
SPECIAL ARTICLE

Male Infertility for General Obstetricians and Gynecologists

Nares Sukcharoen MD.

Department of Obstetrics and Gynaecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

General obstetricians and gynecologists have involved in the initial diagnosis and management of infertility problems. In the last two decades, there were increased knowledge that improved the diagnosis and treatment of male infertility. The recent knowledge of the diagnostic evaluation and treatment of male infertility will be beneficial for most obstetrics and gynecologists. This review article aims to summarize recent data on the management of male infertility.

Definition and causes of infertility

Infertility is defined as the inability to achieve conception despite one year of frequent unprotected intercourse. The distribution of male and female causes of infertility has not been well defined. From World Health Organization multicenter study, 20 percent of cases were attributed to male factors, 38 percent were attributed to female factors, 27 percent had causal factors identified in both partners, and 15 percent could not be satisfactorily attributed to either partner.⁽¹⁾

Evaluation of male infertility

The assessment of the male infertile partner is frustrating for both the patients and clinicians, because a specific cause or treatment can be found in only a few of them. The disorders in most men are characterized primarily by descriptions of observed abnormalities, such as abnormal sperm parameters from semen analysis. Even testicular biopsies have provided limited information; they simply indicated the extent of impaired

spermatogenesis.

The components of the evaluation of the man include:

- History
- Physical examination
- Semen analyses
- Genetic tests
- Endocrine testing

History The evaluation of an infertile man should begin with a detailed history that focuses on potential causes of infertility. In the male, the clinician should ask about: developmental history; chronic medical illness; infection such as mumps orchitis, sexually transmitted infections, and genitourinary tract infections including prostatitis; drugs and environmental exposures; sexual history; prior genito-urinary surgery, etc.

Physical examination The physical examination should include a general medical examination with a focus on the evidence of androgen deficiency. The physical examination should include the following components : general appearance, skin, breast and external genitalia.

Examination of external genitalia includes incomplete sexual development, diseases that affect sperm maturation and transport, varicocele, measurement of testicular size by orchidometer. The Prader orchidometer consists of a series of plastic ellipsoids with a volume from 1 to 35 mL.(Fig. 1) In fertile Thai men, testicular volume are 12-25 ml (mean 17.2 ml).⁽²⁾



Fig. 1 Prader orchidometer

Standard semen analysis The semen analysis is an important assessment of the male partner of an infertile couple. In addition to the standard analysis, specialized analyses can be performed in some laboratories.⁽³⁾ The standard semen analysis consists of the following:

- Measurement of semen volume and pH
- Microscopy for debris and agglutination
- Assessment of sperm concentration, motility, and morphology
- Sperm leukocyte count
- Search for immature germ cells

The semen sample should be collected after two to seven days of sexual abstinence, preferably at the doctor's office by masturbation. The samples should be delivered to the laboratory within an hour of collection. Because of the marked variability of semen analyses, at least two samples should be collected one to two weeks apart. The semen analysis should be performed using standardized methods, preferably those described in the World Health Organization (WHO) Laboratory Manual for Human Semen and Sperm Cervical Mucus Interaction.⁽³⁾

WHO lower reference limits The World Health Organization (WHO) has published revised lower reference limits for semen analyses.⁽³⁾ The following parameters represent the generally accepted 5th

percentile (lower reference limits and 95% confidence intervals in parentheses), derived from a study of over 1,900 men whose partners had a time-to-pregnancy of ≤ 12 months.⁽⁴⁾

- Volume
1.5 mL (95% CI 1.4-1.7)
- Sperm concentration
15 million spermatozoa/mL (95% CI 12-16)
- Total sperm number
39 million spermatozoa per ejaculate (95% CI 33-46)
- Morphology
4 percent normal forms (95% CI 3-4), using "strict" Tygerberg method⁽⁴⁾
- Vitality
58 percent live (95% CI 55-63)
- Progressive motility
32 percent (95% CI 31-34)
- Total (progressive + nonprogressive motility)
40 percent (95% CI 38-42)

Semen volume should be >1.5 mL. Low volume may result from incomplete sample collection (most commonly), low serum testosterone level (hypogonadism), retrograde ejaculation, or ejaculatory duct obstruction. Ejaculatory duct obstruction should be suspected when semen is acidic (pH <7.2) and fructose-negative, which reflects absence of alkaline,

fructose-containing fluid produced by the seminal vesicles.

