THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India
DOI 10.1007/s13224-014-0623-3

INVITED REVIEW ARTICLE

Engaging Practicing Gynecologists in the Management of Infertile Men

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Received: 22 August 2014 / Accepted: 16 September 2014

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Abstract In the modern era, contemporary management of male infertility has undergone groundbreaking changes with the introduction of new concepts, advanced testing, and therapeutic interventions. As practicing gynecologists are often the first physicians who encounter an infertile couple, it is essential that these clinicians are continuously updated about the new pearls and pitfalls of male infertility management. Semen analysis is commonly ordered by gynecologists. In 2010, the WHO released new cutoff reference values for the semen parameters adopting novel methodology, which has incited much debate. Reference values have been lowered in comparison with previous standards, with a direct clinical implication in decision-making strategies. Specialized sperm-function tests, such as sperm oxidative stress and sperm chromatin integrity assessments, became clinically available, thus offering an opportunity to better understand sperm dysfunctions concealed during routine semen analysis. Furthermore, the initial counseling of azoospermic men by an andrologically well educated gynecologist may alleviate the misconception and distress surrounding the false belief of sterility, and will clarify the

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Published online: 05 November 2014

available options of percutaneous and microsurgical sperm-retrieval techniques and assisted conception outcome. Regarding varicocele, which is commonly seen in infertile males, it is now clear that the best treatment option for infertile men with clinical varicocele is the microsurgical vein ligation. Natural conception is significantly improved after varicocelectomy, and recent data suggest that such treatment optimizes reproductive outcome of couples undergoing ICSI or micro-TESE sperm retrieval. Lastly, new therapeutic interventions, including oral antioxidant therapy and lifestyle modifications, have gained increasing attention, as they aid in alleviating male infertility.

Keywords Gynecologist · Male infertility · Semen analysis · Azoospermia · Varicocele · Assisted reproductive technique · Sperm function

Introduction

Male factor infertility (MFI), alone or combined with female factor infertility, accounts for approximately 50 % of fertility problems [1]. MFI has undergone revolutionary changes in terms of diagnostic and treatment options, particularly in the last two decades. The objective of this article is to provide a better understanding of the evolving concepts in the field of male infertility to gynecologists and all health professionals involved in reproductive medicine.

Definitions

The World Health Organization (WHO) defines male factor infertility as the presence of abnormalities in the semen analysis (SA), or the presence of sexual or ejaculatory dysfunction [2]. However, a male infertility factor may be present even when the semen analysis is normal. The results of SA within normal ranges, as conventionally assessed for sperm count, motility, and morphology, have low predictive power of only 60 % to forecast the occurrence of a natural pregnancy [3].

Normal daily sperm production is about 40 million and declines with aging. The duration of spermatogenesis has been recently found to be about 60 days instead of 70 ± 4 days as had previously been described for past many years [4]. Sperm production essentially corresponds to the interactive outcome of biological, physical, and occupational factors, acting within the preceding 2 months from ejaculation. Known male infertility etiologies include reversible and correctable causes to uncorrectable ones. These etiologies may be inherited or acquired. In 37–58 % of the cases, MFI has an unknown origin, which can be idiopathic and unexplained [5–7]. Idiopathic MFI is characterized by an unexplained impairment in semen quality with no previous history of fertility problems, in association with normal findings on physical examination and endocrine laboratory testing [6]. Unexplained MFI is reserved for infertile men with semen profiles within normal ranges, and in whom female infertility factors have been ruled out. This category accounts for 6–27 % of male infertility, and it strongly depends on how exhaustive is the evaluation of the male patient [5]. Table 1 depicts the male infertility history outline, and Table 2 shows the distribution of the causes of MFI in a tertiary care center [8, 9].

Gynecologist's Role in the Initial Male Workup

A thorough history and a preliminary SA must be obtained before referring the male partner to an urologist. Advanced male age and a longstanding history of infertility are negative factors for fecundity, similar to female infertility. Secondary male infertility is often associated with correctable causes such as varicocele, infection, and ejaculatory problems. A history of early miscarriages or fetal genetic abnormalities may suggest a male factor contribution [10, 11]. Other history components should include sexual, family, childhood, and developmental and surgical history of the infertile couple, as well as the presence of systemic medical conditions.

