

**Numerical Chromosomal Abnormality in Male Infertility – A Review Study**

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**Abstract**

Chromosomal abnormalities are one of the major causes of human infertility as they interfere with spermatogenesis. In infertile males, abnormal karyotype is more frequent than in the general population. Defects in Chromosome number are also present with an increased incidence in the sperm of infertile men as compared to fertile men. Study of human chromosomes plays a key role in diagnosis, prognosis and monitoring of chromosomal abnormalities.

**Keywords:** Chromosomal Abnormalities, Chromosomes, Sperm.

**Introduction**

Chromosomal abnormalities are one of the major causes of human infertility as they interfere with spermatogenesis. Study of human chromosomes plays a key role in diagnosis, prognosis and monitoring of chromosomal abnormalities. In infertile males, abnormal karyotype is more frequent than in the general population (Sarrate Z et al, 2005). Genetic abnormalities are considered to make an important contribution to these cases of unexplained spermatogenesis failure. (Rao L et al, 2004). Specific genetic defects have been identified in less than 20% of infertile males and, thus, most causes remain to be

elucidated. Genetic factors accounts to 10-15% of severe male infertility including chromosomal aberrations and single gene mutations (Ferlin et al, 2006). Chromosomal abnormalities are common in infertile men with an incidence of 5.8% as compared to an incidence of 0.5% in the fertile population (Johnson, 1998). Chromosomal abnormalities can occur on several genetic levels: 4.2% of abnormalities occur on the sex chromosomes whereas 1.5% occurs on the autosomes. Sex chromosome anomalies were found in 15.9% and autosomal anomalies in 2.8% of the azoospermic men. The Klinefelter syndrome (47, XXY) is the most commonly found numerical abnormality. Defects in Chromosome number are also present with an increased incidence in the sperm of infertile men as compared to fertile men (Finkelstein et al, 1998).

**Material and Methods:** Research publications from 2009 to 2016, from journals were reviewed.

**Discussion**

In infertile male there are structural, numerical or mosaicism chromosomal abnormality. Sex chromosomal abnormalities are most commonly found in male infertility. Numerical sex chromosome abnormalities include classic and mosaic forms of Klinefelter’s syndrome, YY-aneuploidies and other numerical chromosomal abnormalities. These are

mostly seen in azoospermia group (5.8%-22.7%) than in oligospermia (0.5%-4.4%) (Johnson, 1998; Dohle et al 2002; Rao et al 2004; Akgul et al 2009; Yatsenko et al 2010). In normospermic infertile men sex chromosome aneuploidies have been found in 1.4% and in newborns in 0.1 % (Johnson, 1998).

Klinefelter syndrome is the most frequent sex chromosomal disorder in infertile males, in which atleast one extra X chromosome has been added to a normal male karyotype (Mak and Jarvi, 1996). The additional X chromosome introduces lethal gene dosage in the testis environment that does not permit the survival of germ cells, resulting in azoospermia because of advanced germ cell atresia and aplasia (Johnson, 1998).

The gonadal defect in XXY men is related to germ cell survival and sex chromosome constitution. In association with Klinefelter syndrome testicular maldevelopment can be found (Rao et al 2005). Males with Klinefelter syndrome (47,XXY) usually have small testis and azoospermia (Speroff L et al 1989). Incidence of Klinefelter syndrome is 3.1%- 7% in infertile males, 10.8-18.1% in males with azoospermia and 0.4-1.3% in males with oligospermia (Akgul et al 2009, Yatsenko et al 2010). The classical form of Klinefelter syndrome (47, XXY) is found in 85- 90% of cases. It results either from maternal (60%) or paternal (40%) meiotic nondisjunction of the X chromosomes (Yoshida et al, 1996). The incidence of XY disomy is considered to be increased in relation to age indicating that older males and older females have an increased probability of producing 47, XXY offspring (Shah et al, 2003).

Many Klinefelter syndrome patients are normal before puberty but the concentration of testosterone decreases and luteinising hormone rises after puberty as the

defective Leydig cells will secrete insufficient amount of testosterone but high amount of estradiol. The seminiferous tubules gradually become fibrotic and hayalinised due to constantly elevated gonadotropins. As the lumen obliterates and the germ cell gradually disappears it results in azoospermia and infertility. Generally hyperplasia of leydig cells may be found (Tournaye et al 1996). The mosaic form of Klinefelter syndrome is a mitotic postzygotic event. A new cell line with karyotype 47, XXY appears at stage of 4-5 cells (Mak and Jarvi, 1996).

The more X chromosome present in the patient and the more abnormal cell lines in mosaic forms, the worse the testicular lesion and the more manifestation of the syndrome (Mak and Jarvi, 1996). Though Klinefelter mosaics can produce haploid sperm and normal children, they are at risk of meiotic abnormalities including nondisjunction (Johnson, 1998).

