**Original Article**

# Chromosomal Abnormalities in Iranian Infertile Males who are Candidates for Assisted Reproductive Techniques

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Abstract

**Background:** The present study offers our contribution on the topic by a retrospective analysis of the prevalence of chromosomal abnormalities in a population of Iranian infertile men attending assisted reproduction programs.

**Materials and Methods:** Cytogenetic analysis was performed according to standard methods on cultured cells obtained from the patient peripheral blood. In all, 874 files belonging to male partner of each couple were classified as follows: azoospermic, oligozoospermic and patients with low sperm quality in respect of morphology and motility.

**Results:** Chromosomal abnormalities were observed in 136(15.5%) individuals of the whole population studied including 12.0 %, 1.2 % and 2.0% of azoospermic, oligozoospermic and patients with low sperm quality, respectively. Of those, 116 (13.2%) had sex chromosome abnormalities and 20(2.3%) had autosomal chromosome abnormalities.

**Conclusion:** We observed high frequency of aneuploidy and sex chromosomal mosaicism in azoospermic men and high structural aberrations in males with low sperm quality. We suggested that type of chromosomal abnormalities had an inverse relation to sperm count. So that, high chromosomal aneuploidy was detected in males with lower sperm count and high structural aberration was detected in males with low sperm quality. Chromosomal abnormalities are a major cause of male infertility. Consequently, Genetic testing and counselling is indicated for infertile men with abnormal semen parameters with either abnormal karyotype or normal karyotype before applying assisted reproductive techniques.

***Keywords:*** Chromosomal Abnormalities, Infertility, Assisted Reproductive Techniques

## Introduction

Infertility affects an estimated 10-15 % of couples, and male factor infertility represents >50% of cases (1). The fact that chromosomal abnormalities are more prevalent in infertile men compared to fertile men is well established. Several studies reported the prevalence of chromosomal abnormalities in infertile men, from 2% up to 16.6 % with sample range from 72 up to 2600 cases (2-7).

This study showed prevalence of multifarious numerical and structural chromosomal abnormalities among infertile men. We also found the effective role of chromosomal study to predict probability of transmission of affected gamete to offspring. Thus, in infertile males with abnormal karyotype, preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND) aid in increasing outcome of pregnancy.

## Materials and Methods

In this evaluation, 874 clinical records of male partner of couples from the different areas of whole country since 2006 were reviewed. The informing consent was

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signed up by all the patients. Our subjects were grouped in three classes; azoospermia (n=444), oligozoospermia (n=175) and patients with low sperm quality (n=255) (Table 1).

Spermogram and basic hormone evaluation were studied for each patient, and all the cases were evaluated cytogenetically. Cytogenetic analysis was performed according to standard methods on cultured cells from the patient peripheral blood. The culture was harvested after 72 hours. At last 20 metaphases were examined by trypsin G (GTG) banding (8). ISCN guidelines for chromosome nomenclature were followed (9). In any case with mosaic status, about 50 metaphases were examined. Chromosome heteromorphisms were confirmed with C- and NOR-banding. All the men affected by oligozoospermia or azoospermia with normal karyotype were further investigated for microdeletions of chromosome Y.

## Results

In this retrospective study, 874 infertile men were examined for chromosomal abnormalities. The studied patients consist three groups of infertile men with azoospermia (50%), oligospermia (20%) and with low sperm quality (29%). In total, 136 out of 874 of infertile men had chromosomal aberrations. The frequency and type of chromosomal aberrations are summarized in details in table1.

Also, the standard inversion of chromosome 9, as a normal variant, was observed in 9 patients who excluded from abnormal patients with abnormal karyotype.

