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Approach to Evaluation of Male Factor Infertility

BN Chakravarty, Ratnaboli Bhattacharya, Saktirupa Chakraborty, Runa Bal

APPROACH TO EVALUATION OF MALE FACTOR INFERTILITY

Incidence of male infertility is increasing every day. The rates of detection have also increased due to the recent increase in scope of detection and treatment. The causes of increased infertility are late marriage, modern lifestyle, more stress, random use of synthetic dyes in eatables, pesticides and poultry chicken fattened with estrogens. The causes can also be congenital or acquired urogenital abnormalities, genital infections, endocrine abnormalities, varicocele, genetic and immunological problems. Male infertility is idiopathic in 60–75% of cases. In addition to these, functional defects like erectile and ejaculatory dysfunction have also increased. Currently, male infertility is considered to be the sole reason in 20% couples and a contributory factor in another 30–40% couples.

Evaluating an infertile male revolves on three basic parameters:

1. History
2. Physical examination
3. Investigations.

History

A detailed history can elicit a wide range of information about the cause of male infertility.

- Past history of any illness, abnormality or treatment during childhood can reveal directly and indirectly the cause of subfertility. History of trauma, torsion or undescended testes can affect semen parameters. Surgery or injection of human chorionic gonadotropin (hCG) before 12 years of age has a favorable outcome. Some patients present with history of testicular cancer and treatment by radiotherapy or chemotherapy. Some chemotherapeutic agents have a permanent damage whereas some have a temporary effect for about 3–5 years. Retroperitoneal lymph node dissection can interrupt

the sympathetic chain and can cause erectile dysfunction or retrograde ejaculation. Mumps orchitis causes destruction of seminiferous tubules and azoospermia leading to "Sertoli cell only" syndrome.

- Medical history like respiratory tract infection, including sinusitis, bronchitis, bronchiectasis, can be associated with diseases like Kartagener syndrome (generalized absence of cilia with asthenospermia), Young's syndrome (obstructive azoospermia due to blockage of epididymis with inspissated debris), cystic fibrosis (complete absence of vas leading to obstructive azoospermia). Sexually transmitted infections in patients with semen abnormality can denote stricture of urethra, vas deferens or epididymis. Past history of genitourinary tract tuberculosis (GTB) can cause obstructive azoospermia. Acute viral fever can cause temporary suppression of testicular function but is reversed within 3 months. Endocrine disorders like diabetes can cause erectile dysfunction or retrograde ejaculation (neuropathy or vasculopathy). Other disorders may be hypogonadotropic hypogonadism like Kallmann syndrome. Kallmann syndrome, also known as anosmia-azoospermia syndrome is an autosomal genetic defect leading to defective development of olfactory bulb and hypothalamus. Other diseases like hyperprolactinemia causes decrease in libido, and congenital adrenal hyperplasia can cause delayed puberty and subfertility. Exposure to environmental toxins like pesticides can cause spermatozoal damage while high temperature exposure in agriculture, welding, factory works and ceramics can cause defective spermatogenesis.
- *Lifestyle history*: Stress increases adrenocorticotropic hormone which has an adverse impact on gonadotropic hormone affecting seminal parameters. Tight underwears, sauna baths and long distance cycling may also cause scrotal hyperthermia and trauma. Smoking can increase the oxidative damage to sperm DNA and cause birth defects in offspring. Intake of marijuana, opiates and cocaine, excessive intake of coffee (caffeine—more than 2 cups coffee per day) can also affect spermatogenesis. Moderate alcoholism, however, has not been found to have any effect.
- *Drug history:* Anabolic steroids used by bodybuilders suppress the hypothalamic-pituitary-gonadal axis. Testosterone administration in hypogonadotropic patients may suppress gonadotropic action. The concept of rebound action of gonadotropin following stoppage of testosterone has not been validated. Most chemotherapeutic agents are gonadotoxic. Recovery is better with doxorubicin, methotrexate, estrogens, androgens and poor after bleomycin, etoposide, cisplatin, chlorambucil, procarbazine and vincristine. All antihypertensive drugs have adverse effect on erection; worst are nonselective beta-blockers, e.g. propranolol. Calcium channel blockers interfere with capacitation and acrosome reaction. α-blockers can cause retrograde ejaculation in 10% of patients. Antipsychotic and antidepressant drugs act through central dopamine pathways—suppress hypothalamic-pituitary-ovarian axis and thus suppress libido. They

