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Human Male Meiosis and Sperm Aneuploidies

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1. Introduction

Infertility affects 15% of couples of reproductive age (De Krester, 1997; reviewed by O'Flynn O'Brien et al., 2010). For years most reproductive problems were attributed to women, but recent research has shown that between 30 and 50% of infertility cases result from male factor (Lipshultz & Howards, 1997; reviewed by Stahl et al., 2011).

Reports indicate that infertile males, especially those with low sperm count, have an increase in chromosomally-abnormal spermatozoa, therefore the study of these individuals is critical for the field of assisted reproduction. Importantly, aneuploid sperm remain able to fertilize eggs, often resulting in repetitive intracytoplasmic sperm injection (ICSI) failure, recurrent miscarriage, and offspring with increased genetic risk. Most numerical chromosomal abnormalities, especially monosomies, are inviable and result in spontaneous abortion. However, a subset of chromosomal abnormalities can result in live birth, including trisomies 13, 18, and 21 and sex chromosome aneuploidies. Offspring with these aneuploidies typically display physical disabilities, mental retardation, infertility, etc. (reviewed by Martin, 2008). Thus, effective diagnostic methods to detect sperm aneuploidy are of great interest.

An estimated 5% (minimally) of pregnancies are aneuploid. However, in assisted reproductive technology (ART), estimates are as high as 25% or more. Aneuploid conceptions often derive from aneuploid gametes: the incidence of aneuploidy in human oocytes is about 20-25%, and is more than 2% in sperm (reviewed by Hassold & Hunt, 2001). Aneuploidy in gametes is intimately associated with meiotic errors. This chapter focuses on the etiology of aneuploidy in the human male gamete, particularly examining male meiosis, meiotic errors, and their possible relationship with aneuploidy. We also describe aneuploidy rates in fertile and infertile men and their reproductive outcomes.

2. Male meiosis

2.1 Generalities

Meiosis in humans varies considerably between males and females (Fig. 1). In females, meiosis begins somewhat synchronously in all oocytes during fetal development, but then arrests before birth. Resumption of meiosis occurs asynchronously at or after puberty, at the time of ovulation, but arrests again until fertilization. In contrast, male meiosis does not begin until puberty and occurs continuously and asynchronously throughout adulthood. Primary spermatocytes divide into two secondary spermatocytes through meiosis I (MI), and each secondary spermatocyte divides into two spermatids, which will differentiate and maturate into sperm. The main difference between the male and female production of gametes is that oogenesis only leads to the production of one final ovum from each primary oocyte, in contrast in males four sperm are originated from each primary spermatocyte.

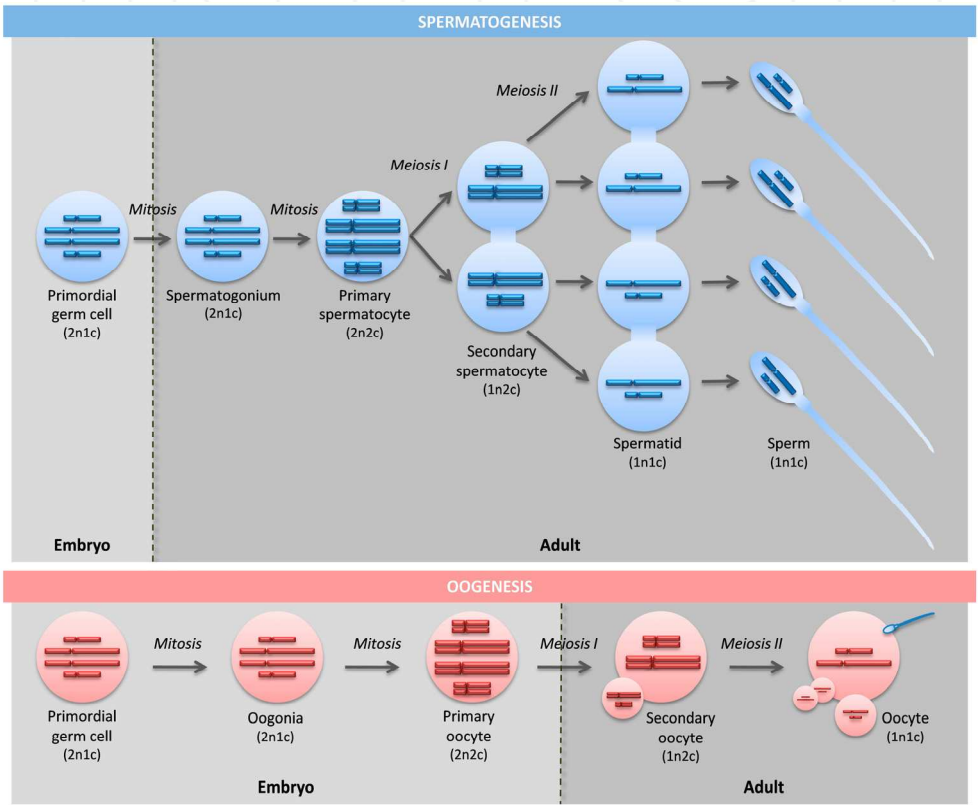

Fig. 1. Gamete formation in males (spermatogenesis) and females (oogenesis).