Azoospermia refers to the complete absence of sperm in the ejaculate, which must be confirmed by absence of sperm in the pellet derived from centrifugation of the semen specimen. This finding generally indicates either complete bilateral obstruction of the male genital ductal system (obstructive azoospermia : OA) or severe impairment of sperm production (non-obstructive azoospermia :NOA).

Prediction of fertility The standard semen analysis provides descriptive data, which do not always distinguish fertile from infertile men. Lack of sperm in the ejaculate does not indicate the absence of testicular sperm production; these patients should be evaluated for retrograde ejaculation, congenital absence of the vas deferens, and other causes of obstructive azoospermia.

Specialized semen analysis More specialized semen tests are not routinely performed, but can be used to help determine the cause of male infertility under certain circumstances.

Sperm autoantibodies Sperm autoantibodies are present in about 4 to 8 percent of infertile men. The presence of agglutination in the initial semen analysis suggests sperm autoimmunity. Mixed antiglobulin reaction (MAR test) or immunobead test is used to confirmed this condition.⁽⁵⁾ The presence of serum antisperm antibody was highly accurate in predicting obstructive azoospermia, particularly after vasectomy.⁽⁶⁾

Semen biochemistry Sperm biochemistry is frequently described in semen analyses, but is rarely useful in clinical practice. The most commonly ordered test is fructose, which is a marker of seminal vesicle function. Low or non-detectable semen fructose is associated with congenital absence of the vas deferens and seminal vesicles or with ejaculatory duct obstruction; in comparison, obstruction of the epididymis is associated with normal semen fructose.

Semen culture Semen culture is frequently performed in men whose semen samples contain inflammatory cells, but the results are usually not diagnostic because of skin contamination. The yield of

semen culture may be improved by performing a prostatic massage before sample collection. The goal of testing and antimicrobial therapy is to avoid transmission of infection to the female partner and to eliminate the adverse effects of infection on semen quality and sperm function.

Sperm-cervical mucus interaction Sperm-cervical mucus interaction identifies whether the problem is in the sperm or in the cervical mucus and is assessed in vivo by the postcoital test and in vitro by the slide or capillary tube tests⁽³⁾ The inability of spermatozoa to penetrate the cervical mucus is correlated with poor sperm motility and the presence of sperm antibodies, and failure of sperm to penetrate zona-free hamster eggs is correlated with failure of in vitro fertilization. ⁽⁷⁾

Sperm function tests Many sperm function tests were developed to predict the fertilizing potential of the sperms, such as, sperm motion characteristics measurement (sperm kinematics) using computer-aided sperm analysis (CASA), acosome reaction assay, zona-free hamster oocyte penetration test, human zona pellucid binding test, etc.⁽⁸⁾ Screening male partners of infertile couples with the following advanced andrology diagnostic tests is impractical and costly, but it is not for routine clinical use.⁽⁹⁾

Sperm biochemistry Generation of reactive oxygen species may be a cause of sperm dysfunction and a predictor of fertilization in vitro.⁽¹⁰⁾ Reactive oxygen species lead to lipid peroxidation of the sperm membrane and are also deleterious to sperm motility. This is still regarded as a research test and is not often used for diagnosis of a specific sperm defect.⁽⁹⁾

Sperm chromatin and DNA assays Sperm DNA integrity has emerged as an alternative measure of semen quality that may enable detection of occult male factors not identified on standard semen analysis. The most commonly used of several available tests are the sperm chromatin structure assay (SCSA) and the terminal deoxynucleotidyl transferase dUTP nick end-labeling (TUNEL) assay. The SCSA is a flow cytometric test that measures the stability of double-stranded sperm chromatin when exposed to a denaturant. Test results are given as the percentage of

sperm with denatured (single-stranded) DNA, which is termed the DNA fragmentation index (DFI). In the TUNEL assay, individual sperm with DNA strand breaks are stained or labeled with a fluorophore. Results are given as the percentage of TUNEL-positive sperm. However, the usefulness of tests of DNA integrity for prediction of fertility remains controversial.⁽¹¹⁾