***Cytogenetic finding in Azoospermic males***

In 106 out of 444 azoospermic men, chromosomal abnormalities were detected. Numerical abnormalities was the most common finding in 74 cases, of those, 73 cases were Kelinfelter syndrome with 47, XXY karyotrype and one patient with 47, XY, +mar karyotype. Individuals with mosaic variants of Kelinfelter syndrome was categorized in mosaicism group. One Kelinfelter patient had inversion of chromosome 9. Three azoospermic patients were identified as 46, XX male, and investigation for presence of SRY (Sex Region on Y) was positive.

Structural aberrations were observed in 11 azoospermic cases; including two cases with inversion, 7 cases with balance translocation, one with addition on chromosome 15p13 and another with deletion in chromosome (Y) (q11.21q11.23) (Table 2).

Of azoospermic males, 18 cases had sex chromosomal mosaicism.

One azoospermic patient was chimerism with chi 46, XX [83]/46, XY [17] classified in mosaicism group.

**Table 1: Frequency and type of chromosomal aberrations in total group of infertile men**

| Type of aberrations without inv (9) | Total n=874 | Azoospermia n=444(50%) | Oligospermia n=175 (20%) | Sperm abnormalities n=255 (29%) |
|---|---|---|---|---|
| **Numberial** | 81(9.3%) | 74(16.6%) | 6(3.4%) | 1(0.4%) |
| **47, XXY** | 79(9.0%) | 73(16.4%) | 6(3.4%) | - |
| **47, XY, +mar** | 1(0.1%) | 1(0.2%) | - | - |
| **47, XYY** | 1(0.1%) | - | - | 1(0.4%) |
| **Structural** | 25(2.8%) | 11(2.5%) | 3(2.2%) | 11(4.3%) |
| **Inversion** | 8(0.91%) | 2(0.45%) | - | 6(2.35%) |
| **Translocation** | 15(1.7%) | 7(1.5%) | 3(1.7%) | 5(1.9%) |
| **Others** | 2(0.2%) | 2(0.4%) | - | - |
| **Mosaic** | 27(3.0%) | 18(4%) | 2(1.14%) | 7(2.74%) |
| **46, XX male** | 3(0.34%) | 3(0.6%) | - | - |
| **Total** | 136(15.5%) | 106(23.8%) | 11(6.2%) | 19(7.5%) |

**Table 2: The type of some structural chromosomal aberrations in infertile males**

| | | |
|---|---|---|
| **Translocation** | 45, xy, t(13; 14) (q10q10) | Oligospermia |
| | 46, xy, t(15; 19) (p12q12) | Oligospermis |
| | 46, xy, t(7; 15) (q35q22) | Treatoastenospermia |
| | 46, xy, t(13; 16; 8) (p26.2q13q21.2) | Azoospermia |
| | 46, xy, t(3; 5) (p24q15.3) | Azoospermia |
| | 46, xy, t(1; 10) (p32q21.2) | Treatoastenospermia |
| | 46, xy, t(2; 3) (p23q21) | Treatoastenospermia |
| | 46, xy, t(4; 21) (p22q11.2) | Oligospermia |
| | 46, XY, t(1; 21) (q21q22.3) | Oligoastenoteratospermia |
| | 46, XY, t(14; 20) (q22q11) | Azoospermia |
| | 46, XY, t(1; Y) (q21q11) | Azoospermia |
| | 46, XY, t(17; Y) (q11.2q11.2) | Azoospermia |
| | 46, XY, t(1; 17) (p13q25) | Azoospermia |
| | 46, xy, t(3; 5) (p24p15) | Azoospermia |
| | 46, xy, t(8; 11) (q24.3q13.1) | astenospermia |
| **Addition** | 46, xy, add(15) (p13) | Azoospermia |
| **Deletion** | 46, XY, del(Y)(q11.21q11.23) | Azoospermia |
| **Inversion** | 46, xy, inv(y) (p11q11) | Azoospermia |
| | 46, xy, inv(y) (p11q11) | Teratospermia |
| | 46, xy, inv(11) (p12q13) | Teratoastenospermia |
| | 46, xy, inv(3) (p11q12) | Oligostenoteratospermia |
| | 46, xy, inv(3) (p22q11.2), inv(9) (p11q12) | Azoospermia |
| | 46, xy, inv(y) (p11q11) in three cases | Teratoastenospermia |

***Cytogenetic findings in Oligozoospermic males***

Of 175 cases categorized as oligozoospermia, 11 cases had abnormal karyotype. Six infertile men were identified as 47, XXY, three with balanced translocations and two with sex chromosome mosaic (Table 2).