As paternal age increases, the conception rate decreases, and the risk of genetic defects in offspring rises. Sperm chromosomal aneuploidy increases with paternal age as well. By around age 35, both sperm DNA fragmentation and germ cell apoptosis start to rise [12–14], while semen volume, sperm morphology, and motility decline [15–17]. The risk of having a child with autosomal dominant disorders for older men is equal to that of having a child with Down syndrome for women aged >45 years [18].

A detailed history about current use of medication is also important. Antihypertensive drugs such as alpha- and beta-blockers, thiazide diuretics, and spironolactone may cause erectile and ejaculatory dysfunction. Calcium-channel blockers may negatively impact sperm-fertilizing ability by blocking the acrosome reaction. Antibiotics such as gentamicin, erythromycin, and nitrofurantoin are gonadotoxic [19]. Cimetidine, spironolactone, certain hormonal preparations, and anabolic steroids may alter the hypothalamic–pituitary gonadal axis, thus affecting spermatogenesis [20]. Cancer treatments such as radiotherapy and chemotherapy also decrease sperm production.

Obesity has been also linked with male subfertility [21, 22]. Obesity is associated with altered semen parameters [23–25]. Furthermore, reduced sperm DNA integrity is common in infertile obese men [26]. These changes are attributed to high estrogen production from fat stores and/or high accumulation of fertility-jeopardizing environmental toxins in fatty tissue. Occupational exposure to toxicants and

Table 1 Clinical male infertility history outline

1. Infertility history
Age of partners, time attempting to conceive
Contraceptive methods/duration
Previous pregnancy (actual partner/other partner)
Previous treatments
Treatments/evaluation of female partner
2. Sexual history
Potency, libido, lubricant use
Ejaculation, timed intercourse, frequency of masturbation
3. Childhood and development
Cryptorchidism, hernia, testicular trauma
Testicular torsion, infection (e.g., mumps)
Sexual development, puberty onset
4. Personal history
Systemic diseases (diabetes, cirrhosis, hypertension)
Sexually transmitted diseases, tuberculosis, viral infections
5. Previous surgeries
Orchidopexy, herniorraphy, orchiectomy (testicular cancer, torsion)
Retroperitoneal and pelvic surgery
Other inguinal, scrotal, and perineal surgery
Bariatric surgery, bladder neck surgery, transurethral resection of the prostate
6. Gonadotoxin exposure
Pesticides, alcohol, cocaine, marijuana abuse
Medication (chemotherapy agents, cimetidine, sulfasalazine, nitrofurantoin, allopurinol, colchicine, thiazide, β- and α-blockers, calcium blockers, finasteride)
Organic solvents, heavy metals
Anabolic steroids, tobacco use
High temperatures, electromagnetic energy
Radiation (therapeutic, nuclear power plant workers), etc.
7. Family history
Cystic fibrosis, endocrine diseases
Infertility in the family
8. Current health status
Respiratory infection, anosmia
Galactorrhea, visual disturbances
Obesity

exposure to excessive heat from sauna and hot tubs are detrimental to sperm production [20]. The use of pesticides, radiation exposure from X-ray, excessive use of cell phones, and heavy metal intoxication may also potentially affect sperm production and quality [27].

Semen Analysis

Semen analysis is the corner stone of infertility evaluation as it provides information on the functional status of the seminiferous tubules, epididymis, and accessory sex glands. Physical properties of semen such as viscosity, color, and pH are assessed as well as semen volume and several microscopic parameters including sperm concentration, motility (percentage of motile sperm), morphology (percentage of normally shaped sperm), viability (percentage of living sperm), and number of leukocytes [28].

Table 2 Distribution of diagnostic categories of couples seeking infertility evaluation in a male infertility clinic*

Category	*N*	%
Varicocele	629	21.9
Infectious	72	2.5
Hormonal	54	1.9
Ejaculatory dysfunction	28	1.0
Systemic diseases	11	0.4
Idiopathic	289	10.0
Normal/female factor	492	17.1
Immunologic	54	1.9
Obstruction	359	12.5
Cancer	11	0.4
Cryptorchidism	342	11.9
Genetic	189	6.6
Testicular failure	345	11.9
Total	2,875	

*Androfert, Brazil

The semen parameters from same individuals are highly variable due to factors such as duration of ejaculatory abstinence, activity of the accessory sex glands, analytic errors, and inherent biological variability [29–31]. Clinicians should request at least two SAs following 2–5 days of ejaculatory abstinence to assess the baseline semen-quality status [32, 33].