Genetic tests Genetic tests should be selected based upon the initial clinical evaluation. Patients with vasal agenesis or unexplained obstructive azoospermia and low semen volume should be tested for abnormalities of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Cytogenetic testing (karyotype) and Y chromosome microdeletion screening are indicated in all cases when severely impaired sperm production due to testicular failure is suspected. Mutational screening of commonly implicated genes should be considered when congenital hypogonadotropic hypogonadism is clinically apparent. In summary, a clinically directed genetic evaluation is indicated in all azoospermic and severely oligozoospermic men. Such genetic testing is informative about the cause of infertility, the prognosis for biological paternity using assisted reproduction, and the risks of genetic abnormalities and disease in offspring. Future genetic testing may reveal a predisposition for medical conditions beyond infertility that warrant clinical management.⁽¹²⁾

Endocrine tests The endocrine assessment of an infertile man includes measurements of serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL)

Serum testosterone Measurement of a morning serum total testosterone is usually sufficient. In men with borderline values, the measurement should be repeated and measurement of serum free testosterone may be helpful.

Serum LH and FSH When the serum testosterone concentration is low, high serum FSH and LH concentrations indicate primary hypogonadism and values that are low or normal indicate secondary hypogonadism. Men with low sperm counts and low serum LH concentrations who are well-androgenized should be suspected of exogenous anabolic or

androgenic steroid abuse.

Prolactin Serum prolactin should be measured in any man with a low serum testosterone concentration and normal to low serum LH concentration. Hyperprolactinemia can result in infertility, low sex drive, orgasmic dysfunction, thus PRL should be a part of routine evaluation of men in infertility and sexual medicine practice.⁽¹³⁾

Ultrasonography Transrectal ultrasonography (TRUS) is indicated in cases of azoospermia or severe oligozoospermia associated with low semen volume, when ejaculatory duct obstruction is suspected.⁽⁵⁾

Postejaculate urinalysis

Evaluation of postejaculate urine for the presence of sperm is indicated in oligozoospermic men with low semen volume (<1.5 ml) in whom the vasa deferentia are palpable and the serum testosterone level is normal.⁽⁵⁾ A urine sample is obtained immediately after ejaculation and centrifuged, after which the spun pellet is examined for sperm presence. Identification of many sperm in the postejaculate urine of an oligozoospermic man confirms the diagnosis of retrograde ejaculation.

The aim of the diagnostic workup is to identify reversible/treatable (central hypogonadism, some coital disorders, some post-testicular forms) and non-reversible forms (the large majority) suitable for symptomatic therapy such as assisted reproductive techniques. The etiology of spermatogenic failure remains undefined in about 50% of cases ("idiopathic infertility") and these cases are likely caused by genetic factors (thousands of genes are involved in spermatogenesis and only a minority of them has been studied so far).⁽¹⁴⁾

Treatment of male infertility

Management of male factor infertility was a frustrating experience for both clinician and patient because of poor understanding of the pathogenesis and inability to treat the causes of male infertility. If the specific causes of male infertility can be identified, specific treatment of the causes of male infertility should be done in the first step. There are a variety of causes of irreversible infertility for which no specific therapy is

available. As an example, there is no known therapy that will stimulate sperm production when the seminiferous tubules have been severely damaged.

The development of assisted reproductive techniques (ART) has improved the outlook for many couples with male factor infertility. Although these techniques are complex, invasive, expensive, it can treat most of the male infertility problems. ART, especially intracytoplasmic sperm injection (ICSI) is an effective treatment for many causes of male infertility. Decision making has become increasingly complex that multiple effective treatment options are available. Treatment directed at the male underlying etiology of infertility, potentially enables natural conception or utilization of less costly and invasive ART (such as IUI rather than ICSI). However, immediate ICSI may be more effective and cost-efficient when confounding female factors (including advanced age) are present or when the male factor is severe.

Although assisted reproduction techniques can help overcome severe male factor infertility, the use of this technology in all infertile couples would certainly represent overtreatment. Identifying reversible causes of infertility and treating the male factor may allow couples to regain fertility and conceive through natural intercourse. A watchful diagnostic workup is essential prior to beginning any treatment so that adequate treatment options can be chosen for each patient.⁽¹⁵⁾

Concurrent male and female infertility

The couples should be investigated together. Problems in the female partner, such as anovulation or irregular ovulation, hyperprolactinemia, endometriosis, and tubal obstruction, should be treated with medications or laparoscopic surgery simultaneously with or before treatment of the male partner. Treatment of the female partner can often compensate for male factor infertility due to mild to moderate decreases in semen parameters, resulting in pregnancy without treatment of the male.

