

Evaluation of Male Infertility

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Abstract: Infertility is one of commonest disorders to afflict young men and women, more so with increasing couples/partners deciding to delay starting family for various reasons. The evaluation of infertility is initiated typically after 1 yr of failure to conceive after unprotected intercourse. The couple should be evaluated together to determine whether the problem resides in the male partner, the female partner, or both. The objectives of evaluation are to exclude treatable conditions—gonadotropin deficiency, obstruction, and coital disorders—and identify those who will benefit with assisted reproductive technologies. All infertile men should undergo several semen analyses according to the World Health Organization manual, as well as measurements of testosterone, LH, and FSH levels. Hormone evaluation can help determine whether the patient has gonadotropin deficiency (low testosterone and low or inappropriately normal LH and FSH), primary testicular failure (low testosterone, elevated LH and FSH), spermatogenic failure (normal testosterone and LH, elevated FSH), or androgen resistance (high testosterone, elevated LH). A majority of infertile men have normal testosterone, LH, and FSH levels. Obstruction should be ruled out in azoospermic men with normal testosterone, LH, and FSH levels.

INTRODUCTION

Reproduction and fertility are central to survival for propagation for future generations. Infertility continues to be a highly prevalent condition; the proportion of couples seeking medical treatment for infertility is estimated at 4–17%. The primary problem resides exclusively in the male partner in approximately 20% of infertile couples; in an additional 30%, problems reside in both the male and the female partner.

The endocrinologist/fertility specialist should play an important role in coordinating the care of the infertile couple and providing counsel on prognosis and treatment options, including ART programs. The treating doctor should identify those who have a treatable cause of infertility, such as gonadotropin deficiency or obstruction. The evaluation should determine which couples can benefit from ART and whether the patient has untreatable sterility, in which case the couple should be counseled about adoption or artificial insemination with donor sperm. The couple should be made aware of the modalities of treatment and its outcome in an explicit way.

LABORATION EVALUATION

Determination of when diagnostic evaluation should be initiated is important because a majority of couples failing to conceive for 12 months will conceive spontaneously. The World Health Organization (WHO) defined infertility as the inability of a sexually active couple to achieve pregnancy despite unprotected intercourse for a period of greater than 12 months. The European Society for Human Reproduction and Embryology (ESHRE) defines infertility as failure of pregnancy to occur within 2 yr of regular coital exposure.

As the duration of nonconception increases, the likelihood of spontaneous conception decreases; among couples reporting infertility for 4 yr, conception rates per month are abysmally low. Thus, the pressures to initiate evaluation and treatment should be resisted if the period of nonconception is less than 1 yr. However, in couples with known reproductive disorders, an earlier intervention is justified.

Causes and pathophysiology

The frequency of etiological factors varies among different surveys. In general, 15–20% of infertile men are azoospermic, and 10% have sperm density below 1 million/ml. A specific cause of infertility is not determinable in 40–60% men. Most infertile men have idiopathic oligozoospermia.

Correctable or treatable causes of infertility, such as gonadotropin

deficiency, obstruction, and coital disorders, are present in only a small fraction, but it is important to recognize them because effective therapies are available. Varicoceles are present in 10–30% of infertile men but their role in pathophysiology of infertility remains unclear. A number of genetic disorders have been implicated in spermatogenic failure; of these, Klinefelter syndrome and Y chromosome microdeletions are the most prevalent. The mechanism by which antisperm antibodies cause infertility are unclear.