Meiosis is characterized by an extended prophase followed by two divisions that produce haploid gametes. Prior to meiosis, during S phase, DNA is replicated and sister chromatids remain connected through proteins called cohesins. Meiosis begins with prophase I, arguably the most critical stage thanks to two key events: synapsis and recombination

(explained in detail later). Prophase I is divided into four stages: leptotene, zygotene, pachytene, and diplotene. During leptotene, homologous chromosomes begin to condense and approach each other to align, but do not yet pair. With the aid of cohesins (e.g., REC8 and SMC1B), a chromosomal scaffold—the synaptonemal complex (SC)—begins to form via assembly of axial elements composed of SC-specific proteins [e.g., synaptonemal complex protein 2 (SYCP2) and SYCP3]. Additionally, DNA double-strand breaks (DSB) are induced by the protein SPO11; this is the initiating event of recombination, or DNA exchange between homologous chromosomes. During zygotene chromosomes continue condensing and homologues pair and begin synapsis (reviewed by Handel & Schimenti, 2010). Axial elements become lateral elements and, joined by the transverse filaments (e.g., SYCP1), form the SC to maintain synapsis. Subsequently, during pachytene—the longest stage of prophase I—synapsis is completed and DSB are repaired by DNA break repair machinery; a small subset of DSB are repaired as crossovers (chiasmata). Finally, during diplotene the SC is disassembled. Each pair of homologues (bivalents) begins to separate, but they remain temporarily joined at chiasmata (reviewed by Burgoyne et al., 2009).

Following prophase I, germ cells continue into the first meiotic metaphase, in which axial elements are disassembled and cohesins are removed, except those located at centromeres. In this phase, homologous pairs of chromosomes migrate to the equatorial plane of the spindle, with their centromeres facing different poles, forming the metaphase plate. In anaphase I, homologous chromosomes separate. Finally, cell division at telophase I results in two secondary spermatocytes with haploid chromosomes, but with two chromatids per chromosome.

The second meiotic division is an equational division similar to mitosis except that, in this case, the parent cells are haploid. Four spermatids are thus generated from one pre-meiotic germ cell; each should contain 23 chromosomes, with a single chromatid for each chromosome.

Three events can lead to aneuploidy during MI: failure to resolve chiasmata, resulting in a true non-disjunction; no chiasma formation or early disappearance of one, resulting in an achiasmate non-disjunction; and, finally, a premature separation of sister chromatids. In meiosis II (MII) the only cause of aneuploidy is non-disjunction of sister chromatids (reviewed by Hassold & Hunt, 2001).

The importance of MI versus MII errors varies among chromosomes. For example, trisomy 16 is caused by MI errors, while trisomy 18 is usually caused by non-disjunction in MII (reviewed by Hassold & Hunt, 2001). In male, the chromosome with the highest estimated frequency of non-disjunction in MI is the XY bivalent and in MII is the Y chromosome (reviewed by Hall et al., 2006). Further, autosomal trisomies are usually maternal in origin, while sex chromosome aneuploidies are more frequently paternal in origin (reviewed by Templado et al., 2011).

The critical events of meiosis are reflected in two series of specific processes: First, pairing, synapsis, and formation of the SC between homologues establish and regulate cohesion between sister chromatids. Second, recombination between homologous chromosomes and proper orientation of the two centromeres of each bivalent must be completed. Both sets of events are controlled by a pachytene checkpoint, which induces delay or arrest of cells that have not completed these steps to avoid aberrant chromosome segregation and formation of

defective gametes (reviewed by Roeder & Bailis, 2000). However, a failure in any of these steps together with a checkpoint failure can result in aneuploidy or segregation failure.

2.2 Synapsis

The SC is a protein structure that mediates pairing, synapsis, and recombination between homologous chromosomes during meiosis. The SC is formed by two parallel lateral elements and a central element that links them with transverse filaments. Three protein components of the SC have been identified: SYCP1, forming the central element, and SYCP2 and SYCP3, which are recruited to the chromosomal cores to form the axial elements (reviewed by Handel & Schimenti, 2010). These structures have been visualized using monoclonal antibodies, particularly against SYCP3, in immunocytogenetic assays. As the first component to localize to the forming SC, SYCP3 can be used to monitor its assembly and disassembly during prophase I. Indeed, SYCP3 distribution varies greatly during prophase (Fig. 2): in leptotene SYCP3 appears as small linear fragments; in zygotene the axial elements begin to elongate and synapse; in pachytene synapsis is complete revealing 22 structures (one for each bivalent) and one sex vesicle (XY bivalent); and, finally, in diplotene each pair of sister chromatids starts to separate, visualized as forks in the SC.

It has been observed that the synaptic initiation occurs in subtelomeric regions and not in the telomeres as initially was thought. Furthermore it has been seen that the centromere avoids spreading the synapsis from q-arm to p-arm and vice versa (Brown et al., 2005).

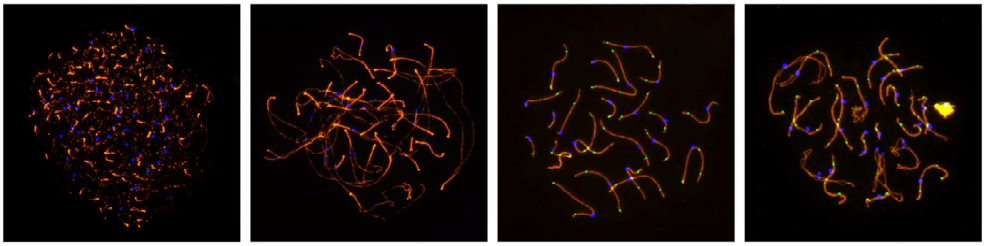

Fig. 2. SYCP3, MLH1, and CREST (stained in orange, green, and blue respectively) distribution in prophase I stages (from left to right: leptotene, zygotene, pachytene, and diplotene).