Guidelines for evaluation, such as those issued by the American Urological Association and European Association of Urology, rely to a large extent upon the concept of abnormal SA for management [6, 34]. These recommendations understate the limitations of the SA results and do not discuss the paradigm shift that is likely to occur in referrals and management in the light of the recent changes in the WHO reference thresholds [35, 36]. Much debate has taken place thereafter, and a series of reports have questioned the validity of the newly released reference values [36–38]. Table 3 highlights the cutoff values for SA as published in consecutive WHO guidelines [35, 36]

Recommendation for treatment has been also based on the results of SAs. Current guidelines for varicocele indicate that treatment should be offered to men with clinical varicocele in the presence of abnormal semen parameters [39, 40]. Application of the new WHO reference values might lead to patients, earlier deemed to be candidates for

varicocele repair, now being considered ineligible for treatment if their semen parameters are above cutoff limits. Of note, the most recent report on varicocele by the American Society for Reproductive Medicine acknowledged the limitations of the routine SA and included the presence of an abnormal sperm-function test as an indication for treatment [40].

Yet another example is sperm morphology thresholds of which were lowered to 4 % in the 2010 WHO guidelines compared with 14 % prescribed in the previous 1999 standards [41–43]. Infertility specialists recommend intracytoplasmic sperm injection (ICSI) instead of conventional IVF or intrauterine insemination (IUI) in situations when the morphology results are below 4 %, owing to the markedly lower pregnancy outcomes of these two treatment methods when using semen with low percentage of normal sperm [44, 45]. Interestingly, the results of distribution of SA of fertile men in centiles, as shown by the new WHO standards, clearly show that, although 5 % of the studied men had morphology values below the 4 % cutoff point, they still initiated an unassisted pregnancy within 12 months of unprotected intercourse [35, 36]. Physicians treating infertile couples should exercise circumspection when interpreting the results of routine SA because it is only a tool among several others for determining clinical care. The male infertility evaluation has to be complemented with a proper physical examination, a comprehensive history taking, and relevant endocrine, genetic, and other investigations [46, 47].

Current Sperm Function Tests

Before the advent of ICSI, tests which assessed antisperm antibodies [48], sperm hyperactivation and acrosome reaction, sperm binding, and penetration to the human zona pellucida were widely used both to investigate males with unexplained infertility and to predict the fertilizing potential of sperm in conventional IVF.

Our improved understanding of the molecular mechanisms controlling sperm function enabled the development of new diagnostic tests, particularly oxidative stress (OS), and nuclear DNA integrity testing [49–51]. These markers cannot be detected by routine SA but seems to better correlate with the male fertility status than the latter [52–58].

Sperm Chromatin Integrity Testing

Sperm DNA damage is the loss of DNA integrity, and it may occur at any level in vivo during spermatogenesis, spermiogenesis, epididymis transit, or in vitro when spermatozoa are prepared for assisted conception [59]. Sperm DNA damage is a broad term that accounts for many defects in the DNA structure including single or double DNA strand breaks, base deletion or modification, interstrand or intrastrand DNA crosslinkage, and protamine mispackage via defective DNA–protein crosslinking [60].

Sperm with damaged DNA although defective may still retain the ability to fertilize the ova. However, such DNA damage has been associated with several infertility phenotypes, such as unexplained and idiopathic infertility, repeated IUI and IVF failures, and recurrent miscarriage [61–67]. Furthermore, the increased risks of imprinting defects and cancer in the offspring have been linked with sperm DNA damage [68, 69].

Several assays used to measure sperm DNA damage are based on different principles and therefore differ in their ability to detect DNA damage [59, 70]. In Table 4, we summarize the principles and interpretations of the most commonly used assays. A comprehensive review about the methods to measure sperm DNA damage can be found elsewhere [51].

Reactive Oxygen Species Testing

Sperm reactive oxygen species (ROS) are the byproducts of oxygen metabolism, which in small concentrations regulate physiological cellular functions such as capacitation, acrosomal reaction, hyperactivation, and the fusion with the oocyte [71]. In semen, leukocytes and spermatozoa are the two main sources for ROS. In sperm, ROS are generated by both the NADPH oxidase and NADH-dependent oxido-reductase systems at the plasma membrane and mitochondrial levels, respectively [72]. When ROS levels increase disproportionately, mainly due to the presence of superoxide, hydroxyl radicals or nitric derivatives, compared with the neutralizing capacities of intracellular and extracellular antioxidants; or when a reduction in the antioxidant capacity occurs, OS is sustained.