Other numerical sex chromosomal abnormalities include 46, XX reversal males, 45, XO/46, XY mosaic males or mixed gonadal dysgenesis. Etem et al (2009) reported that 24/214 subjects had chromosomal abnormality. Most common being numerical abnormality (18/24). They reported 16/24 (7.5%) of Klinefelter syndrome i.e. 47, XXY, 1/24 subject 47, XYY (0.5) %, 1/24 subject 45, X, mar(Y) (0.5) %. Ceylan et al (2009) reported chromosomal abnormalities in 13/94 (13.8%) cases. The most frequent chromosomal anomaly was Klinefelter syndrome 12/94 (46, XXY) (12.8%). They also reported mosaic 47, XXY in one subject. The rate of mosaicism was 47, XYY (%76)/46, XY (%24). Mahjoubi et al (2010) carried out cytogenetic analysis in 1052 subjects out of which 161 (15.30%) cases had abnormal karyotypes. The most frequent abnormality was Klinefelter's syndrome (47, XXY) which was

detected in 94 (58.38%) patients. One of the individuals with the syndrome had a mosaic karyotype: mos 47, XX [54]/47, XXY [18]/46, XY. Akin et al (2011) reported sex chromosomal abnormality in 9 subjects (9/187=4.8%). Five of these patients had 47, XXY karyotype (5/9=55%), one patient had 47, XYY and one patient had 46, XX karyotypes. Gagare et al (2012) reported 7/112 (6.25%) with numerical abnormalities in which 6 had Klinefelter's syndrome of classic pattern 47,XXY karyotype in azoospermic group and one case had mosaic forms of 47XXY[86]/46,XY[14] pattern in oligospermic group. Azimi et al (2012) reported that 272/ 829 (32.81%) showed some kind of constitutional chromosome aberrations. Klinefelter syndrome, which was found in 195 patients (23.52%), was the most frequent anomaly in their study. Drugkar et al (2013) reported 9/70 (12.85%) subjects showed chromosomal alteration. Among the chromosomal abnormalities, Numerical abnormalities were present in 6 subjects (8.57%). Among the 6 subjects with Numerical abnormalities, Two subjects (2.85%) showed 47,XXY karyotype, 2 subjects (2.85%) were found with a 46,XX karyotype; one subject (1.43%) was found with Mosaicism i.e. 46,XY(20%)/47,XXY(80%); one subject (1.43%) showed a karyotype of 47,X,i (Xq)Y. Ambulkar et al (2014) did both cytogenetic as well as molecular study on 160 infertile men. They reported 3 subjects with 47, XXY Klinefelter's Syndrome (KFS) and one with 47, XYY male.

Rahma Belmokhtar et al (2016) studied 27 infertile men , 03 showed chromosomal abnormality corresponding to a frequency of 11.11%. All of chromosomal abnormalities in patient group were found to be gonosomal. Two patients were diagnosed as a non-mosaic form Klinefelter's syndrome (47.XXY) and one

patient was diagnosed as a mosaic form Klinefelter's syndrome (47.XXY/46.XY).

Table 1: showing percentage of numerical sex chromosomal abnormality reported in different studies.

Author	Total no. Of chromosomal abnormality reported	No. Of numerical sex chromosomal abnormality
Ceylan et al(2009)	13/94 (13.8%)	13/94 (13.8%)
Etem et al (2009)	24/214 (11.21%)	18/214 (8.41%)
Mahjoubi et al (2010)	161/1052 (15.30%)	94/1052 (8.93%)
Akin et al(2011)	9/187 (4.8%)	7/187 (3.74%)
Azimi et al (2012)	272/829 (32.81%)	195/829(23.52%)
Gagare et al(2012)	13/112 (11.6%)	7/112 (6.2%)
Drugkar et al(2013)	9/70 (12.85%)	6/70(8.57%)
Ambulkar et al (2014)	4/160 (2.5%)	4/160 (2.5%)
Rahma Belmokhtar et (2016)	3/27 (11.11%)	3/27 (11.11%)

**Conclusion**

All these authors have conducted the same study and they have reported that the most common chromosomal abnormality that is present in infertile male is numerical sex chromosomal abnormality in the form of Klinefelter syndrome.

Thus this high frequency of chromosomal abnormalities strongly suggests that chromosomal analysis should be included in routine investigations for infertile men,

especially before using assisted reproduction techniques. Moreover, prenatal diagnosis in the case of abnormalities is of utmost importance. Such investigation is a pre-requisite to minimize the risk of propagation of chromosomal abnormalities into the next generation. Additionally, a thorough follow-up of babies conceived through ICSI in particular the male progeny is essential.

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