Synapsis fidelity can be measured by observing the frequency of certain anomalies: gaps, splits, and lack of crossovers. Gaps are discontinuities in the SC and occur often in normal males. Splits are misaligned chromosomal regions that form looplike structures; these occur less commonly than gaps. Finally, SCs without crossovers are detected by absence of MutL protein homolog 1 (MLH1) foci on the bivalent. This anomaly is less common than gaps and even splits. The existence of gaps is reported to correlate with the location of the MLH1 protein. Further, recombination frequency is reduced on SCs with gaps, but not those with splits, which suggests that the nature of splits and gaps differs (Sun et al., 2005, 2007).

2.3 Recombination

Proper recombination between homologous chromosomes is required for normal meiosis and segregation of chromosomes. Chiasmata, physical structures corresponding to

crossover points between homologous chromosomes, keep homologues joined until anaphase I. The distribution of these points is not entirely random; rather, there are genomic regions that exhibit much higher rates of recombination, called hot spots, and other locations that rarely have recombination events, called cold spots. For example, centromeres seem to be cold spots, while subtelomeric regions seem to be hot spots with an excess of recombination points. Several studies of human chromosomes have shown that at least one crossover occurs in each arm, except in short arms of acrocentric chromosomes, where crossovers occur infrequently. Further, the existence of a crossover inhibits the formation of another in a nearby region, a phenomenon known as "interference" (Brown et al., 2005; reviewed by Lynn et al., 2004; Sun et al., 2004a).

Antibodies against MLH1, a DNA mismatch-repair protein involved in crossing-over, are used to localize recombination sites. Applying this method in human spermatocytes, groups have described inter-individual variations in MLH1 frequency (Hassold et al., 2004; Lynn et al., 2002; Sun et al., 2005, 2006). Additional findings demonstrated that patient age does not affect meiotic recombination frequency (Lynn et al., 2002). Further, a role for the SC in mediating recombination levels was observed, with a correlation between the number of MLH1 foci and chromosome arm lengths (Lynn et al., 2002; Sun et al., 2004a). Despite these advances, the basis of crossover formation remains incompletely understood, e.g., why crossovers form at a particular site. This indicates the importance of continued efforts toward revealing the mechanistic basis of recombination.

2.4 Methods for studying critical events of meiosis

Male meiosis can be studied using indirect methods, like linkage mapping, or direct assays such as cytogenetics and immunocytogenetics.

Linkage maps, also called genetic or meiotic maps, are derived from genotype data in families by examining heredity of short tandem repeat polymorphisms to detect all recombination events per meiosis. This type of assay provides high resolution, but has some disadvantages. First, at least three generations need to be examined, and second, only half of all recombination events can be observed since only two of the four chromatids are involved in the exchange process (reviewed by Lynn et al., 2004).

Direct assays, although they forfeit some resolution, can help combat these disadvantages. For example, analysis of diakinesis/metaphase I stage cells by conventional cytogenetic techniques is used to directly observe crossovers. However, because diakinesis and metaphase I have a short duration, finding these cells can be difficult. Additionally, material for this kind of study requires testicular biopsy. Finally, chromosomes are highly condensed, making it difficult to identify them correctly (reviewed by Lynn et al., 2004; reviewed by Vallente et al., 2006). This last problem can be solved by adding M-FISH (Multiplex-fluorescent *in situ* hybridization), which allows the identification of individual bivalents. Unfortunately, this technique is costly and quite laborious, prohibiting its application in clinical practice (Sarrate et al., 2004).

Another, more recently developed direct assay uses immunocytogenetics to study prophase I, particularly pachytene, germ cells. Antibodies against lateral element proteins (SYCP3) and transverse filament proteins (SYCP1) are used to visualize the SC, anti-MLH1 antibodies are used to detect recombination sites, and the centromere can be localized with

CREST sera (calcinosis-Raynaud's phenomenon-esophageal dysfunction-sclerodactyly-telangiectasia) (Fig. 2). This assay allows the study of meiotic progression, synaptic defects, recombination rates, etc. Additionally, immunocytogenetics can be combined with FISH to analyze recombination rates and crossover placement in individual chromosomes. While this assay also requires testicular biopsies to obtain material, pachytene has a long duration and nuclei are not as condensed as in diakinesis (Gonsalves et al., 2004, 2005; Judis et al., 2004; Lynn et al., 2002; Ma et al., 2006; Sun et al., 2004a, 2004b, 2006, 2007, 2008a, 2008b).

3. Male meiosis abnormalities

Different types of meiotic abnormalities have been described, and they are not mutually exclusive. One type of abnormality is meiotic arrest, which occurs when spermatogenesis stops at any stage of maturation of the germ line (spermatogonia, primary spermatocyte, secondary spermatocyte, or spermatid). Arrest can be partial, affecting only some germline cells and causing oligozoospermia, or complete, affecting all germline cells and causing azoospermia. In 74% of cases, meiotic arrest is caused by *synaptic defects*, which are due to a decrease in the number of exchanges (chiasmata) between homologous chromosomes in prophase I. This can induce abnormal chromosome segregation in MI, resulting in secondary spermatocytes with an altered chromosome complement (reviewed by Egozcue et al., 2005).