***Cytogenetic findings in males with low sperm quality***

Males with reduced and impaired sperm motility (Asthenozoospermia), increased abnormal forms of sperm (Teratozoospermia) or both combined with oligozoospermia (Oligoasthenoteratozoospermia) were classified in this group. In this group, 19 out of 255 cases had abnormal karyotype. Structural aberration was a common finding in 11 infertile male (Table 2). In one patient 47, XYY pattern and in 7 patients chromosomal mosaicism was detected.

## Discussion

The prevalence of high chromosomal abnormalities in infertile men is depending on several factors, and this figure is inversely related to the sperm count.

Totally, we have found 15.5% chromosomal abnormalities (2.3% autosomal and 13.2% sex chromosomal aberrations) in the studied population. The prevalence of aberrations in azoospermic, oligozoospermic and males with low sperm quality in total group was 12.0%, 1.2% and 2% respectively. In total population, aneuploidy (9.38%) was the most frequent chromosome-related cause among infertile males. Of those, sex chromosome aneuploidy was the most common (9%). Klinefelter syndrome was the most frequent sex chromosome anomaly in males with azoospermia (2-6) (Table 1). Among all the aberrations (gonosomal and autosomal), the 47, XXY karyotype was found in 9% of total group. Among the group of 444 azoospermic males, 73 individuals with (16.4%) 47, XXY pattern were found. In oligozoospermic males the 47, XXY karyotype was not as frequent and constitutes only 4.4% (6 out of 136) of all abnormalities. In the group of infertile males with low sperm quality no case of Klinefelter syndrome was found.

Males with a 46, XX karyotype were mainly found in the group of azoospermic males (Table 1). Three out of 444 (0.7%) males with azoospermia revealed this karyotype

with SRY material. Most XX males originate from a crossing over between Xp and Yp during paternal meiosis, so that SRY gene translocated on X chromosome. The SRY gene is present in these cases (SRY+ XX males), but they have azoospermia and a phenotype similar to that of Klinefelter syndrome (10). In present study, frequency of autosomal abnormalities in oligozoospermic males was lower than sex chromosomal abnormalities, contrary to some studies (10). Noteworthy, some studies included males with low sperm quality in oligozoospermic group.

Structural aberrations in azoospermic and oligozoospermic males were approximately similar. In infertile males with severe spermatogenesis impairment, chromosomal aneuploidy (especially sex chromosome) seems to be more common than other abnormalities in comparison with males with low sperm quality (5-7). In cases with low sperm quality, the frequency of structural chromosomal aberrations was reported higher than other abnormalities (6, 7), as in 4.3% of males with low sperm quality in comparison with 2.5% in azoospermic and 2.2% in oligozoospermic males (Table 1). This shows that structural aberrations may possibly involve in morphology and motility of sperm. Consequently, preparation of high resolution chromosome in group with low sperm quality is crucial to detect complicated rearrangement. We suggested that type of chromosomal abnormalities would inversely be related to sperm parameters. So that, high chromosomal aneuploidy was detected in males with severe spermatogenesis impairment and high structural aberration was detected in males with low sperm quality.

## Conclusion

In conclusion, infertile males with abnormal semen parameters and normal karyotype form the majority of cases as complicated group with unexplained infertility. Therefore, genetic testing and counselling is indicated for infertile men with abnormal semen parameters with either abnormal karyotype or normal karyotype before applying assisted reproductive techniques.

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