Specific treatment available

Hypogonadatropic hypogonadism Specific endocrine treatment is available only for men whose infertility results from hypogonadatropic hypogonadism.

Hypogonadatropic hypogonadism due to hyperprolactinemia If hypogonadatropic hypogonadism results from hyperprolactinemia, the hypogonadism can often be corrected and fertility restored by lowering the serum prolactin concentration.

- If the hyperprolactinemia results from a medication, that medication should be discontinued, if possible.

- If the hyperprolactinemia results from a lactotroph adenoma, the adenoma should be treated with a dopamine agonist, such as cabergoline or bromocriptine.

Normal spermatogenesis takes three months. As a result, restoration of a normal sperm count usually does not occur for at least three and sometimes six months or more after the serum prolactin and testosterone concentrations have returned to normal.

(13)

Hypogonadatropic hypogonadism due to other causes This category is a rare form of male subfertility that may be congenital (i.e., Kallman's syndrome), acquired (i.e., pituitary tumor or infarct), or idiopathic. Men who have hypogonadatropic hypogonadism due to hypothalamic or pituitary diseases can be treated with gonadotropins, but only men who have hypogonadatropic hypogonadism due to hypothalamic disease can be treated with gonadotropin-releasing hormone (GnRH).⁽¹⁶⁾

Apart from male infertility problem, the accompanying hypogonadism can be treated with testosterone to improve sexual function and mood, and an increase in or maintenance of bone and muscle mass.⁽¹⁶⁾

Sperm autoimmunity Immunologic infertility may be treated medically with immunosuppressive therapy, such as high dosage of prednisolone, although this approach has not been prospectively validated in a randomized clinical trial. The probability of pregnancy with IUI is reduced in the presence of semen antisperm antibodies, but pregnancy rates with IVF and ICSI are largely unaffected.⁽¹⁷⁾

Retrograde ejaculation Retrograde ejaculation may be caused by urogenital tract surgery, sympathetic denervation, and diabetes, can be treated with

intrauterine insemination (IUI), using the male partner's spermatozoa collected after alkalization of the urine and extensive washing of the sperm. Alternatively, the washed spermatozoa can be used for in vitro fertilization or ICSI procedures.⁽¹⁸⁾

Varicocele Although the presence of varicocele can be associated with normal semen parameters and normal fertility, most men with varicocele and presumptive infertility have abnormal semen parameters, including low sperm concentration and abnormal sperm morphology. However, data on the efficacy of varicocele repair for improved fertility are conflicting. Therefore, routine varicocele repaired in infertile couples is not recommended.

Varicocele repair must be proposed in young adult men with impairment of seminal parameters and not yet interested in pregnancy. Men of infertile couples should be adequately counselled concerning the high possibility of attaining a significant improvement in seminal parameters after varicocele repair. This condition can be associated with a spontaneous pregnancy rate of 30%. The main alternative remains the use of artificial reproductive techniques.⁽¹⁹⁾

Sexual or ejaculatory dysfunction Sexual dysfunction may interfere with intercourse and/or intravaginal ejaculation. Disorders of arousal related to low testosterone level may be corrected with oral estrogen receptor modulators (clomiphene or tamoxifen), aromatase inhibitors (anastrozole, letrozole, or testolactone), or with intramuscular hCG injections. Erectile dysfunction may be treated with oral phosphodiesterase-5 inhibitors (sildenafil, vardenafil, or tadalafil) or with intracavernosal injection therapy. In patients with retrograde ejaculation, normal antegrade ejaculation may be induced with sympathomimetic drugs (ephedrine, imipramine, midodrin, or pseudoephedrine), or sperm may be harvested from the postejaculate urine. For anorgasmic or anejaculatory patients, options for sperm acquisition include penile vibratory stimulation, transrectal electroejaculation, and surgical sperm retrieval.^(11, 20)

Empirical therapy Many treatments have been used empirically for male infertility, including clomiphene citrate and other hormones, vitamins, anti-oxidants and

kallikrein. Empiric treatment may enable natural conception or improve outcomes with assisted reproduction. However, the evidence supporting most empiric treatments for male infertility is limited. Couples who elect to proceed with empiric treatment must be counseled that such treatment may be ineffective and could lead to delays in assisted reproduction that may adversely affect outcome. In conclusion, unless new studies provide high quality evidence in favor of medical treatment, assisted reproductive technologies will remain the mainstay of treatment of male infertility. (21)