Importantly, a decrease in the total number of crossovers can result from homologues devoid of recombination sites. This, in turn, could cause misalignment of chromosomes on the metaphase plate and, subsequently, improper segregation (reviewed by Martin et al., 2008). The XY bivalent is particularly susceptible to this phenomenon, since only a small region of homology exists between the X and Y chromosomes, and, thus, the pair has only a single recombination site (Shi & Martin, 2000; Thomas & Hassold, 2003). In fact, several studies have demonstrated that sex chromosomes have the highest frequency of achiasmate bivalents (Sun et al., 2006).

In addition to altered frequency of recombination, abnormal crossover distribution can also occur. In a recent study was found an altered MLH1 distribution in one of four infertile males, these could have negative consequences as aneuploid sperm (Ferguson et al., 2009).

3.1 Abnormal meiosis in infertile males

Reports indicate that up to 8% of the general infertile population exhibit meiotic defects (reviewed by Egozcue et al., 2005). Studies of patients with obstructive azoospermia (OA) are typically used to define normal meiosis, since, in these cases, the absence of sperm in semen is due exclusively to a physical barrier (reviewed by Vallente et al., 2006). In fact, recent studies in testicular sperm from OA patients did not show differences in aneuploidy rates compared to testicular control subjects (Rodrigo et al., 2011). Further, recombination levels showed a similar pattern in all patients, with a mean recombination level of 49.5±0.7 crossovers (MLH1 foci) (Al-Asmar et al., 2010, 2011).

On the other hand, in most non-obstructive azoospermic (NOA) patients the cause of testicular damage is idiopathic (Judis et al., 2004). In these individuals various meiotic abnormalities have been observed. Indeed, several studies have reported a significant decrease in recombination levels in NOA, with averages of 32.7-42.7 MLH1 foci versus 46.0-

48.5 for controls (Sun et al., 2004b, 2007). Additionally, one report described a NOA patient with a significant increase (73% vs. 4.5% in controls) in cells with at least one autosomal bivalent without an MLH1 focus (Sun et al., 2004b). Further, NOA samples may have altered distributions of germ cells in meiotic stages. In particular, leptotene and zygotene stage cells are more common in azoospermic patients than in controls (7.95% vs. 2.30% and 9.75% vs. 1.45% respectively), with corresponding decreases in pachytene stage cells (75.30% vs. 96.25% in controls). This phenomenon may reflect meiotic arrest in the earlier stages of prophase (Tassistro et al., 2009). In fact, complete meiotic arrest was observed in one case of NOA (Judis et al., 2004), in which the blockage was at zygotene/pachytene stage and no evidence was detected for synapsis or crossovers between homologues. Another study reported a partial or complete arrest during zygotene in 4 of 40 NOA patients (Gonsalves et al., 2004).

Other types of meiotic abnormalities have been observed in NOA patients. For example, SC discontinuities are more frequent in these patients than in controls (Sun et al., 2004b; Tassistro et al., 2009). In addition, differences have been detected in the frequency of asynapsis events between NOA and control populations (7.97% vs. 2.95%) (Tassistro et al., 2009).

Meiotic abnormalities have also been found in other patients. In a study with oligoasthenozoospermic patients, 17.5% of individuals had an increased incidence of meiotic anomalies (reviewed by Egozcue et al., 2000; Vendrell et al., 1999). Additionally, in a retrospective study of 500 patients with different types of infertility or sterility, the incidence of synaptic abnormalities was inversely proportional to the quantitative level of spermatogenesis. Specifically, altered or incomplete meiosis was found in 24% of azoospermic males, 33% of asthenoteratozoospermic males, 51.5% of oligoastheno-teratozoospermia (OAT) patients, and in 90% of NOA males (García et al., 2005).

Furthermore, genetic studies have identified mutations for proteins involved in meiosis in infertile males. For example, mutations in SCP3, MLH1, SPO11 –a protein involved in the formation of DSB– and RAD54 –a protein that participates in recombination and DNA repair- have been found (reviewed by Sanderson et al., 2008). Otherwise, variations in DNA sequence and their relationship with an increase or decrease in the recombination rate have been described (Kong et al., 2008).

3.2 Abnormal meiosis and reproductive outcomes

Alterations in meiosis do not necessarily lead to azoospermia. Indeed, meiotic errors can produce abnormal sperm that retain fertilization capabilities, resulting in abnormal embryos and either recurrent miscarriage or abnormal offspring. Aran et al. (2004) observed a high number o chromosomal abnormalities (42.5%) in embryos from ICSI cycles for males with meiotic abnormalities (Aran et al., 2004). Furthermore, it has been reported that approximately 50% of individuals with Klinefelter syndrome (47,XXY) have resulted from paternal non-disjunction. Indeed, paternal origin has been associated with a decrease in recombination for sex chromosomes (reviewed by Martin et al., 2008).