ROS can modify lipids, proteins, and DNA through a variety of oxidative mechanisms [71, 73] causing lipid peroxidation, protein carbomoylation, and oxidized DNA, respectively. Oxidative DNA modifications can sustain serious damages to DNA, such as point mutations, polymorphisms, deletions, chromosomal rearrangements, frame shifts, and single-stranded or double-stranded breaks [74].

The assays to measure ROS, their principle, methodology, clinical utility, and drawbacks are summarized in Table 5 [75–77].

Genetic Conditions Associated with Male Infertility

Approximately 6 % of infertile men have chromosomal abnormalities; the rate is even higher ($\sim$16 %) in men with azoospermia [78]. Sex chromosomal aneuploidy (Klinefelter syndrome [KS]; 47, XXY) is the most common

Table 3 Cutoff reference values for semen characteristics as published in consecutive WHO manuals

Semen characteristics	WHO 1980	WHO 1987	WHO 1992	WHO 1999	WHO 2010[a]
Volume (mL)	ND	≥2	≥2	≥2	1.5
Sperm count (10^6/mL)	20–200	≥20	≥20	≥20	15
Total sperm count (10^6)	ND	≥40	≥40	≥40	39
Total motility (% motile)	≥60	≥50	≥50	≥50	40
Progressive motility[b]	≥2[c]	≥25 %	≥25 % (grade a)	≥25 % (grade a)	32 % (a + b)
Vitality (% alive)	ND	≥50	≥75	≥75	58
Morphology (% normal forms)	80.5	≥50	≥30[d]	(14)	4[f]
Leukocyte count (10^6/mL)	<4.7	<1.0	<1.0	<1.0	<1.0

ND not defined, *ART* assisted reproductive techniques, *G-band karyotype* Giemsa band karyotype, *CFTR* cystic fibrosis transmembrane conductance regulator

[a] Lower reference limit obtained from the lower fifth centile value

[b] Grade a = rapid progressive motility (> 25 μm/s); grade b = slow/sluggish progressive motility (5–25 μm/s); Normal = 50 % motility (grades a + b) or 25 % progressive motility (grade a) within 60 min of ejaculation

[c] Forward progression (scale 0–3)

[d] Arbitrary value

[e] Value not defined but strict criterion is suggested

[f] Strict (Tygerberg) criterion

chromosomal disorder in infertile men and is generally associated with hypotrophic or atrophic testicles, elevated serum FSH levels and azoospermia or severe oligozoospermia. In men with KS presenting with azoospermia, sperm are present in approximately 20–50 % of cases on testicular exploration, and pregnancy rates associated with ICSI range from 30 to 50 % [79]. Men with KS can have biological offspring with a normal karyotype because germ cells are usually euploid (46, XY) and thus can form normal, haploid gametes [80].

The long arm (q) of Y-chromosome contains genes regulating spermatogenesis [81]. The Y-chromosome region related to infertility is called azoospermia factor *locus* (AZF). This *locus* can harbor complete or partial microscopic deletions, isolated or in combination, in subregions called AZFa, AZFb, and AZFc (Fig. 1).

Yq chromosome microdeletions (YCMDs) are found in 15 % of men with azoospermia and in 6 % of men presenting with severe oligozoospermia (<1 million/mL) [78, 82, 83]. For sperm counts between 1 and 5 million/mL, the detection rate drops down to 1.7 % [84]. YCMD affecting the AZFc region usually results in severe oligozoospermia or azoospermia. Patients with AZFa microdeletions generally present with germ cell aplasia on testicular histopathology, while most patients with AZFb microdeletions present with maturation arrest [85, 86]. To test for YCMD, peripheral blood is obtained, and polymerase chain reaction is used to amplify the long arm of the Y-chromosome, which will identify deletions of the AZF regions. YCMD screening may also predict the chance of sperm retrieval (SR) for candidates of assisted conception. The findings of complete AZFa and/or AZFb microdeletions normally preclude a sperm-retrieval attempt as there is no evidence that testicular sperm can be found irrespective of the retrieval method. However, in cases with AZFc microdeletion, sperm can be retrieved in 50–71 % of patients [84]. Clinical pregnancy rates are virtually the same as those of idiopathic azoospermic patients [87]. However, the offspring of a father with YCMD will inherit the same genetic trait. The main indications for genetic testing in male infertility and the tests used to assess such conditions are highlighted in Table 6.

