REVIEW ARTICLE

MALE INFERTILITY: CAUSES AND OPTIMAL EVALUATION

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Abstract

Objective: *To find out the optimum evaluation tools for male infertility.*

Methods*: Hinari database were searched for articles related to male infertility for review to find out how a male infertile patient can be evaluated optimally.EUA guidelines on Male Infertility and AUA best practice statement on* Optimal Evaluation of the Infertile Male updated on 2010 were also considered for review.

Results: *Initially thirty five articles were obtained and finally twenty eight articles were considered for review. Some cross references were considered to be cited in the reference section. We have mentioned in this review the evaluation tools those are necessary for male factor infertility at the optimum.*

Conclusion *: As male infertility problem are increasing so optimum evaluation should be carried out to diagnose every possible underlying cause.*

Key Words: *Male infertility,optimum evaluation,investigation, Epidemiology.*

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Introduction:

The World Health Organization currently defines infertility as the inability of a sexually active couple (at least three times per month), not using contraception, to achieve pregnancy within one year [1]. Infertility can be classified as primary infertility when no pregnancy has ever occurred or secondary if it occurred after one or more pregnancies. Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is solely responsible in about 20% of infertile couples and contributory in another 30-40% [2]. Male infertility refers to a male's inability to result pregnancy in a fertile female. "Male factor" infertility is seen as an alteration in sperm concentration and/or motility and/or morphology in at least one sample of two sperm analyzes, collected 1 and 4 weeks apart . Males with sperm parameters below the WHO normal values are considered to have male factor infertility[3].

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The prevalent rate varies between and within countries. For instance, in the United Kingdom and the United States of America it is estimated to be 6% and 10% respectively[4] . Male infertility is increasing on a global level is controversial and challenging to confirm [5,6]. Beyond the increasing burden of disease, male infertility causes significant psychosocial and marital stress, and is associated with a high cost of infertility care [7,8] .In Bangladesh one study suggest in 60% cases male are responsible for infertility either fully or partially. Of them 40% were azoospermic, 34% were oligospermic, 5% were asthenospermia and teratospermia and 1% were unexplained infertility[9]. In a World Health Organization multicentre study, 45% of infertile men were found to have either oligo-zoospermia or azoospermia [10]. In addition to the impact on family building, male infertility may be associated with increased risks of testis and prostate cancer[11,12]. .Kolettis and Sabanegh found that 6% of all men referred for infertility harbored a serious disease [13]. Failure to identify diseases such as testicular cancer or pituitary tumors may have serious consequences, including, in rare cases, death. So, a

full evaluation preferably by a urologist or other specialist in male reproduction should be done for proper diagnosis and treatment. Detection of conditions for which there is no treatment will spare couples the distress of attempting ineffective therapies. Detection of certain genetic causes of male infertility allows couples to be informed about the potential to transmit genetic abnormalities that may affect the health of offspring. Thus, an appropriate male evaluation may allow the couple to better understand the basis of their infertility and to obtain genetic counseling when appropriate.

Causes of male infertility:

There are both known and unknown causes of male infertility . Unfortunately, 30 — 50% of the etiologies of male infertility are unknown [14]. Possible known male factors that affect fertility include the following categories:

Pre testicular:

The pre testicular causes of infertility may be defined as extragonadal endocrine disorders, such as those originating in the hypothalamus, pituitary, or adrenals, which have an adverse effect on spermatogenesis through aberrant hormonal stimulation or suppression.

Hypothalamic causes

Gonadotropin deficiency (Kallmann syndrome)

Isolated LH deficiency ("fertile eunuch")

Isolated FSH deficiency

Congenital hypogonadotropic syndromes

Pituitary causes

Pituitary insufficiency (tumors, infiltrative processes, operation,radiation, deposits)

Hyperprolactinemia

Exogenous hormones (estrogen-androgen excess,glucocorticoid excess, hyper- and hypothyroidism)

Growth hormone deficiency

Testicular:

The testicular causes of infertility are primary defects of the testes. These may be congenital or occur secondarily to environmental insults or other disease processes.

Congenital

Chromosomal (Klinefelter syndrome [XXY], XX sex reversal, XYY syndrome)

Noonan syndrome (male Turner syndrome)

Myotonic dystrophy

Vanishing testis syndrome (bilateral anorchia)

Sertoli-cell-only syndrome (germ cell aplasia)

Y chromosome microdeletions (*DAZ*)

Acquired

Gonadotoxins (radiation, drugs)

Systemic disease (renal failure, liver failure, sickle cell anemia)

Defective androgen activity

Testis injury (orchitis, torsion, trauma)

Cryptorchidism

Varicocele

Idiopathic

Post testicular

The posttesticular causes of infertility consist primarily of obstructions of the ducts leading away from the testes. Congenital or acquired factors that disrupt normal transport of sperm through the ductal system.