3.3 Correlation with sperm aneuploidy

Both aberrant meiosis and increased frequency of sperm aneuploidy have been described in infertile men. However, very few studies have examined meiosis and chromosomal

abnormalities in the same patients. One study to determine the relationship between frequency of recombination in pachytene cells and frequency of sperm aneuploidy in six fertile men did not find a significant correlation (Sun et al., 2008b). Other studies observed that recombination frequency in 24,XY spermatozoa was significantly lower than in normal sperm (25.3 vs. 38.3%) (Shi et al., 2001) and that 67.1% of those XY bivalents were achiasmate (Thomas & Hassold, 2003). Also, in one infertile male with extremely high sperm aneuploidy rates, a correlation was observed between low recombination frequency in pachytene cells for chromosomes 13, 21, and the sex chromosomes and a high aneuploidy frequency for the same chromosomes (Ma et al., 2006).

A study in testicular tissue of seven NOA patients reported an increase in the frequency of pachytene cells with at least one achiasmate bivalent compared with controls (12.4% vs. 4.2% respectively). The same patients exhibited an increase in the frequency of aneuploidies, specifically more sperm disomy than controls for chromosomes 21 (1.00% vs. 0.24%), X, (0.16% vs. 0.03%), and Y (0.12% vs. 0.03%). Further, a significant correlation was found between cells with sex vesicles lacking MLH1 foci and sex chromosome disomy in sperm (Sun et al., 2008a).

Another recent study by Peinado and colleagues (2011) analyzed testicular biopsies of 11 NOA patients and compared these with a control group of 10 patients with obstructive azoospermia post-vasectomy. NOA patients had a mean of 44.9±3.6 MLH1 foci versus 48.2±2.1 in controls. This decrease in recombination levels resulted from a significant increase in the percentage of SC without exchanges (1.1% vs. 0.4%) and with one exchange (19.4% vs. 14.6%) and a significant decrease in complexes with three (19.7% vs. 22.8%) and four exchanges (3.6% vs. 5.5%) compared to the control group. In the same study using FISH analysis, NOA patients displayed an increase in sex chromosome disomies (0.39% vs. 0.18%) and a three-fold increase in disomy for chromosomes 13 (0.4% vs. 0.09%) and 21 (0.3% vs. 0.09%) as well as in diploidy rates (0.13% vs. 0.05%). These findings corroborate the correlation between both parameters, recombination frequency and synapsis defects, and higher aneuploidy risk for offspring in NOA patients (Peinado et al., 2011).

4. Sperm aneuploidies in males

In recent years, the use of ICSI has significantly improved the fertility prognosis of infertile couples affected by severe oligozoospermia (Palermo et al., 1992; Van Steirteghem et al., 1993) or azoospermia, in the latter case using spermatozoa retrieved from the epididymis (Tournaye et al., 1994) or testicle (Devroey et al., 1995; Gil-Salom et al., 1995a, 1995b, 1996, 2000); Schoysman et al., 1993). However, prenatal diagnosis (i.e., preimplantation genetic diagnosis, PGD) following ICSI has shown statistically significant increases in *de novo* sex chromosome abnormalities and structural autosomal aberrations (Bonduelle et al., 2002; Van Steirteghem et al., 2002), most of which seem to have a paternal origin (Meschede et al., 1998; Van Opstal et al., 1997). This finding emphasizes the importance of a strict genetic evaluation of ICSI candidates.

4.1 Approaches to studying aneuploidy in sperm samples

The first chromosomal studies of spermatozoa were developed in 1970, with differential staining of concrete regions of chromosomes (Barlow & Vosa, 1970; Pearson & Bobrow, 1970). These showed that 1.4% of sperm have aneuploidies for sex chromosomes. Other

authors published an individual chromosomal aneuploidy rate of 2% and a global aneuploidy rate of 38% (Pawlowitzki & Pearson, 1972). However, this method was later demonstrated to be non-specific, resulting in over-reporting of aneuploidy. Thus, more reliable techniques were needed.

A later technique introduced spermatozoa to hamster oocytes (Yanagimachi et al., 1976) to directly study human sperm chromosomes (Rudak et al., 1978). After incubating spermatozoa with several hamster eggs, cells were fixed and stained using karyotyping methods to observe metaphase nuclei and analyze numerical and structural chromosome abnormalities. However, this method could not test samples from men with severe male factor because their sperm were not able to capacitate and penetrate zona-free oocytes. Additionally, this technique allowed analysis of only a limited number of sperm (reviewed by Carrell, 2008). Finally, the time and animals required limited the use of this technique in clinical practice (reviewed by Martin, 2008).

In the 1990s, the first FISH assays were developed, offering a faster, easier, and less costly method to detect aneuploidies in human spermatozoa (reviewed by Martin, 2008). This technique uses fluorescent nucleic acid probes complementary to DNA to visualize regions of interest. This approach permits analysis of a large number of sperm from the same sample. However, FISH cannot be performed for all chromosomes of a single sperm nucleus because the sperm head is too small and signals overlap. Therefore, FISH is typically performed for just five chromosomes (13, 18, 21, X, and Y—aneuploidies for these chromosomes can result in live offspring), and resulting aneuploidy rates refer only to those chromosomes analyzed (Fig. 3) (reviewed by Templado et al., 2011). Despite the drawbacks, FISH remains the most widely used technique to detect aneuploidies.