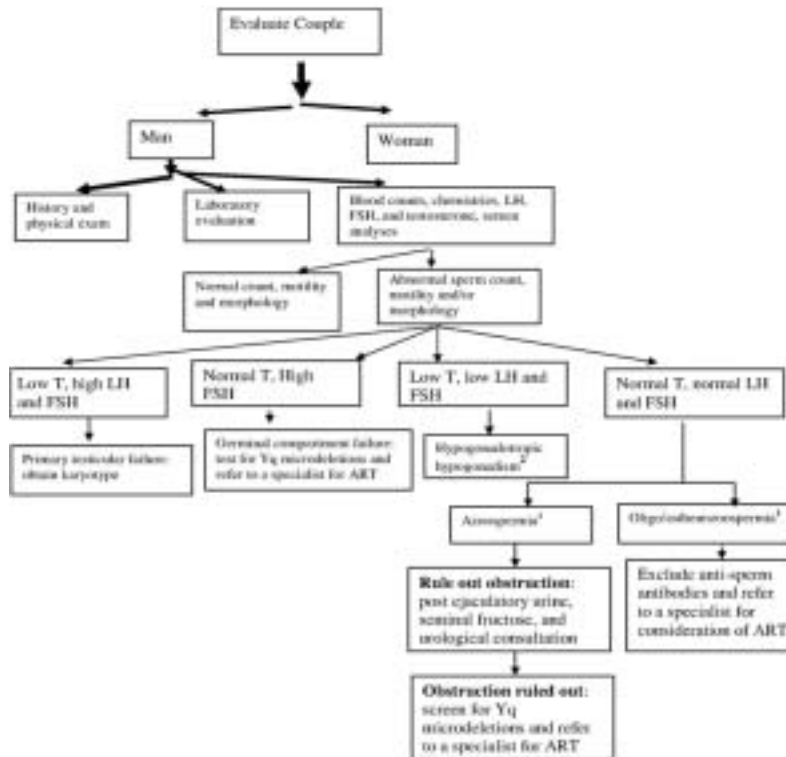
Diagnostic evaluation

The objectives of evaluation are to exclude treatable conditions—gonadotropin deficiency, obstruction, and coital disorders—and to identify those who are candidates for ART.

1. Evaluate the couple together and determine whether the problem resides in the male partner, the female partner, or both.
2. Initial work up should involve evaluation of general health and exclusion of systemic diseases.
3. History should focus on duration of infertility, previous fertility in the man or the woman, contraceptive use, sexual function, frequency and timing of intercourse, and sexual practices. Ascertain the timing of pubertal development, shaving frequency, and hair loss. Inquire about scrotal trauma, genitourinary infection, sexually transmitted disease, and scrotal or inguinal surgery including hernioplasty and vasectomy. Ask for history of cancer, especially previous treatment with cancer chemotherapy and radiation to the inguinal or scrotal area. Evaluate hair distribution and escutcheon, body proportions, and voice. Measure testicular and palpate epididymis for cysts and vas deferens for total or segmental absence.
4. Analyze three or more semen samples after at least 48-h abstinence; determine sperm density, motility, and morphology, using rigorous quality control in accordance with WHO manual.
5. Measure testosterone, LH, and FSH in early morning to determine whether patient has gonadotropin deficiency, primary testicular failure (low testosterone, elevated LH and FSH), selective spermatogenic failure (normal testosterone and LH, elevated FSH), or androgen resistance (high testosterone, elevated LH). *Keep in mind that majority of infertile men have normal testosterone, LH, and FSH levels.*
6. In men with azoospermia and normal testosterone, LH, and FSH

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EVALUATION OF MALE INFERTILITY- Flow chart



Infertile men with nonobstructive azoospermia and severe oligozoospermia with normal or elevated FSH should undergo a karyotype and screening for Yq microdeletions before being referred for ICSI.² Men deemed to have hypogonadotropic hypogonadism should be evaluated further by an magnetic resonance imaging scan, prolactin, and measurement of other pituitary hormones to exclude space occupying neoplastic or infiltrative lesions of the hypothalamic pituitary region. T, Testosterone

levels, exclude obstruction by measuring seminal fructose and obtaining urological evaluation; perform cystic fibrosis transmembrane conductance regulator (CFTR) mutation analysis in those with absence of vas.

7. Normal testosterone, normal LH, and elevated FSH levels in an azoospermic or severely oligozoospermic man are suggestive of primary spermatogenic failure. These men should undergo measurement of testicular volume, karyotyping and screening for Yq microdeletions.

TREATMENT

1. Testosterone, human chorionic gonadotropin (hCG), clomiphene citrate and other aromatase inhibitors, and bromocriptine have not been shown to be effective in men with idiopathic oligo/azoospermia; *INFACT* Testosterone therapy can further suppress spermatogenesis.
2. Men with hypogonadotropic hypogonadism in whom pituitary neoplastic lesions and hyperprolactinemia have been excluded are candidates for gonadotropin or pulsatile GnRH therapy.
3. Men with obstructive azoospermia should be referred to a urologist for surgical correction. With microsurgical techniques, restoration of patency can be achieved in 70–90% of patients, although restoration of fertility is achieved only in 50%. In men with failed vasectomy reversal, verification of patency restoration

and surgical revision, if indicated, or ICSI using epididymal sperm are reasonable options.

4. Men with idiopathic oligozoospermia should undergo genetic testing and be referred to a specialized fertility center for consideration of ART treatment. IVF should be attempted if there are more than 2 million motile sperm. If there are less than 2 million sperm in the ejaculate, less than 5% sperm with normal morphology, or less than 5% sperm with progressive motility, ICSI should be offered.
5. Men with nonobstructive azoospermia should be offered karyotype and screening for Yq microdeletions. In some men with nonobstructive azoospermia, no sperm or spermatids may be retrievable from testicular biopsy, whereas for some couples the expense of ICSI may be prohibitive; for these couples, artificial insemination by donor sperm and adoption are realistic options.

