Editorial

The Urological Society of India guidelines for the management of male infertility (Executive Summary)

These guidelines have been drafted by the Urological Society of India Male Infertility guidelines panel and address management of male infertility. The guidelines are intended for urologists and the recommendations are updated till January 2021. These will remain valid until the next update or for a maximum period of 5 years. The guidelines should not be regarded as a rigid clinical pathway for every patient and are not intended to replace clinical judgment. These guidelines should not be viewed as legal standards of care. This executive summary includes some salient aspects of the guidelines and the guideline statements. The complete guidelines document can be accessed from the Urological Society of India website at www.usi.org.in.

METHODOLOGY

A nonsystematic review of the literature available on the subject on PubMed and Google Scholar was performed. A total of 135,775 abstracts obtained from 1990 till present date using keywords "male infertility," "Semen," "Azoospemia," "Oligospermia," "Sperm retrieval," "Hypogonadism," "microlithiasis," and "testicular cancer" were analyzed, and after removal of nonrelevant results and duplicates, a total of 833 articles were analyzed. Results of these studies and meta-analyses were combined in a simple narrative fashion. Articles published from India and pertaining to the Asian subpopulation were given a special attention. The recommendations are graded (GR) as strong where an action should or should not be undertaken because net benefit or net harm is substantial; moderate/optional where an action may or may not be undertaken because net benefit or net harm is equivocal; and weak or conditional/selective when net benefit or net harm of taking an action is justified only in selective circumstances. Clinical principle (CP) is a statement that is widely agreed upon by clinicians, for which there may or may not be evidence in the medical literature. Expert opinion is a statement agreed upon by the guidelines panel in the absence of evidence. Level of evidence (LE) was evaluated by the Centre for Evidence-Based Medicine method.

DEFINITION

"Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in 1 year."

EPIDEMIOLOGY

Infertility is the problem affecting 15% of married couples globally.[1] The male factor contributes for about 20%–40%.[2,3] As per the WHO, approximately 60–80 million couples suffer from infertility,[4-6] and the prevalence varies from region to region.[7] It is higher in countries with high fertility rate, which is termed as "barrenness amid plenty!."[8,9]

As per a WHO multicentric study, 27% had etiological factors identified in both the male and the female, 20% only in male, 30% only in female and about 15% could not be clearly attributed to either.[10] As per an Indian report, 50% of infertility results from reproductive diseases in men and 25% of infertility cases have no clearly defined etiology and are termed as unexplained infertility.[11,12] Infertility varies widely among different Indian states. Its reported incidence is 3.7% in Uttar Pradesh, Himachal Pradesh, and Maharashtra,[13] 5% in Andhra Pradesh,[14] and 15% in Kashmir.[15,16] In another multicentric study by the WHO, 45% of subfertile men had oligozoospermia or azoospermia.[17]

GUIDELINE STATEMENTS

Epidemiology and etiology

1. To categorize infertility, both the partners should be investigated simultaneously (moderate recommendation)
2. There are no reliable figures for the global prevalence of infertility. It is estimated to be 8%–12%, of which only the male partner accounts for 20%, females 38%, mixed 27% and unknown 15%. In India, it varies from 3.9% to 16.8% with wide variations not only in different states but also different castes and tribes of the same region
3. The primary cause of infertility could be defined only in 40%. They are grouped as nonobstructive, obstructive, and coital.[18] Reasons in 75% of cases of oligospermia remained unknown.

Evaluation and semen analysis

1. Relevant reproductive clinical history and focused clinical examination should be done (strong recommendation)
2. Perform semen analysis as per the WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edn) reference criteria[19] (strong recommendation)
3. Offer blood endocrine profile only if semen analysis is abnormal on at least two occasions (strong recommendation)

4. Offer ultrasound scrotum for patients who are obese, with previous scrotal surgery or have tight small scrotum (moderate recommendation)
5. Transrectal ultrasound is offered only when ejaculatory duct obstruction (EDO) is suspected (Strong recommendation).

Obstructive azoospermia

1. For patients with nonpalpable vas, congenital bilateral absent vas deferens (CBAVD) must be suspected and CFTR mutation tested (strong recommendation)
2. Diagnostic testicular biopsy should be done preferably in a center where there is a facility of sperm retrieval and cryopreservation (moderate recommendation)
3. Vasography should not be used as a diagnostic procedure alone and only to be used intraoperatively before reconstructive surgery (strong recommendation)
4. In men with female partners of good ovarian reserve, microsurgical vasovasostomy or epididymovasostomy for azoospermia due to obstruction in epididymis and vas,[20] respectively, can be performed (strong recommendation)
5. When the ovarian reserve of the partner is limited, sperm retrieval techniques such as MESA, TESE, PESA, TESA must be used in adjunct to reconstructive surgery (strong recommendation)
6. For patients with irreparable reproductive tract, sperm retrieval techniques are preferred for ICSI/IVF (strong recommendation)
7. Men with EDO and dilated ejaculatory ducts may benefit from transurethral resection of the ejaculatory ducts (TURED)[21] (strong recommendation)
8. Men with suspected EDO but normal transrectal ultrasound findings are likely to have a fibrous type of ejaculatory duct obstruction (postinfective). They are not candidates for TURED and will need PESA-ICSI (strong recommendation).