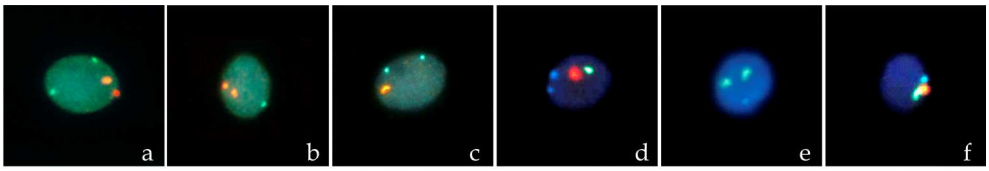

Fig. 3. FISH assays in human spermatozoa. a: diploid spermatozoon (13,13,21,21), b: disomy for chromosome 21 (13,21,21), c: disomy for chromosome 13 (13,13,21), d: diploid spermatozoon (X,Y,18,18), e: disomy for chromosome X (X,X,18), f: disomy for sex chromosomes (X,Y,18).

Recently, an automated tool for the analysis of sperm aneuploidy has been developed. This system has several advantages over manual FISH. First, automated FISH reduces the time required from 10-20 hours to 1 hour. Additionally, the software is able to store all images captured under microscopy. However, this system is costly (reviewed by Carrell, 2008; reviewed by Templado et al., 2011) and is less efficient in identifying diploid sperm than manual analysis (i.e., manual analysis found higher diploidy rates than automatic analysis, Molina et al., 2009).

4.2 Incidence of aneuploidy in fertile males

The detection of alterations in aneuploidy rates first requires establishment of normal parameters. Such values must be based on sperm from normozoospermic males with

proven fertility to establish the baseline levels of human sperm aneuploidy. Notably, baseline sperm aneuploidy rates may be subject to inter-individual and intra-individual variability. Studies published to date show considerable variability in aneuploidy rates in fertile men. However, it is unclear whether this variability is real or is due to different methodologies used in each laboratory (reviewed by Templado et al., 2011). One study on intra-individual and inter-individual variability indicates that unknown life events may sporadically or consistently affect sperm aneuploidy rates (Tempest et al., 2009). Despite these factors, a recent review analyzed 32 studies that described aneuploidy rates from normal men. The authors found that total aneuploidy frequency in sperm is about 4.5%. However, disomy rates for autosomes were highly variable, ranging from 0.03% for chromosome 8 to 0.47% for chromosome 22. Sex chromosomes, the most commonly analyzed, exhibited a disomy rate of 0.27% (reviewed by Templado et al., 2011).

4.3 Incidence of aneuploidy in infertile males

FISH studies reveal a significantly increased incidence of numerical chromosomal abnormalities in sperm from infertile males, mainly in sex chromosomes, and in sperm from OAT patients (Aran et al., 1999; Bernardini et al., 1998, 2000; Calogero et al., 2001a,b; Colombero et al., 1999; Martin et al., 2003; Moosani et al., 1995; Nishikawa et al., 2000; Pang et al., 1999; Pfeffer et al., 1999; Rubio et al., 2001; Ushijima1 et al., 2000; Vegetti et al., 2000). Indeed, Rubio et al. observed statistically significant differences in disomies for chromosome 21 and sex chromosomes and in diploidy in OAT males compared to normozoospermic (Normo), asthenozoospermic (Astheno), teratozoospermic (Terato), and asthenoteratozoospermic (AT) males (Table 1).

	Normo (n=14)	**Astheno (n=14)**	**Terato (n=8)**	**AT (n=6)**	**OAT (n=21)**
% sex chromosome disomy	0.44	0.36	0.42	0.29	0.68[a]
% disomy 13	0.14	0.09	0.07	0.11	0.17
% disomy 18	0.02	0.04	0.03	0.02	0.05
% disomy 21	0.17	0.12	0.10	0.08	0.24[b]
% diploidy	0.10	0.11	0.15	0.06	0.25[a]

Table 1. Percentage of chromosome aneuploidies. [a]$p<0.0001$, [b]$p=0.0423$ (Rubio et al., 2001).

Additionally, at a lower sperm concentration aneuploidy rates were higher. The highest percentage of abnormal FISH results was found at concentrations $<1x10^6$ sperm/mL (severe oligozoospermia)—57% of these patients presented some kind of chromosomal abnormality (Fig. 4).

Although some studies have found similar incidences of chromosomal abnormalities in testicular sperm from NOA patients (Martin et al., 2000) and OA patients (Viville et al., 2000) compared to ejaculated sperm from fertile males, most FISH studies report a higher incidence of chromosomal abnormalities in testicular spermatozoa, particularly in NOA patients (Bernardini et al., 2000; Burrello et al., 2002; Levron et al., 2001; Mateizel et al., 2002; Palermo et al., 2002) than in ejaculated spermatozoa from normozoospermic donors. This difference seems to be more appreciable in sex chromosomes (Rodrigo et al., 2004).

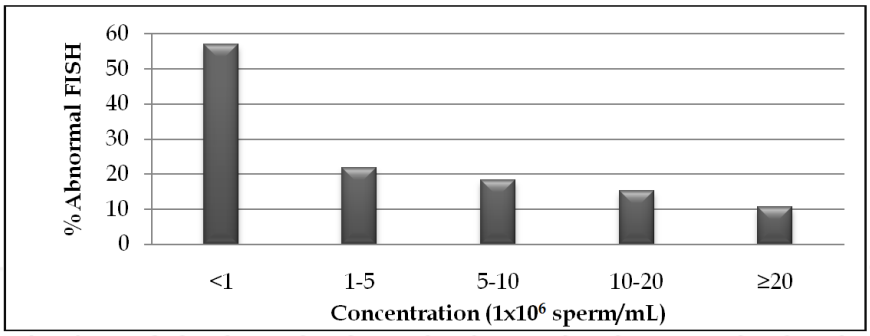

Fig. 4. Percentage of abnormal FISH for different sperm concentration (Rodrigo, L. Unpublished data).