The most common genetic sperm-transport disorder is the congenital bilateral absence of the vas deferens (CBAVD). Approximately 80 % of men presenting with CBAVD have mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located on the long arm of chromosome 7. Depending on the extension of the mutation, cystic fibrosis can manifest in a full clinical presentation (an autosomic recessive potentially fatal disease) or in a mild form, i.e., CBAVD, which affects approximately 1.3 % of infertile men [88]. The female partner should also be tested for the CFTR mutation; she may be a carrier (approximately 4 % risk). Such testing should be done before the man's sperm is used for assisted conception because the cystic fibrosis gene can be transmitted to offspring [87].

Varicocele

Varicocele is an elongated, dilated, and tortuous testicular vein in the spermatic cord. It is identified in 7 and 10–25 % of

prepubertal and postpubertal males, respectively [89, 90]. Higher prevalence in elderly males and in men with secondary MFI suggests it to be a progressive disease [91, 92].

Recent data suggest that varicocele causes infertility by inducing ultrastructural testicular changes and OS, with implications for the seminal antioxidant capacity and sperm chromatin integrity [93–95]. Abnormalities of semen parameters in patients with varicocele are variable and involve sperm count, motility, and morphology [96, 97]. Men with varicocele were also shown to have lower testosterone levels, as well as reduced testicular size on the same side of varicose vessels compared to those without varicocele [98, 99].

Physical examination with the patient standing in a warm room is currently the preferred method for varicocele diagnosis and has a sensitivity and specificity of around 70 % compared with other diagnostic tools [100, 101]. The most widely used classification is as follows:

- Grade 3: visible and palpable at rest (Fig. 2)
- Grade 2: palpable at rest
- Grade 1: palpable during Valsalva maneuver
- Subclinical: not palpable or visible at rest or under Valsalva maneuver but detectable by Doppler ultrasound

Whenever physical examination is inconclusive or difficult to perform, imaging studies are recommended. Color Doppler ultrasound (CDU) has been shown to be the best diagnostic tool. Using a cutoff value of 3 mm for vein diameter, CDU has a sensitivity of about 50 % and specificity of 90 % compared with physical examination [102].

Current recommendations propose varicocele treatment for couples with documented infertility, whose male partner has a clinical varicocele and at least one abnormal semen parameter. Men not attempting to achieve conception but who fit into this description and have a desire for future fertility are also candidates for treatment [6, 103]. After varicocelectomy, the chances of natural conception increase 2.8-fold [104], and varicocele repair is more cost effective than ART [105].

In azoospermic men with favorable testicular histopathology, clinical varicocele repair may lead to sperm appearance in the ejaculate [106]. As such, IVF/ICSI can be performed without the need to surgically retrieve sperm. Sperm-retrieval success rates seems to be increased in azoospermic men with treated varicocele compared with untreated ones [107]. Live birth rates were also shown to be significantly higher in men who had the varicocele treated before ICSI (46.2 %) compared to those undergoing ICSI in the presence of a clinical varicocele (31.4 %) [108].

Azoospermia

Azoospermia is defined by the complete absence of sperm cells in the ejaculate after centrifugation without implying an underlying cause [109]. It affects approximately 1 % of the male population. Men diagnosed with azoospermia are broadly categorized as having a mechanical obstruction along the seminal tract (obstructive) or an intrinsic testicular impairment of sperm production (nonobstructive azoospermia).

In obstructive azoospermia (OA), the blockage is located between the epididymis and the ejaculatory duct. Causes of OA include CBAVD, infection, and vasectomy. Surgical reconstructive procedures are available for select patients with OA (e.g., vasectomy reversal), and surgical SR is usually successful in noncorrectable cases [110, 111].