Nonobstructive azoospermia

1. Nonobstructive azoospermia (NOA) patients should undergo a comprehensive assessment including detailed medical history, hormonal profile, and genetic tests for assessing the etiology[22] (strong recommendation)
2. In men with AZFa and AZFb microdeletions, surgical sperm retrieval is contraindicated[23] (strong recommendation)
3. Microdissection TESE (mTESE) is the most efficient method for surgical sperm retrieval in NOA[24] (strong recommendation)

Hypogonadotropic hypogonadism

1. Male hypogonadotropic hypogonadism (HH) is the failure of the testes to produce androgens and sperms secondary to congenital or acquired diseases affecting the hypothalamus and/or the pituitary gland[25]
2. Diagnosis is confirmed by low serum FSH, LH, and testosterone levels. Imaging (MRI/CT) of the brain should be done (strong recommendation)
3. Clinical features depend on the age of presentation[26]
4. Treatment requires androgen replacement therapy till/when fertility is not desired. For fertility, gonadotropins are started to stimulate spermatogenesis[27] (strong recommendation)
5. Testosterone replacement therapy must not be done for management of infertility[28] (strong recommendation)
6. HH is one of the rare conditions in which specific medical treatment can reverse infertility[29] (strong recommendation).

Infections in infertility

1. Infections have been associated with male infertility but direct causation has not been proven[30]
2. Antibiotics and anti-inflammatory agents (NSAIDs) for up to 3–6 weeks may have a role in the management of MAGI, especially in cases of complex of Prostatitis, prostatovesiculitis, and prostato-vesiculo-epididymitis (weak recommendation)
3. Antioxidant therapy in the presence of epididymitis to restore ROS balance after resolving infections and inflammation may be used (weak recommendation).

Genetics in male infertility

1. Elevated LH and FSH in men with azoospermia should prompt genetic testing (moderate recommendation)
2. Sperm concentrations <10 million/mL (especially <5 million/ml) due to idiopathic spermatogenic defects should be referred for genetic counseling, karyotyping, and Y chromosome microdeletion (strong recommendation)
3. NOA will often require microdissection TESE for best chance of sperm retrieval (moderate recommendation)
4. In men with Klinefelter syndrome, the chances of sperm retrieval at microdissection TESE are around 22%–50%[31] (moderate recommendation)
5. The chances of transmission of Klinefelter syndrome to offspring are low
6. Young men with AZFc deletions require genetic counseling regarding transmission to offspring. They have better chances of sperm retrieval (up to 55%) on microdissection TESE[32] (moderate recommendation)
7. Low-volume ejaculate, acidic pH and absent fructose suggests obstructive azoospermia, most commonly due to CBAVDs or EDO (Strong recommendation)
8. CBAVD contributes to up to 30% of men with obstructive azoospermia
9. CBAVD is a clinical diagnosis, made by absence of bilateral vasa on palpation (strong recommendation)
10. The most common genetic evaluation for CBAVD is CFTR gene mutation evaluation[33] (strong recommendation)

11. Comprehensive testing in the couple is necessary to avoid CF child (strong recommendation)
12. Sperm retrieval is successful in up to 97% of men with CBAVD by testicular sperm aspiration or epididymal aspiration (weak recommendation).

Varicocele

1. Only clinically palpable varicocele requires treatment[34] (strong recommendation)
2. Microsurgical varicocelectomy is the preferred modality of treatment[35] (strong recommendation).

Unconsummated marriage

1. Unconsummated marriage may be due to erectile dysfunction (ED) or female factors such as vaginismus or dyspareunia and lack of understanding of reproductive anatomy (CP)
2. Perform office sildenafil test to assess erectile function (weak recommendation)
3. Consider office intracavernosal injection of vasoactive drug (ICIVAD) as the next step to identify vasculogenic ED, if unresponsive to oral PDE5i (moderate recommendation)
4. In men with vasculogenic ED requiring ICIVAD or not responding to any nonsurgical options, shared decision-making should be done along with the patient for the role of penile prosthesis implantation as a treatment option (strong recommendation).

Testicular microlithiasis

1. Microlithiasis is associated with abnormal semen parameters but direct causation cannot be proven[36]
2. Testicular self-examination must be taught and encouraged in patients with microlithiasis (moderate recommendation)

Cancer and infertility

1. Cryopreservation is mandatory and counseling should be done for all cases regarding fertility options[37] (strong recommendation)
2. Orchiectomy should not be delayed in the process of fertility preservation[38] (moderate recommendation)
3. Risk of hypogonadism should also be explained and baseline hormones should be established (moderate recommendation)
4. Onco-TESE is an option in rare cases with azoospermia and bilateral testicular tumors[39] (moderate recommendation).

Cryptorchidism

1. Testicular biopsy should be done during orchiopexy to rule out malignancy (moderate recommendation)
2. Sperm retrieval with TESE may be done in cryptorchidism with azoospermia (moderate recommendation)
3. Unilateral cryptorchidism shows paternity similar to that of normal individuals
4. Orchiopexy done after 6–12 months has resulted in significant reduction of spermatogenesis, compared to those done before 6–12 months (moderate recommendation).

Idiopathic infertility

1. Before labeling an infertile male as unexplained or idiopathic infertility, all other causes should be excluded[40] (strong recommendation)
2. Idiopathic and unexplained infertility do not have definitive treatment (moderate recommendation)
3. Empirical medical treatment (EMT) consists of two broad categories, hormonal and antioxidants, which can be offered to these patients[41] (moderate recommendation)
4. EMT should be offered initially for at least 4–6 months (two spermatogenic cycles) before going for assisted reproductive techniques (weak recommendation)
5. Patients with an abnormal T/E2 ratio may benefit from a cotreatment with aromatase inhibitors (moderate recommendation)
6. 30%–80% of infertile men have elevated seminal ROS levels, a potentially treatable condition (weak recommendation)
7. Oxidation–reduction potential is a better representative for oxidative stress (OS) as it provides an overall measure of the activity of both oxidants and reductants[42] (weak recommendation).

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