may also cause hyperprolactinemia, impair sexual function and also the semen parameters. Antibiotics like gentamicin and neomycin, high dose nitrofurantoin may affect sperm maturation and spermatogenesis. Prolonged use of erythromycin and tetracycline can decrease motility. Cimetidine inhibits pulsatile release of luteinizing hormone (LH). Colchicine for gout impairs sperm-ovum binding during fertilization. Sulfasalazine decreases sperm density, motility and morphology. Previous fertility does not exclude the presence of a new onset secondary male factor.

Physical Examination

A lot of information can be gathered from a systematic examination of the male partner.

Hypogonadism or Klinefelter's syndrome can be easily recognized by clinical features like absence of beard, moustache and sometimes presence of gynecomastia. Klinefelter patients are tall and well-built.

Local Examination

The curvature of the penis and position of external urethral meatus should be observed to rule out hypospadias. The scrotal sac and testis is examined for any abnormality. Length of the testis should be more than 4 cm and volume should be more than 20 mL. Vas deferens should be palpated and varicocele excluded.

Rectal examination is not performed as a routine. In obstructive azoospermia or in asthenospermia with infection, rectal examination may find an enlarged prostate or midline prostate cyst.

Investigations

Investigations are based on clinical findings:

- Tall patients without beard and moustache can present in individuals with Klinefelter syndrome. Karyotype (47XXY) confirms a diagnosis.
- Palpable lymph nodes in neck or elsewhere → tuberculosis should be excluded.
- Empty scrotal sac can denote undescended testis. Ultrasound (USG) scan of inguinal region or lower abdomen should be done.
- Varicocele should be examined in standing position and confirmed on ultrasound.
- Patients with urethral discharge should have a prostatic smear for bacteriological examination.
- If prostate is enlarged or a cyst is palpated on rectal examination, the findings should be confirmed by transrectal sonography.

Semen analysis is one basic way to evaluate male infertility. Physicians should instruct patients of 2–5 days abstinence. Semen can be collected by masturbation in a cup or by means of intercourse in a condom that is specialized for sperm collection and do not contain substances that are

toxic to sperm. Ideally, the semen should be collected in the laboratory but if collected at home the specimen should reach the laboratory within one hour of collection and should be maintained at room temperature or body temperature during this period. The diagnosis of azoospermia should be made only after centrifugation of the sample at 3,000 g for at least 15 minutes and examining the pellet for presence of spermatozoa. The cause of azoospermia can be related to the presence of fructose in seminal fluid (Table 1).

The lower limit of the reference values for semen parameters (World Health Organization 2010) are as follows (Table 2).

An endocrine evaluation of the male partner is indicated in cases of abnormal sperm parameters especially if the total count is less than 10 million/mL, in patients with sexual dysfunction and in those where a specific endocrinopathy is suspected. Serum follicle-stimulating hormone (FSH) and total testosterone is estimated. If FSH and total testosterone values are decreased, further serum LH, prolactin and magnetic resonance imaging (MRI) for pituitary tumor should be done. If the testicular volume, serum FSH, testosterone, and karyotype are normal, causes of obstructive azoospermia should be excluded. Male partners with elevated serum FSH and abnormal karyotype should consider intrauterine insemination with donor sperm or in vitro fertilization with testicular sperm extraction and intracytoplasmic sperm injection (ICSI). Thyroid-stimulating hormone (TSH) evaluation is required for male partners who require a thorough endocrine evaluation (Table 3).

Table 1: Biochemical analysis of semen.

Fructose absent	*Fructose present*
Congenital absence of seminal vesicle or vas deferens	Obstruction in rete testis, epididymis
Ejaculatory duct obstruction	• Primary testicular failure • Hypogonadotropic hypogonadism

Table 2: Macroscopic and microscopic analysis of semen.

