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## Review Article

# Cytogenetic Study in Male Infertility – A Review

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**Abstract:** Infertility is a major clinical, social and economical concern. Infertility not only affects one's ability to have children but also has emotional, psychological, social and familial effects. It affects approximately 15% of couples in reproductive age. For many years, it was assumed that most reproductive problems could be attributed to the female partner but research in recent years has demonstrated that nearly 40-50% of infertility is caused by a male factor. Male factor infertility has been linked with numerous irregularities including sperm number, motility and morphology. ICSI (Intra cytoplasmic sperm injection) is the most recent development in the treatment of male infertility enabling couples who were previously deemed infertile to produce offsprings. Therefore the risk is that genetic cause of infertility increases in future generations, as demonstrated for male infertility. Thus, the identification of genetic factors in the infertile couple has become good practice for appropriate management of the infertile couple.
**Keywords:** Cytogenetics, Male Infertility.

## INTRODUCTION

Infertility is a major clinical, social and economical concern. Infertility not only affects one's ability to have children but also has emotional, psychological, social and familial effects. It affects approximately 15% of couples in reproductive age [8]. Despite the prevalence and significance of this health problem, resources and proper attention has not been given to this important issue

For many years, it was assumed that most reproductive problems could be attributed to the female partner but research in recent years has demonstrated that nearly 40-50% of infertility is caused by a male factor [8]. Male factor infertility has been linked with numerous irregularities including sperm number, motility and morphology. Several factors are proposed to cause infertility in men. These include varicocele, obstruction of spermatic ducts, hypogonadism, cryptorchidism, agglutination of spermatozoa, testicular tumours, presence of antisperm antibodies, idiopathic male infertility, maldescended testis, disturbances of semen deposition and sexual factors, general and systemic diseases, immunological factors, low volume of ejaculate and necrospermia. Out of the known causes of male infertility chromosomal aberrations occur in about 2-3 per cent of unselected patients with proven subfertility. However, the primary cause of infertility remains unclear.

Spermatogenesis is a long and complex process requiring about 70 days and involving an elaborate succession of distinct cell type's gene [2] rated by mitotic and meiotic divisions. Normal sperm production (spermatogenesis), maturation (spermiogenesis), delivery to and passage through the female genital tract (ejaculation and sperm transport), and function (capacitation, egg penetration, and decondensation of the head) are essential to achieve fertilization and early embryonic development [9].

In the initial stages, spermatogonia divide by mitosis, giving rise to primary spermatocytes, which in turn undergo the first meiotic division leading to secondary spermatocytes. Through the second meiosis these cells produce haploid cells (round spermatids) which undergo metamorphism during the spermiogenesis process in which they elongate (elongated spermatids) and finally differentiate into mature spermatozoa, by condensation of the chromatin, substitution of histones with protamines and formation of the acrosome and the other sperm components. However, our knowledge of the mechanisms regulating spermatogenesis is not yet fully resolved and advanced molecular research is focused on the identification of genes specifically involved in its regulation.

To achieve fertility a man requires normal spermatogenesis, successful maturation and transport of spermatozoa through male genital tract, normal functioning of accessory male sex organs together with

appropriately timed deposition of sperms in the female reproductive tract. These are long and complex processes, which not only require an appropriate hormonal environment, but also well-balanced autocrine, paracrine and juxtacrine signalling events between the various components of the male reproductive system. Accordingly when the molecules involved in these signalling cascades fail, male infertility occurs [9]. It has been known for some 20 years [1] that the prevalence of chromosome abnormalities is higher in infertile men, this figure being inversely related to the sperm count.

Seminal analysis is the primary investigation for men despite being a poor predictor of sperm function and male fertility. One poor analysis is insufficient for making a diagnosis of sperm disorder. If the first result shows a low sperm count or complete absence of sperm, it should be repeated, preferably two to three months later because of the long development cycle for sperm, which can be influenced by various factors (such as a fever) [14].

A significant proportion of infertile males are affected either by oligozoospermia (reduced sperm production) or azoospermia (lack of any sperm in the ejaculate). Such alterations in sperm production may be related to different underlying testicular histological pathologies ranging from the complete absence of germ cells (Sertoli cell-only syndrome) to hypospermatogenesis and maturation arrest. The alteration of spermatogenesis can be the consequence of many causes such as systemic diseases, cryptorchidism, endocrinological disorders and obstruction/absence of seminal pathways or infections. 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 [12].