Nonobstructive azoospermia (NOA) is caused by genetic factors, prior testicular toxic exposures such as radiation or chemotherapy, trauma, infection, and idiopathic reasons. While about 50 % of NOA patients have mature spermatozoa in their testicles, no reliable predictive factors exist to prospectively distinguish which patients

Table 4 Examples of the commonly used methods for assessment of sperm DNA damage

Assay	Principle	How results are expressed	Normal limits
Terminal deoxy nucleotide transferase-mediated dUTP nick end labeling (TUNEL) assay	Measure DNA damage by incorporating DNA probes or modified nucleotides at the site of damage	Percentage of sperm with DNA damage, represented by those with the probes incorporated to DNA breaks	<19 % for TUNEL when used to discriminate fertile from unselected infertile men with 70 % accuracy
Sperm chromatin structure assay (SCSA)	Measure the susceptibility of DNA to denaturation	Percentage of sperm with fragmented DNA	<30 %
Sperm chromatin dispersion test (SCD)	Measure the susceptibility of DNA to denaturation	Percentage of sperm with fragmented DNA	<30 %
Comet assay	Measure the susceptibility of DNA to denaturation	Degree of DNA fragmentation in a single spermatozoon as assessed by the percentage of DNA in the tail of the comet, tail length and intensity of staining (Comet)	Not defined
Aniline blue staining (AB)	Measure the level of chromatin compaction	Percentage of sperm with loose chromatin packing	Not defined

may have sperm that can be surgically retrieved except in cases of YCMD as indicated above [112].

Given its untreatable nature, men with NOA seeking fertility should rely on SR and ICSI for achieving biological offspring. Among the SR methods, microsurgical testicular sperm extraction (micro-TESE) is considered to be the best option for SR in men with NOA (retrieval rates ranging from 40 to 60 %). Micro-TESE also provides the opportunity for both preserving testicular vasculature and minimizing the amount of extracted parenchyma [112, 113].

ICSI is associated with lower fertilization rates per injected oocyte as well as clinical pregnancy and delivery rates when testicular spermatozoa from men with NOA are used in comparison to epididymal/testicular sperm from men with OA [113–115]. Once a live birth is achieved, newborn parameters of infants conceived were not significantly different among the groups, and no major differences are noted in the offspring's neonatal profile [113]. If there is no worthy sperm for fertilization, then the couple must consider adoption or donor insemination.

Prescription of Antioxidants

Fair evidence suggests that antioxidant therapy has a beneficial role in MFI. However, it is also essential to encourage lifestyle modifications, which helps in reducing the generation of free radicals. For example, increased intake of vegetables and fruits, reduction in excess weight, smoking cessation, and moderation in alcohol consumption are advised [116]. Exposures to various environmental pollutants and/or radiation should be avoided or reduced. Chemical gonadotoxins, including pesticides found in vegetables and industrial waste, can increase the formation of free radicals due to the unstable chemical compounds found in these products. Radiation exposures from cell phones and laptop computers, can produce OS by inducing cellular chemical changes through the electromagnetic waves emitted from the devices, and decrease semen quality [117].

Antioxidant therapy, including vitamins E and C, carotenoids, zinc, and selenium, enhances total antioxidant capacity of body fluids including semen resulting in scavenging of excess free radicals [118–129]. Improvements in sperm motility, sperm DNA fragmentation, fertilization capacity, and odds of normal sperm count were observed in most studies [120–123], albeit, in a few of them, no advantage was documented [124, 130]. A Cochrane meta-analysis on the use of oral antioxidants in male infertility found that these agents significantly improved pregnancy rates and live births and decreased sperm DNA damage [131]. Nevertheless, improvements in semen parameters are not well evident [131] (Table 7). These observations support the concept that antioxidants can improve sperm function by improving sperm DNA integrity and fertilizing capabilities.

Counseling of Male Infertile Patients

Infertile men are often anxious, and feel guilty regarding their inability to induce a pregnancy [132]. Proper counseling of both partners should be one of the top priorities of the treating physician, and in this sense, the gynecologist