A recent study examined sperm aneuploidy rates in NOA and OA patients (Rodrigo et al., 2011). Importantly, this study used two control groups: one group included ejaculated sperm samples from normozoospermic donors with proven fertility (ejaculated control group, EC); the other included testicular sperm samples of males with proven fertility, for whom a testicular sperm aspiration was performed at the time of vasectomy (testicular control group, TC) because the endocrine environment of the testis had not been altered. In control samples, testicular sperm showed higher incidences of aneuploidies than ejaculated sperm. For azoospermic patients (both NOA and OA), the differences were greater when compared to EC than to TC. Additionally, these differences were greater in NOA than in OA patients. Therefore, to better assess NOA patients, testicular sperm from controls should be used for statistical comparisons.

5. Sperm aneuploidies and reproductive outcomes

5.1 Sperm aneuploidies in ART/infertile populations

Sperm aneuploidies can impact reproductive outcome at different stages: fertilization, embryo development, pregnancy, or birth. Several studies have analyzed the clinical consequences of aneuploidies during *in vitro* fertilization (IVF) cycles.

Fertilization rate

Chromosomally abnormal sperm have been related to repetitive ICSI failures in a prospective study. The authors found a higher aneuploidy rate in those with unsuccessful ICSI outcome, especially for chromosome 18 and the sex chromosomes (Nicopoullos et al., 2008).

Embryo development

Sperm aneuploidies can also result in abnormal embryos. A FISH study in couples with abnormal sperm detected a significant decrease in the number of normal embryos and a significant increase in mosaic embryos (Rodrigo et al., 2003). A similar study in couples with abnormal FISH and low sperm concentration (<5X10^6 sperm/mL) also found a significant increase in abnormal embryos, especially in mosaic embryos –embryos with cells with different chromosome complement– and sex chromosome aneuploidies (Pehlivan et al.,

2003). Mosaicism rate as high as 53% has been reported in patients with NOA (Silber et al., 2003). These findings could be explained by fertilization with sperm carrying multiple chromosomal alterations or centrosome abnormalities. Sperm defective centrosomes impede the formation of asters or lead to an abnormal spindle, with an abnormal distribution of chromosomes, resulting in aneuploid embryos (Chatzimeletiou et al., 2008). In addition, an abnormal number of male centrioles in the centrosome has been related with the production of haploid, poliploid, or mosaic embryos (Munne et al., 2002; Silber et al., 2003).

Sanchez-Castro et al. (2009) studied sperm aneuploidy rates and embryo chromosomal abnormalities in couples with oocyte donation. They found more abnormal embryos in the study group compared to the control group. Further, oligozoospermic patients showed a higher proportion of abnormal embryos (Sanchez-Castro et al., 2009). Recently, an increase in sperm chromosomal abnormalities has been reported to directly affect chromosomal constitution of preimplantation embryos. This study showed that an increase in disomy for sex chromosomes is associated with an elevated risk of generating potentially viable embryos whose sex chromosomes are affected. Additionally, they observed that an increase in diploid sperm results in a higher incidence of triploid embryos, which are associated with more spontaneous abortions (Rodrigo et al., 2010).

Implantation rate

Oocyte fertilization by a chromosomally abnormal sperm is believed to cause implantation failure (Pang et al., 1999). A study in patients with three or more implantation failures reported an increase in sex chromosome disomies in 31.6% of males (Rubio et al., 2001). Further, later studies correlated abnormal FISH in spermatozoa with a decrease in pregnancy and implantation rates in ICSI cycles (Burrello et al., 2003; Nicopoullos et al., 2008).

Miscarriage

Abnormal sperm has also been related to recurrent miscarriage. A study in sperm samples from couples with recurrent miscarriage showed that sex chromosome disomy was significantly increased compared to internal controls. Further, in a subset of seven couples who underwent oocyte donation, mean frequencies for sex chromosome disomy were even higher and diploidy was also significantly increased (Rubio et al., 1999). These results suggest an implication of sperm chromosome abnormalities in some cases of recurrent pregnancy loss. Later, other studies corroborated this hypothesis, reporting an increase in sex chromosome disomies and diploid spermatozoa in couples with recurrent miscarriage (Al-Hassan et al., 2005; Bernardini et al., 2004; Giorlandino et al., 1998; Rubio et al., 2001). Finally, a recent study described that approximately 66% of abnormal karyotypes from miscarriages originate from male factor (Kim et al., 2010).

5.2 Sperm aneuploidies and abnormal offspring

Although most embryonic abnormalities end in implantation failure or spontaneous abortion, a variable percentage of abnormal offspring has been reported and associated with the presence of aneuploid spermatozoa in the father.

Down syndrome

Blanco et al. (1998) studied two fathers of children with Down syndrome who had a paternally-derived extra chromosome 21. FISH sperm studies showed elevated incidences of

spermatozoa with disomy 21. Further, in one patient, an increase in diploid sperm and disomy for sex chromosomes was observed (Blanco et al., 1998). Later chromosomes 4, 13, and 22 were analyzed in the same patients; an increase in disomies for chromosomes 13 and 22 was reported (Soares et al., 2001).