OTHER HEALTH CONSIDERATIONS IN TREATING INFERTILE MEN

Some causes of infertility (Klinefelter's syndrome, IHH) in men also are associated with androgen deficiency. Also, spermatogenic failure may be associated with impaired Leydig cell function. In men with gonadotropin deficiency, hCG and pulsatile GnRH therapy may restore both spermatogenesis and testosterone concentrations. However, exogenous testosterone administration suppresses

spermatogenesis; infertility is a common complication of androgen abuse by body builders.

Hormonal treatment of men with hypogonadotropic hypogonadism Gonadotropin therapy and pulsatile GnRH are highly effective in inducing spermatogenesis in men with IHH. The two therapies do not differ in the time to first appearance of sperm, sperm densities, or pregnancy rates but pulsatile GnRH therapy is not an option for patients with panhypopituitarism.

The therapy of IHH is started with hCG 1000 U three times weekly; the dose is adjusted to achieve nadir testosterone level measured 48 h after hCG injection in the mid-normal range. Recombinant human LH also has become available for clinical use. If after 6–9 months of hCG or recombinant human LH therapy no sperm is detected in the semen, recombinant or highly purified human FSH is added at a dose of 75 U three times weekly. The dose may be increased by 75 U three times weekly every 3 months depending upon the clinical response. Men with postpubertal onset of hypogonadotropic hypogonadism are more likely to respond to hCG alone with reinitiation of spermatogenesis than those with prepubertal onset who are likely to require addition of FSH.

Pulsatile GnRH administration is initiated at an initial dose of 25 ng/kg per pulse administered sc every 2 h by a portable infusion pump. Dose of GnRH is adjusted until serum testosterone level is in the midnormal range. Doses ranging from 25 to 200 ng/kg may be required to induce virilization. After successful induction of secondary sex characteristics, GnRH dose can be reduced.

The best predictors of response to gonadotropin therapy are testicular volume and time of onset of gonadotropin deficiency (pre- or postpubertal). Those with testicular volumes greater than 8 ml reflecting less severe gonadotropin deficiency and postpubertal onset of gonadotropin deficiency are more likely to respond than those with testicular volumes less than 4 ml and prepubertal onset. Prior androgen therapy does not affect outcome.

ICSI for male factor infertility

ICSI has emerged as the treatment of choice for idiopathic male factor infertility. The pregnancy rates per transfer are higher if fresh sperm is used instead of cryopreserved sperm, and higher if fresh embryos are used instead of frozen-thawed embryos. The pregnancy rates are similar for obstructive and nonobstructive azoospermia. The results of ICSI are affected by the age of the female partner and the quality of the oocyte. The success rates of ICSI are lower in men in whom sperm has been retrieved from the testis by biopsy and in men with necro- or globozoospermia. In men with obstructive azoospermia, there is insufficient evidence to recommend any specific sperm retrieval procedure before ICSI.

Complications of ICSI: Multiple gestation, with its associated risks of low birth weight and preterm delivery, is the most frequent complication of ICSI. The risk of obstetric and perinatal complications is higher for pregnancies resulting from ICSI than for naturally conceived pregnancies. Chromosomal abnormalities have been reported with higher frequency in offspring of ICSI than controls; there is also a small but significant increase in the frequency of chromosome aneuploidy, especially sex chromosome aneuploidy, among offspring of ICSI. The frequency of major congenital malformations is not significantly different between ICSI and IVF. When multiplicity is taken into account, the incidence of major or minor malformations is not increased. Even among singleton births

resulting from ARTs, the risk of low birth weight, preterm delivery, and adverse perinatal outcomes is increased. Although ICSI is an effective therapy for many couples with male factor infertility, it is expensive and its long-term safety is unclear.

TREATMENT OPTIONS FOR PATIENTS WITH AZOOSPERMIA

The prognosis for men with nonobstructive azoospermia and total teratozoospermia has improved with the advent of ICSI. There are several reports of successful pregnancies in partners of men with Klinefelter syndrome by ICSI using sperm retrieved from testicular biopsy. Adoption, artificial insemination using donor sperm, and acceptance of childlessness are realistic options.

NOTE

Several societies, including the American Urological Association, American Society for Reproductive Medicine, ESHRE, and European Association of Urologists, have published guidelines for the management of infertile men. Guidelines for standardized testing for Yq microdeletions, semen analyses, genetic counseling, and prenatal diagnosis have also been published. The readers are encouraged to go through those guidelines for complete and better understanding of management of male infertility.

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