Table 5 Examples of the methods commonly used for assessing oxidative stress

Assay	Principle	Specimen	How results are expressed	Normal limits
ROS by chemiluminescence	Intra- and extracellular ROS levels (mainly H_2O_2, $O2^-$, and OH^-) react with probes and emit photons that are measured using a luminometer. The final chemiluminescent signal is the integrated sum of the partial signals generated by every spermatozoon	Semen	$\times 10^6$ counted photons per minute (cpm) per 20×10^6 sperm/mL	$<0.0185 \times 10^6$ cpm/ 20×10^6 sperm
Thiobarbituric acid reactive substances (TBARS)	Malondialdehyde (MDA), a byproduct of lipid peroxidation, condenses with two equivalents thiobarbituric acid and give a fluorescent red derivative that can be assayed spectrophotometrically. Absorbance at 532 nm is recorded	Semen and seminal plasma	nmoL MDA/ 10×10^7 sperm, nmol MDA mL^{-1} seminal plasma, or nmoL MDA/total seminal plasma	0.0287 ± 0.0162 nmol/ 10^8 sperm and 0.65 ± 0.17 nmol/mL-1 seminal plasma
Seminal total antioxidant capacity (TAC) by enhanced chemiluminescence	Capacity of the antioxidants in a given sample to prevent ABTS oxidation is proportional to their Concentration. Suppression of absorbance at 750 nm is measured and compared with that of standard Trolox, a water-soluble tocopherol analog	Seminal plasma	Molar Trolox equivalents	>2,000 micromoles of Trolox

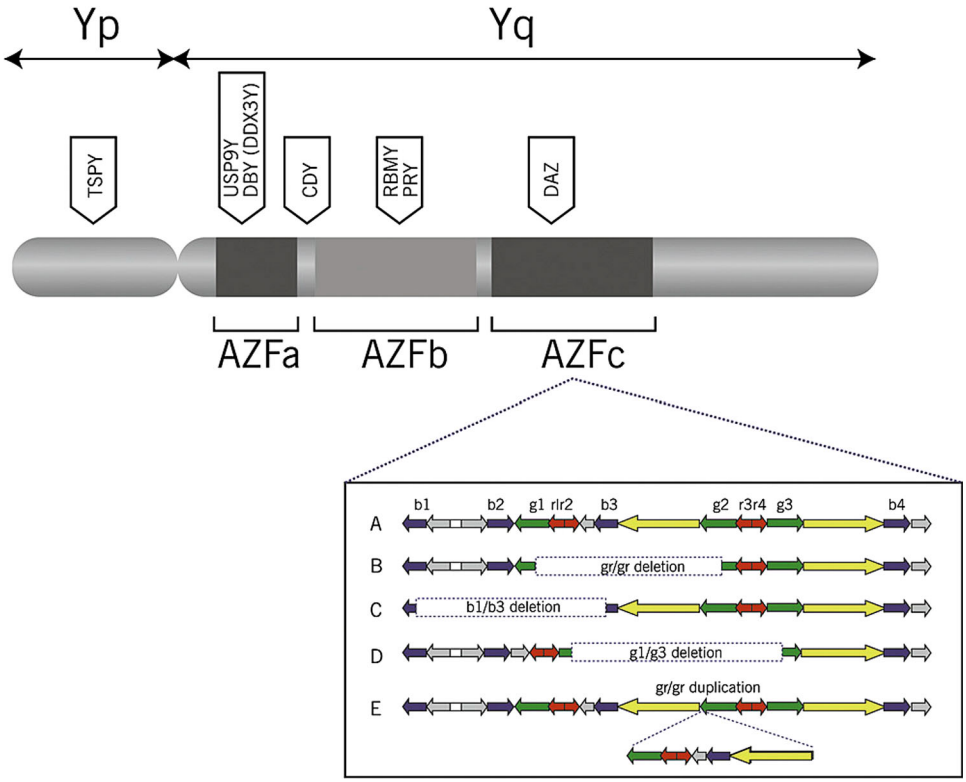

Fig. 1 Image of Y chromosome. Reprinted with permission from: O'Flynn O'Brien KL Varghese AC, Agarwal A. The genetic causes of male factor infertility: a review. Fertil Steril. 2010 Jan;93 [1]:1–12

Table 6 Main indications for genetic testing in male infertility

Indications	Recommended tests
Men with infertility of unknown etiology and sperm concentration <10 million/mL who are candidates for ART	Y-chromosome microdeletion and G-band karyotype
Nonobstructive azoospermia in a male considering testicular sperm retrieval for ART	Y-chromosome microdeletion and G-band karyotype
Azoospermic or oligozoospermic men with absence of at least one vas deferens at physical examination	CFTR gene mutation
Azoospermic men with signs of normal spermatogenesis (e.g., obstructive azoospermia of unknown origin)	CFTR gene mutation
History of recurrent miscarriage or personal/familiar history of genetic syndromes	G-band karyotype

