

MALE MEIOSIS IN THE FRAMEWORK OF HUMAN INFERTILITY STUDIES

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Meiosis is a key process in mammalian gametogenesis. Male infertility is frequently associated to meiotic anomalies, either due to the behaviour of constitutional chromosome abnormalities or to specific meiotic disorders. These anomalies can result in the production of chromosomally abnormal gametes or be concomitant to a meiotic arrest, both leading to the decrease in the reproductive fitness observed in the individuals affected.

The scientific significance of tracing meiotic disorders in the screening of male infertility is well acknowledged. However, direct meiotic studies have been seldom used, mostly due to the minor surgery required to obtain testicular material but also because of the expertise needed to analyze meiotic configurations. On the contrary, since the description of protocols to analyze sperm nuclei by FISH there has been an explosion of sperm FISH analyses providing indirect evidences of the occurrence of meiotic anomalies. Furthermore, molecular studies are growing progressively and thus improving our understanding of the roles of different gene products involved in meiotic events.

In the last few years, the reluctance to perform testicular biopsies has clearly decreased, probably as an indirect effect of the use of testicular spermatozoa for ICS, and meiotic studies have improved their status. Cytogenetic studies on testicular biopsy material obtained from fertility clinics have provided important data on the chromosome meiotic abnormalities in infertile males. These analyses have been focused on the evaluation of the characteristics of chromosome pairing along prophase I, on chiasmata count and bivalent analysis in metaphase I and on the evaluation of the number and characteristics of the chromosomes in metaphase II. Results from large series have revealed that meiotic anomalies can be found in 6-8% of the infertile males analyzed, may increase to 17.6% in males with severe oligozoospermia and to 27% in males with one or more previous IVF failures.

Multiplex fluorescence in situ hybridization (M-FISH) has also been used in combination with classical cytogenetic protocols, allowing for an accurate karyotyping of meiotic chromosomes in metaphase I and in metaphase II. Results have confirmed the preferential implication of the sex chromosomes in synaptic anomalies. Furthermore, synaptic anomalies observed in infertile males do not seem to affect any specific autosome preferentially.

In a recent study from our group, data from chromosomal abnormalities found by sperm FISH analysis were compared to the cytogenetic results from meiotic studies performed in the same patients. In the population analyzed (113 individuals) and in line with previous findings, we observed two types of meiotic abnormalities: synaptic anomalies (81%) and meiotic arrest (16%), although in some cases both abnormalities were present (3%). Only 21.8% of the individuals displaying synaptic anomalies showed a significantly increased rate of aneuploidy in their gametes. In 74% of patients there had been a clear reduction of abnormal cells across the process of spermatogenesis, probably due to the activation of checkpoints that would selectively eliminate aneuploid cells. In any case, the percentage of patients with meiotic abnormalities who were carriers of chromosome abnormalities in their spermatozoa (26%) was also higher than the 14% reported for infertile men, providing evidence for its implication in the generation of chromosomal aneuploidies in gametes.

In the "OMICS-age", cytogenetic meiotic studies still can be of help on the research of male infertility.

Suggested reading: Burgoyne P, Mahadevaiah SK, Turner JMA. "The consequences of asynapsis for mammalian meiosis". *Nat Rev Genet.* 2009;10:207-216; Egozcue S, Blanco J, Vendrell JM, García F, Veiga A, Aran B, Barri PN, Vidal F, Egozcue J. "Human male infertility: chromosome anomalies, meiotic disorders, abnormal spermatozoa and recurrent abortion" *Hum Reprod Update.* 2000;6:93-105.; Egozcue J, Sarrate Z, Codina-Pascual M, Egozcue S, Oliver-Bonet M, Blanco J, Navarro J, Benet J, Vidal F. "Meiotic abnormalities in infertile males". *Cytogenet Genome Res* 2005;111:337-42; Martin RH. "Cytogenetic determinants of male fertility". *Hum Reprod* 2008; 14:379-390; Rubio C, Gil-Salom M, Simón C, Vidal F, Rodrigo L, Mínguez Y, Remohí J, Pellicer A. "Incidence of sperm chromosomal abnormalities in a risk population: relationship with sperm quality and ICSI outcome". *Hum Reprod.* 2001;16:2084-92; Sarrate Z, Vidal F, Blanco J. "Role of sperm fluorescent in situ hybridization studies in infertile patients: indications, study approach, and clinical relevance". *Fertil Steril* doi:10.1016/j.fertnstert.2008.12.139

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