Parameters	*Reference values*
Ejaculate volume	1.5 mL
pH	7.2
Sperm concentration	15×10^6 spermatozoa/mL
Total sperm count	39×10^6 spermatozoa/ejaculate
Motility	40%
Forward progression	32%
Normal morphology	4%
Sperm agglutination	Absent
Viscosity	≤2 cm thread after liquefaction

Table 3: Endocrine evaluation.

	Semen volume	*Total testosterone*	*Serum follicle-stimulating hormone*
Hypogonadotropic hypogonadism	N/decreased	Decreased	Decreased
Anabolic steroid	N/ decreased	N/ decreased/increased	Decreased
Primary testicular failure	N	Decreased	Increased
Obstructive azoospermia	N/decreased	N	N

A low volume or absent ejaculate can suggest incomplete semen collection, retrograde ejaculation, failure of ejaculation, congenital bilateral absence of the vas deferens, hypogonadism or blockage of ejaculatory ducts. In cases of suspected retrograde ejaculation, the post ejaculatory urinalysis should be done by centrifuging the sample at 300 g for 10 minutes followed by examination of the pellet at × 400 magnification.

Transrectal USG may be used to detect dilated seminal vesicles or ejaculatory ducts or midline cystic prostratic structures and point towards complete or partial ejaculatory duct obstruction. Scrotal USG can be avoided with meticulous clinical examination. However, it can detect occult varicocele and can be used in male partners with risk factor for testicular cancer like cryptorchidism or previous testicular neoplasm. However, it is not a routine screening procedure.

Specialized Tests

These tests are not used as a routine but are reserved for cases where they can directly influence the mode of treatment.

- *Leukocytes in semen:* Patients with pyospermia (>1 million leukocytes/mL) should be evaluated for presence of any genital tract infection.
- *Antisperm antibodies (ASA):* The clinical utility of this test is in doubt. ASA is unnecessary for patients planned for ICSI. Azoospermia and presence of ASA can raise the suspicion of reproductive tract obstruction.
- *Sperm viability test:* Using supravital dyes, hypoosmotic swelling test (HOST).
- *Sperm DNA fragmentation test*: Studies on abnormal DNA integrity and reproductive outcome are too limited to perform these tests as a routine.
- Genetic screening for cystic fibrosis transmembrane conductance regulator (CFTR) causing cystic fibrosis and congenital bilateral absence of vas deferens can be done. Y chromosome microdeletions, and karyotypic abnormalities should be tested in male partners with nonobstructive azoospermia and severe oligospermia before ICSI.

Indication for Testicular Biopsy

Diagnostic testicular biopsy does not have any role as a prognostic marker for surgical sperm retrieval. If it is done, there should be provision for cryopreservation to avoid second procedure.

Investigations in male infertility are based on the history of the patient keeping the provisional diagnosis in mind (Table 4).

Table 4: Evaluation from history.

Relevant history	*Provisional diagnosis*	*Investigation suggested*
Cancer-radiation, chemotherapy	After some varieties of chemotherapy––irreversible damage may occur	Semen analysis (azoospermia) Normal investigations and sperm function test
Surgery for cancer	• Injury to sympathetic chain • Loss of erection • Loss of ejaculation • Retrograde ejaculation	• Semen analysis (Azoospermia) • Postcoital urine (for evidence of sperm)
History of surgery for inguinal hernia (pre-pubertal)	Undescended testis	Semen analysis FSH, LH
Surgery for neck gland biopsy	Obstructive azoospermia—may be tubercular	Blood for Hb%, TC, DC and ESR; • X-ray chest • Semen plasma—PCR • Mantoux test—controversial
Laparotomy in childhood for abdominal lump, intestinal obstruction, etc.	Tubercular	Relevant investigation including PCR of seminal plasma
Medical illness especially mumps or other viral infection	Mumps orchitis	Azoospermia (Sertoli cell only syndrome)
History of diabetes—personal in the patient or in patient's family	Longstanding diabetes, leading to neuropathy or vasculopathy→ sexual dysfunction	Blood sugar, semen analysis, postcoital urine
History of STD	Obstructive azoospermia	Semen analysis: FSH, LH

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