ART assisted reproductive techniques

G-band karyotype giemsa band karyotype

CFTR cystic fibrosis transmembrane conductance regulator

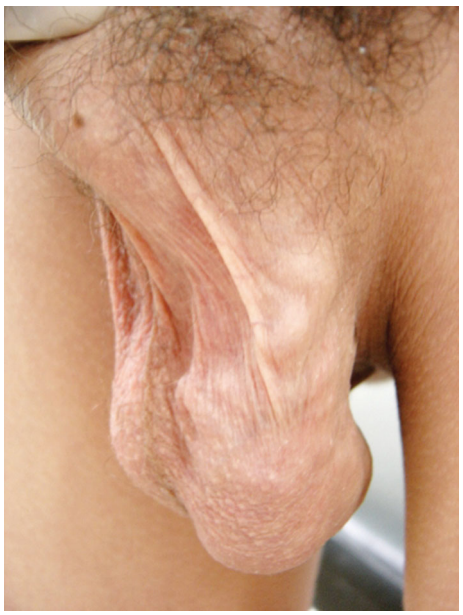

Fig. 2 Image of grade III varicocele. Reprinted with permission from Clinics (São Paulo) 2011, Esteves, Miyaoka, Agarwal. An update on the clinical assessment of the infertile male, vol. 66, issue 4, pages 691–700

plays a crucial role. The following list contains practical recommendations for couples with male factor infertility, who are attempting to conceive:

1. All commercially available lubricants decrease sperm motility and increase sperm DNA damage. Hydroxylethylcellulose-based lubricant was shown to be relatively less detrimental to sperm than other substances [133]. Saliva and vegetable oil also decrease sperm motility [134, 135].

Table 7 Results of Cochrane review 2011 [131]

Semen parameter	No. of studies No. of patients	Average duration of treatment	Mean difference (MD) ± SD, 95 % CI	Pooled cumulative grade of response
Total motile sperm	10 trials 514 patients	3 months or less	MD 11.72, 95 % CI 6.94 to 16.49; $P < 0.00001$	+ Very low
	7 trials 963 patients	6 months	MD 4.19, 95 % CI 3.81 to 4.56; $P < 0.00001$	+ Very low
	3 trials 332 patients	9 months	MD 1.38, 95 % CI 0.81 to 1.95; $P < 0.00001$	+ Very low
Sperm Count	7 trials 320 patients	3 months or less	MD 6.04, 95 % CI −5.42 to 17.50; $P = 0.30$	No effect
	6 trials 825 patients	6 months	MD 5.25, 95 % CI 4.43 to 6.08; $P < 0.00001$	+ Very low
	3 trials 332 patients T181, C151	9 months	MD 1.61, 95 % CI 0.61 to 2.61; $P = 0.002$	+ Very low
Sperm DNA fragmentation index (DFI)	1 trial 64 patients T32, C32	2 months	MD -13.80, 95 % CI −17.50 to −10.10; $P < 0.00001$	Decrease DFI
Pregnancy rate	15 trials 964 couples	4.5 months	OR 4.18, 95 % CI 2.65 to 6.59; $P < 0.00001$	+ + + + High
Live birth per couple	3 trials 214 couples	4 months	OR 3.94, 95 % CI 1.14 to 13.55; $P = 0.03$	+ + + Moderate

2. Male partners should stop smoking, and limit alcohol use to 3–4 units/week, and abstain from illicit drug use [136, 137].
3. Prescribe exercise and weight loss for overweight or obese men. A healthy BMI ranges from 20 to 27 [137–139].
4. Advise the male partner to avoid any situations that can increase scrotal temperature such as sitting in a hot tubs/sauna, and placing portable computers directly on the lap. If occupational exposure to a hot work environment is unavoidable, the patient can take proper precautionary measures to minimize testicular heat exposure [93].
5. Abnormal findings in SA require thorough physical examination and further laboratory investigation. This workup should be discussed with the patient, and it should be explained that referral to an urologist/andrologist is recommended. In the presence of azoospermia in SA, the couple should not be discouraged and should be informed that treatment modalities are available.
6. If a palpable varicocele is present, then advise that surgical repair may be an option to improve fertility.
7. Be aware that elderly infertile men usually have chronic medical diseases, which should be identified and treated because they can negatively affect fertility.

Compliance with ethical requirements and Conflict of interest This article complies with the ethical standards as per the Journal's policies. Each author indicates that there is no financial interest or conflict of any kind to disclose. In addition, this article does not contain any studies with animals performed by any of the authors.

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