Reproductive tract obstruction

Congenital blockages

Congenital absence of the vas deferens (CAVD)

Idiopathic epididymal obstruction

Ejaculatory duct obstruction

Acquired blockages

Vasectomy

Groin surgery

Infection

Functional blockages

Sympathetic nerve injury

Pharmacologic

Disorders of sperm function or motility

Immotile cilia syndromes

Maturation defects

Immunologic infertility

Infection

Disorders of coitus

Impotence

Hypospadias

Timing and frequency

Other Factors that affect the fertility :

- Environmental/occupational factors
- Toxic effects related to tobacco, marijuana, or other drugs
- Excessive exercise
- Inadequate diet associated with extreme weight loss or gain
- Advanced age

Evaluation

Male factor infertility contributes partially and solely to the problem of childlessness in around 50% of the cases. Thus, evaluation of male infertility is essential in counseling couples for their fertility options . The full evaluation for male infertility should include a complete medical and reproductive history, a physical examination by a urologist or other specialist in male reproduction .The goals of the optimal evaluation of the infertile male are to identify:

- potentially correctable conditions;
- irreversible conditions that are amenable to assisted reproductive techniques using the sperm of the male partner;
- irreversible conditions that are not amenable to the above, and for which donor insemination or adoption are possible options;
- life- or health-threatening conditions that may underlie the infertility and require medical attention; and
- genetic abnormalities that may affect the health of offspring if assisted reproductive techniques are to be employed.

Clinical evaluation

Clinical evaluation of male fertility begins with a detailed history and physical examination, which generally will provide valuable information to guide what additional laboratory investigations or imaging studies to complete the evaluation.

History

The cornerstone of the male partner evaluation is the history. It should note the duration of infertility, earlier pregnancies with present or past partners, and whether there was previous difficulty with conception. A sexual history should be addressed. Most men (80%) do not know how to precisely time intercourse to achieve a pregnancy. A general medical history is also important . Because any generalized insult such as a fever, viremia, or other acute infection can decrease testis function and semen quality. The effects of such insults are not noted in the semen until 2 months after the event, because spermatogenesis requires at least 60 days to complete[Smith]. Surgical procedures on the bladder, retro peritoneum, or pelvis can also lead to infertility, by causing either retrograde ejaculation of sperm into the bladder or anejaculation (aspermia).

Childhood diseases may also affect fertility. A history of mumps can be significant if it occurs post ubertally. After age 11, unilateral orchitis occurs in 30% of mumps infections and bilateral orchitis in 10%. Mumps orchitis is thought to cause pressure necrosis of testis tissue from viral edema. Marked testis atrophy is usually obvious later in life [15].

Physical Examination

A general physical examination is an integral part of the evaluation of male infertility. In addition to the general physical examination, particular focus should be given to the genitaliaincluding 1) examination of the penis; including the location of the urethral meatus; 2) palpation of the testes and measurement of their size; 3) presence and consistency of both the vasa and epididymides; 4) presence of a varicocele; 5) secondary sex characteristics including body habitus, hair distribution and breast development; and 6) digital rectal exam. The diagnosis of congenital bilateral absence of the vasa deferentia (CBAVD) is established by physical examination. Scrotal exploration is not needed to make this diagnosis.[optimal evaluation]

Two features should be noted about the testis: size and consistency. Size is assessed by measuring the long axis and width; as an alternative, an orchidometer can be placed next to the testis for volume determination Standard values of testis size have been reported for normal men and include a mean testis length of 4.6 cm (range 3.6–5.5 cm), a mean width of 2.6 cm (range 2.1–3.2 cm), and a mean volume of 18.6 mL (± 4.6 mL) Consistency is more difficult to assess but can be described as firm (normal) or soft (abnormal). A smaller or softer than normal testis usually indicates impaired spermatogenesis[16]

Diagnostic evaluation

Based on the results of the full evaluation, the physician may recommend other procedures and tests to elucidate the etiology of a patient's infertility. These tests may include additional semen analyses, endocrine evaluation, post-ejaculatory urinalysis, ultrasonography, specialized tests on semen and sperm, and genetic screening.

Semen analysis

A medical history and physical examination are standard assessments in all men, including semen analysis. In 2010 the World Health Organization (WHO) updated its reference values for the Semen Analysis[17].

Table-I

Lower reference limits (5th centiles and their 95% CIs) for semen characteristics [WHO]

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number	(10^6/ejaculate) 39 (33-46)
Sperm concentration	(10^6/mL) 15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms,%)	4 (3.0-4.0)
Other consensus threshold values pH >	7.2
Peroxidase-positive leukocytes (106/mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (μmol/ejaculate)	*≥ 2.4*
Seminal fructose (μmol/ejaculate)	*≥ 13*
Seminal neutral glucosidase (mU/ejaculate)	*≤ 20*

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

If the results of semen analysis are normal according to WHO criteria, one test is sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated.

