromosomal aberrations in people with more spontaneous abortions. For example, in the research conducted by Kiss et al. in 108 couples (216 individuals) with a history of frequent spontaneous disorders, a frequency of chromosomal aberrations of 5% was recorded in couples with two miscarriages, 10.3% in couples with three miscarriages and a frequency of 14.3% in couples with four or more miscarriages. (18).

The frequency of chromosomal aberrations in the general population ranges from 0.37%-1.86%, while this percentage in people with sterility is 3.95%-14.3% (19). In our subjects with spontaneous abortions, 3aberrant karyotypes out of 124 karyotypes were recorded, which agrees with other studies.

According to some authors, chromosomal aberrations are more frequent in women with secondary sterility than in women with primary sterility (20, 21). However, according to research by scientists Liu et al., the frequency of chromosomal aberrations is higher in persons with primary sterility and was 9.29% (800/8606), while in persons with secondary sterility, it is 5.47% (285/5213) (19). All of these studies confirm an increased frequency of chromosomal aberrations in women with sterility (20, 22). Due to the small number of samples, our study did not show a difference in the frequency of chromosomal aberrations in women with primary or secondary sterility. Also, there is no statistically significant difference in the frequency of chromosomal aberrations between the male and female populations in this study. A total of three chromosomal aberrations were recorded in men (5%; 5/100) and five aberrations in women (6%; 6/100). According to research by Benchikh et al., the percentage of chromosomal rearrangements is higher in men with reproductive problems than in women. In our previous research, there was a more significant number of men with reproductive problems caused by chromosomal aberrations (23).

There is a growing trend of postponing family planning so that couples want to have children in the later years of reproductive age, more precisely in the middle or late thirties. A woman's age is recognized as the main limiting factor of fertility and good reproductive success. The trend of older parents applies not only to women but also to men. For example, 19/1000 pregnancies in Germany were in the 40-44 age group in 1991. This rate increased to 61/1000 births in 2013 (24). Our research also showed that the number of couples over 40 (20%) underwent cytogenetic analysis increased. Due to the impossibility of natural conception, most of these couples decided on in vitro fertilization. Some reasons they did not want to have children earlier, before age 35, are career reasons and living conditions. Given the increasing worldwide rate of women of advanced childbearing age over recent decades, increasing attention is being paid to this paternal influence on reproductive success (25). Also, premature menopause in the reproductive age and the increased prevalence of deliberately delaying pregnancy in developed countries contribute to female infertility (26, 27).

Given that more and more couples with reproductive problems are recently deciding on assisted reproduction (ART), it is very important to determine the cause of infertility (28). This is why cytogenetic analysis is essential, as well as genetic counseling, which will give couples adequate guidance and information about the existing risks when it comes to such procedures for the treatment of infertility, as well as about the benefits and possible outcomes thereof (29).

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4. CONCLUSION

Cytogenetic testing of couples with reproductive problems can help discover the cause of infertility. Finding the cause of infertility in men and women is essential for genetic counseling, especially in cases where couples decide on assisted fertilization.

CONSENT (WHEREEVER APPLICABLE)

The samples for analysis were marked with a code, and in this way, the identity of the persons who participated in this research was protected.

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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