Genetic abnormalities are considered to make an important contribution to these cases of unexplained spermatogenesis failure [11]. 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 [3]. 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 [5]. 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. Notably, the corresponding figure in azoospermic infertile men was 3.0% including both sex chromosome aneuploidies (i.e. 47, XXY, mosaicisms) (1.4%) and balanced structural abnormalities (1.6%).

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 [4]. These infertile men demonstrate normal somatic karyotype by blood exam indicating the presence of a mosaicism between somatic and nonsomatic tissues or the presence of a mitotic or meiotic defect during spermatogenesis. Along with this Deletion of q arm of Y chromosome as well as numerical changes of Y chromosome and some of the autosomes also play an important role in male infertility. Apart from these established causes, there is a large body of literature either claiming or refuting the association of certain genetic variants with spermatogenic failure [10].

In fact, nearly one quarter of all male infertility patients are diagnosed as ‘‘idiopathic,’’ meaning we do not understand the etiology. Today, it is thought that much of what we currently diagnose as idiopathic may have a genetic basis. Unfortunately, there is a paucity of information available concerning the molecular events regulating these complex processes, hence an inability to properly diagnose the cause of infertility for many patients.

Tiepolo and Zuffardi in 1976 were the first to hypothesize a correlation between Y chromosome deletions and male infertility. These authors examined the karyotype of 1,170 men; in six sterile males with azoospermia they observed large deletions including the entire heterochromatic region (Yq12) and an undefined amount of the adjacent euchromaticpart (Yq11). In two cases they demonstrated that the fathers of the patients with deletions carried a normal Y chromosome indicating that these mutations were *de novo* events. This suggested that the deletions were the cause of the azoospermia and they postulated that a genetic factor located in Yq11 was important for male germ cell development. This gene or gene cluster was defined as “azoospermia factor” (*AZF*). However, the genetic complexity of the *AZF* locus could be revealed only with the development of STS andYAC-based mapping. These analyses permitted the detectionof interstitial submicroscopic deletions not visible atthe cytogenetic level and detectable only by STS-PCR orSouthern hybridization. Such deletions are called microdeletions.Molecular mapping analyses on patients with microdeletions have complicated the original hypothesis of a single locus for spermatogenesis on Yq, suggesting that three nonoverlapping regions in deletion intervals 5 and 6 may be deleted in infertile men. These spermatogenesis loci are termed *AZFa*, *AZFb*, and *AZFc*[13] from proximal to distal Yq. Furthermore, a fourth region (*AZFd*) has been proposed between *AZFb*and *AZFc*[6]. According to Vogt *et al.* 1997 *AZFa*is located at the proximal portion of deletion interval 5 (subinterval 5C), *AZFb*spans from the distal portion of deletion interval5 to the proximal end of deletion interval 6 (subinterval 5O–6B), and *AZFc*is

located at the distal part of deletion interval 6 (subintervals 6C–6E) [5].

Natural selection prevents the transmission of mutations causing infertility while this protective mechanism is overcome by the assisted reproduction techniques (ART). Couples in which the man has sperm dysfunction need early referral for in vitro fertilisation, usually with intra-cytoplasmic sperm injection. ICSI is the direct introduction of a spermatozoon into an oocyte to achieve fertilization and pregnancy when the number of spermatozoa in the ejaculate is very low or even absent. In the latter case, ICSI can be performed using spermatozoa obtained from the epididymis or directly extracted from testicular tissue [5].

ICSI (Intra cytoplasmic sperm injection) is the most recent development in the treatment of male infertility enabling couples who were previously deemed infertile to produce offsprings. Therefore the risk is that genetic cause of infertility increases in future generations, as demonstrated for male infertility. Thus, the identification of genetic factors in the infertile couple has become good practice for appropriate management of the infertile couple.

## CONCLUSION

Therefore, genetic testing and counselling can provide support for patterns of inheritance, recurrence risks, natural history of diseases, increased risk for birth defects and genetic testing options when planning a pregnancy in patients with abnormal karyotypes. These patients can be advised in vitro fertilization (IVF) and genetic screening of embryos in relation to assisted reproductive techniques.Thus to assess the couple's risk of transmitting a genetic abnormality and to discuss the necessity of geneticcounseling to these infertile couples genetic studies should be conducted.

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