Hormonal Essay

Hormonal abnormalities of the hypothalamic-pituitary testicular axis are well-recognized, though not common causes of male infertility. An initial endocrine evaluation should include at least a serum testosterone and FSH. It should be performed if there is: (1) an abnormally low sperm concentration, especially if less than 10 million/ml; (2) impaired sexual function; or (3) other clinical findings suggestive of a specific endocrinopathy.

Post-ejaculatory urinalysis

Low-volume or absent ejaculate suggests retrograde ejaculation, lack of emission, ejaculatory duct obstruction, hypogonadism or CBAVD. In order to diagnose possible retrograde ejaculation, the physician should perform a post-ejaculatory urinalysis for any man whose ejaculate volume is less than 1.0 ml, and who has not been diagnosed with hypogonadism or CBAVD.

Scrotal ultrasonography

Most scrotal pathology is palpable on physical examination. This includes varicoceles, spermatoceles, absence of the vasa, epididymal induration and testicular masses. Scrotal ultrasonography is indicated in those patients in whom physical examination of the scrotum is difficult or inadequate or in whom a testicular mass is suspected.

Transrectal ultrasonography

Normal seminal vesicles are less than 2.0cm in anteroposterior diameter[18]. The finding of dilated seminal vesicles, dilated ejaculatory ducts and/or midline prostatic cystic structures on transrectal ultrasonography (TRUS) is suggestive of, but not diagnostic of, complete or partial ejaculatory duct obstruction[19]. Transrectal ultrasonography is indicated in azoospermic patients with palpable vasa and low ejaculate volumes to determine if ejaculatory duct obstruction exists.

Tests for antisperm antibodies

Pregnancy rates may be reduced by antisperm antibodies (ASA) in the semen[20]. Risk factors for ASA include ductal obstruction, prior genital infection, testicular trauma and prior vasovasostomy or vasoepididymostomy. ASA testing should be considered when there is isolated asthenospermia with normal

sperm concentration, sperm agglutination or an abnormal postcoital test. Some physicians recommend ASA testing for couples with unexplained infertility.

Sperm viability tests

The use of the hypoosmotic swelling (HOS) test [21] assays determine whether non-motile sperm are viable by identifying which sperm have intact cell membranes. Nonmotile but viable sperm, as determined by the HOS test, may be used successfully for ICSI.

Computer-aided sperm analysis

In principle, CASA can be used to objectively measure sperm numbers, motility and morphology. They may be useful in a small number of patients for identifying a male factor contributing to unexplained infertility, or for selecting therapy, such as assisted reproductive technology.

Genetic testing

A male presenting with infertility is more likely than the general population to harbor a gene mutation or chromosomal abnormality. Indeed, up to 15% of men with azoospermia have an abnormality in their karyotype[22,23,24,25], Y chromosome microdeletion[26,27] or mutation in the cystic fibrosis transmembrane conductance regulating (CFTR) gene.

Karyotype

Chromosome abnormalities account for about 6% of all male infertility, and the prevalence increases with increased spermatogenic impairment (severe oligospermia and nonobstructive azoospermia. Karyotyping and genetic counseling should be offered to all patients with nonobstructive azoospermia and severe oligospermia (<5 million sperm/ml).

Y-chromosome microdeletions

Approximately 13 % of men with nonobstructive azoospermia or severe oligospermia have an underlying Y-chromosome microdeletion[28].The results of Y chromosome deletion analysis cannot absolutely predict the absence of sperm.

Genetic screening

Genetic abnormalities may cause infertility by affecting sperm production or sperm transport. The three most common genetic factors known to be related to male infertility are: 1) cystic fibrosis gene mutations associated with congenital absence of the vas deferens; 2) chromosomal abnormalities resulting in impaired testicular function; and 3) Y-chromosome microdeletions associated with isolated spermatogenic impairment. Approximately 70% of men with CBAVD and no clinical evidence of cystic fibrosis have an identifiable abnormality of CFTR gene[29,30]. Men with congenital bilateral absence of the vasa deferentia should be offered genetic counseling and testing for cystic fibrosis transmembrane conductance regulator mutations.

Testicular biopsy

Testicular biopsy is generally reserved for men with azoospermia, or absence of sperm from the ejaculate, a finding identified in about 5% to 10% of men evaluated for infertility[31]. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e., TESE) for cryopreservation.

Conclusion:

Optimal evaluation for male infertility should include a complete medical and reproductive history, a physical examination by a urologist or other specialist in male reproduction and at least two semen analyses. Based on the results of history and physical examination the physician may recommend other procedures and tests to elucidate the etiology of a patient's infertility. These tests may include additional semen analyses,hormonal evaluation, post-ejaculatory urinalysis, ultrasonography, specialized tests on semen and sperm, and genetic testing.

Conflict of interest: None declared

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Abbreviations:

ASA	Antisperm Antibodies
HOS	Hypoosmotic swelling
CASA	*Computer-aided sperm analysis*
CBAVD	Congenital Bilateral Absence of Vasa Deferentia