Sex chromosomes

Several studies of sperm samples in fathers of children with sex chromosome abnormalities have described higher rates of sex chromosome aneuploidy in sperm, especially related to Klinefelter syndrome (47,XXY) and Turner syndrome (X0). Moosani et al. (1999) performed FISH in sperm from males with normal karyotypes whose children had Klinefelter syndrome. They observed a higher percentage of XY disomy in sperm from these patients compared to fertile donors (Moosani et al., 1999). In another study the incidence of sperm with XY disomy was compared among males with children with Klinefelter syndrome of paternal or maternal origin. A significant increase in disomic sperm was detected in the paternal origin group (Eskenazi et al., 2002).

One study of males having children with Turner syndrome (45,X0) of paternal origin analyzed aneuploidy incidence for sex chromosomes. An increase in disomies and nullisomies for sex chromosomes was observed compared to the control group. Oocyte fertilization by sperm with nullisomy for sex chromosomes can produce a (45,X0) embryo (Martinez-Pasarell et al., 1999). Later, aneuploidy incidences for chromosomes 4, 13, 21, and 22 were assessed in ejaculated sperm from the same four males. A significant increase in chromosomes 13 and 22 disomies was observed in one male and in chromosome 21 in two other males (Soares et al., 2001). Another group studied the incidence of sex chromosomal aneuploidies in a male with a previous miscarriage with Turner syndrome of paternal origin. This study reported a significant increase in sex chromosomal disomies and nullisomies compared to the control group (Tang et al., 2004).

6. Conclusion

Many couples with infertility receive a diagnosis of “male origin”. Thus, the study of male gametogenesis and accurate evaluation of male gametes are extremely important.

As a key step of spermatogenesis, meiosis has been the focus of many recent studies. These studies often use immunocytogenetic assays to detect relevant proteins for recombination and synapsis. Thanks to this technique, meiotic abnormalities in infertile males have been well-described, especially for NOA males. Importantly, meiotic abnormalities can result in abnormal chromosome segregation; in fact, a correlation between meiotic abnormalities and sperm aneuploidy has already been described.

Chromosome abnormalities are increasingly found in sperm of many infertile men. This makes the direct analysis of sperm aneuploidy of clinical relevance, since male infertility is now treated by ICSI, which has the implicit risk of transmitting chromosomal aberrations from paternal side. Therefore, in IVF settings, the analysis of sperm chromosomal aneuploidies by FISH is of great interest. Using sperm FISH analysis, an increased incidence of sex chromosome disomies has been described in patients with impaired sperm parameters and in patients with recurrent spontaneous abortions. In this regard, an inverse correlation between sperm quality and sperm aneuploidy rates has been reported.

Another important issue is how sperm aneuploidy may influence ICSI outcome in infertile patients. The studies published so far suggest that sperm aneuploidy may be associated with implantation failure and/or early fetal loss. For these couples at risk, several treatment options has been postulated that range from regular ICSI cycles, to genetic diagnosis or donor sperm. Genetic screening studies in male factor infertility have reported a higher incidence of chromosome abnormalities in embryos from infertile men with altered sperm parameters. In azoospermic patients, higher rates of mosaic and chromosomally abnormal embryos have been reported, most frequently for sex chromosomes.

Therefore, accurate detection of sperm aneuploidies by FISH could be an useful tool for reproductive counseling in couples with male infertility.

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8. List of abbreviations

ART	Assisted reproductive technology
CREST	Calcinosis-Raynaud's phenomenon-esophageal dysfunction sclerodactyly-telangiectasia
DSB	Double-strand breaks
EC	Ejaculated control
FISH	Fluorescent in situ hybridization
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
M-FISH	Multiplex-fluorescent in situ hybridization
MI	Meiosis I
MII	Meiosis II
MLH1	MutL protein homolog 1
NOA	Non-obstructive azoospermia
OA	Obstructive azzospermia
OAT	Oligoasthenoteratozoospermia
RAD54	DNA repair and recombination protein RAD54-like
REC8	Meiotic recombination protein REC8 homolog
SC	Synaptonemal complex
SMC1B	Structural maintenance of chromosomes protein 1B
SPO11	Meiotic recombination protein SPO11
SYCP	Synaptonemal complex protein
TC	Testicular control

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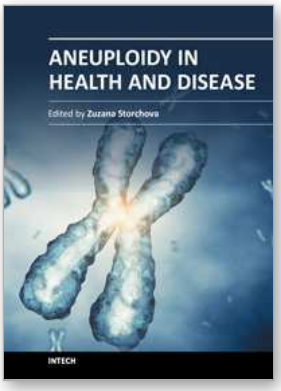

Aneuploidy in Health and Disease

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Aneuploidy means any karyotype that is not euploid, anything that stands outside the norm. Two particular characteristics make the research of aneuploidy challenging. First, it is often hard to distinguish what is a cause and what is a consequence. Secondly, aneuploidy is often associated with a persistent defect in maintenance of genome stability. Thus, working with aneuploid, unstable cells means analyzing an ever changing creature and capturing the features that persist. In the book Aneuploidy in Health and Disease we summarize the recent advances in understanding the causes and consequences of aneuploidy and its link to human pathologies.

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