Surgical treatment

Surgeries for male infertility are divided into four major categories: (i) diagnostic surgery; (ii) surgery to improve sperm production; (iii) surgery to improve sperm delivery; and (iv) surgery to retrieve sperm for use with in vitro fertilization and intracytoplasmic sperm injection (IVF-ICSI). Clinicians treating infertility should advocate for couple-based therapy, and require that both partners have a thorough evaluation and an informed discussion before undergoing specific surgical therapies.^(22,23)

Assisted reproductive techniques (ART)

Apart from specific causes of male infertility, treatments for male infertility range from intrauterine insemination (IUI) to various forms of ART, such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). ART are commonly used for the treatment of the female partner of men with moderate or severe oligospermia and azospermia.

Intrauterine insemination The intrauterine insemination (IUI) procedure consists of washing an ejaculated semen specimen to remove prostaglandins, concentrating the sperm in a small volume of culture media, and injecting the sperm suspension directly into the upper uterine cavity using a small catheter threaded through the cervix. The insemination is timed to take place on the time of ovulation. It is reasonable to offer IUI as first-line treatment if total motile sperm count is greater than 10 million when balancing the risk and cost of alternate treatments, such as in vitro fertilization (IVF).⁽²⁴⁾

In vitro fertilization When in vitro fertilization

(IVF) is employed using the ejaculated sperm from a man with moderate oligospermia, the pregnancy rates are very low. Therefore, intracytoplasmic sperm injection is preferable for male factor infertility.

Intracytoplasmic sperm injection

Intracytoplasmic sperm injection (ICSI) has revolutionized the treatment and improved the prognosis for fertility of men with very severe oligospermia, asthenospermia (low sperm motility), teratospermia (a higher rate of abnormal sperm morphology), and even azoospermia. This technique involves the direct injection of a single spermatozoon into the cytoplasm of a human oocyte, usually obtained from follicles produced under controlled ovarian hyperstimulation. The ICSI results are not influenced by either the cause of the azoospermia or the origin of the spermatozoa. ⁽²⁵⁾

In the past, men with azoospermia were untreatable as determined by persistent absence of any sperm in the ejaculate but who do have sperm that can be extracted from the seminiferous tubules of the testes. If mature spermatozoa or spermatids are found in the testicular biopsy, they can be retrieved and used to fertilize oocytes in vitro, resulting in pregnancies in the partner using ART. Successful fertility has been achieved in patients with Klinefelter syndrome⁽²⁶⁾ and Sertoli cell only syndrome using testicular sperm retrieval and intracytoplasmic sperm injection.

Treatment of obstructive azoospermia The two main treatment strategies are surgical correction of the obstruction and sperm retrieval followed by ICSI. Sperm retrieval (Microsurgical epididymal sperm aspiration : MESA or Percutaneous epididymal sperm aspiration : PESA) with ICSI is the preferred initial approach when female factors requiring assisted reproduction are present, reconstruction is impossible (as in patients with CBAVD), or ART is more cost-effective. The success rate of vasectomy reversal decreases dramatically according to the time intervals since vasectomy, but the time interval between vasectomy and surgical sperm retrieval with ICSI treatment has no effect on the ART outcome.⁽²⁷⁾ Therefore, vasectomy reversal may be favored as the initial treatment strategy when the interval of vasectomy

is less than 10 years (since reconstruction is more likely to be successful) and no female factors requiring assisted reproduction are present.

Treatment of non-obstructive azoospermia

NOA reflects severe impairment of sperm production and is characterized clinically by small, soft testes and elevated serum FSH. The treatment is retrieval of sperm from the testis (Testicular sperm extraction : TESE) and ICSI.

Artificial insemination with donor semen The alternative to ART for many couples, including those who fail ART, is artificial insemination with donor sperm. This time-tested method has a very high success rate in apparently normal female recipients: 50 percent pregnancy rate with six cycles of insemination. Children born from pregnancies resulting from donor insemination grow and develop normally, both physically and psychologically. This alternative, together with adoption and childlessness, must be offered to all couples with male factor infertility.

An increased understanding of male factor infertility and the recent advances made in many aspects, such as, sperm retrieval techniques, assisted reproductive techniques, cryopreservation, etc. are now giving men who never thought they could have biological children the chance to father a child. Successful fertility outcomes at any reproductive center today remain the result of a combination of technological advances, scientific expertise and consistent andrological laboratory standards.

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