INTRODUCTION
Infertility is a common condition with important psychologic, economic, demographic and medical implications. Demand for infertility services has grown substantially even though the prevalence of infertility has been stable.

DEFINITION
Infertility is defined as failure of a couple to conceive after 12 months of regular intercourse without use of contraception in women less than 35 years of age; and after 6 months of regular intercourse without use of contraception in women 35 years and older.

EPIDEMIOLOGY
The World Health Organization (WHO) estimates that 60–80 million couples worldwide currently suffer from infertility. Infertility varies across regions of the world and is estimated to affect 8–12% of couples worldwide. Infertility tends to be highest in countries with high fertility rates, an occurrence termed "barrenness amid plenty." The WHO estimates the overall prevalence of primary infertility in India to be between 3.9% and 16.8%. Estimates of infertility vary widely among Indian states from 3.7% in Uttar Pradesh, Himachal Pradesh and Maharashtra, to 5% in Andhra Pradesh, and 15% in Kashmir. Moreover, the prevalence of primary infertility has also been shown to vary across tribes and castes within the same region in India. However, it should be noted that many of these estimates use different definitions of infertility and consider different time periods, which makes direct comparisons difficult between any studies.

TRENDS IN MALE INFERTILITY
Reports of declining sperm counts and increasing incidence of urogenital abnormalities and testicular cancer in some regions of the world have stirred public interest and concern. The role of environmental pollutants or toxins has been identified and its impact remains unclear.

ETIOLOGY
The causes of male infertility can be divided into four main areas:
1. Hypothalamic-pituitary disease: 1–2%
2. Testicular disease: 30–40%
3. Disorders of sperm transport: 10–20%
4. Idiopathic: 40–50%

Hypothalamic-Pituitary Disease
Any hypothalamic or pituitary disease can cause gonadotropin-releasing hormone (GnRH) or gonadotropin deficiency (hypogonadotropic hypogonadism) and therefore infertility. These conditions can be subdivided into congenital, acquired, or systemic disorders. It is important to diagnose hypogonadotropic hypogonadism as there are specific therapies available.

Primary Hypogonadism
Primary gonadal deficiency (hypergonadotropic hypogonadism) is an important cause of azoospermia and oligozoospermia. Congenital or developmental disorders, disorders of the androgen receptor, Y chromosome defects, and acquired disorders such as infection, drugs, environmental toxins, and smoking can cause male infertility.

Disorders of Sperm Transport
The epididymis is an important site for sperm maturation and an essential part of the sperm transport system. The vas deferens then transports sperm from the epididymis to the urethra, where they are diluted by secretions from the seminal vesicles and prostate. Abnormalities at any of these sites, particularly the epididymis and vas deferens, can cause infertility.

Idiopathic Male Infertility
Despite careful assessment of all possible causal mechanisms, a cause of abnormal sperm number, morphology, or function cannot be identified in a substantial proportion of infertile men. There are also men who have repeatedly normal semen analyses but cannot impregnate an apparently normal female partner.

EVALUATION
History
A detailed history of the female partner should also be obtained. In the male, the clinician should inquire about:
- Developmental history, including testicular descent, pubertal development, loss of body hair, or decrease in shaving frequency
- Chronic medical illness
- Infections, such as mumps orchitis, sinopulmonary symptoms, sexually transmitted infections, and genitourinary tract infections including prostatitis
- Surgical procedures involving the inguinal and scrotal areas such as vasectomy, orchidectomy, and herniorrhaphy
- Drugs and environmental exposures
- Sexual history, including libido, frequency of intercourse, and previous fertility assessments of the man and his partner.
Physical Examination
Androgen deficiency during early gestation presents as ambiguous genitalia; in late gestation as micropenis; in childhood as delayed pubertal development; and in adulthood as decreased sexual function, infertility, and eventually, loss of secondary sex characteristics.

General Appearance
Eunuchoidal proportions suggest androgen deficiency antedating puberty. On the other hand, increased body fat and decreased muscle mass suggest current androgen deficiency.

Skin
Loss of pubic, axillary, and facial hair, decreased oiliness of the skin, and fine facial wrinkling suggest long-standing androgen deficiency.

External Genitalia
Several abnormalities that can affect fertility can be recognized by examination of the external genitalia:

- Incomplete sexual development can be recognized by examining the phallus and testes and finding a Tanner stage less than 5.
- Diseases that affect sperm maturation and transport can be detected by examination of the scrotum for absence of the vas deferens, epididymal thickening, varicocele, and hernia. The presence of a varicocele should be confirmed with the man standing and performing a Valsalva maneuver.
- Decreased volume of the seminal vesicles can be detected by measuring testicular size by Prader orchidometer or calipers. In an adult man, testicular volume below 15 mL and testicular length between 3.6 cm are considered small.

Breasts
Gynecomastia suggests a decreased androgen to estrogen ratio.

STANDARD SEMEN ANALYSIS
A semen analysis is the cornerstone of the assessment of the male partner of an infertile couple.

WHO Lower Reference Limits
The WHO has published revised lower reference limits for semen analyses. Volume, 1.5 mL; sperm concentration, 15 million spermatozoa/mL; total sperm number, 39 million spermatozoa per ejaculate; morphology, 4% normal forms; vitality, 58% live; progressive motility, 32%, total (progressive + nonprogressive motility), 40%.

Specialized Semen Analysis
More specialized semen tests are not routinely performed. Sperm autoantibodies, semen biochemistry, semen culture, sperm-cervical mucus interaction, sperm function tests, computer-aided sperm analysis, acrosome reaction, zona-free hamster oocyte penetration test, human zona pellucida binding test, sperm biochemistry and sperm chromatin and DNA assays can be used to help to determine the cause of male infertility under certain circumstances.

Genetic Tests
The introduction of intracytoplasmic sperm injection (ICSI) has made it possible for men with severe oligozoospermia and azoospermia to father children, but the genetic risks of this highly invasive technique must be considered. These include the risks of transferring the cystic fibrosis conductance regulator (CFTR) gene, somatic and sex chromosome abnormalities, and microdeletions of the Y chromosome.

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

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 Luteinizing Hormone and Follicle-Stimulating Hormone
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.

Presence of low sperm counts and low serum LH concentrations in men who are well androgenized give a suspicion of exogenous anabolic or androgenic steroid abuse.

Other Hormones
Serum prolactin should be measured in any man with a low serum testosterone concentration and normal to low serum LH concentration. Although inhibin assays are not widely available outside of research laboratories, low serum inhibin concentrations may be an even more sensitive test of primary testicular dysfunction than high serum FSH concentrations, provided the assay is specific for inhibin B.

TREATMENT
Treatment of male infertility involves the couple.

Specific endocrine treatment is available for men whose infertility results from hypogonadotropic hypogonadism. Hypogonadotropic hypogonadism due to hyperprolactinemia can often be corrected and fertility restored by lowering the serum prolactin concentration. If the hyperprolactinemia results from a medication, as is often the case, that medication should be discontinued, if possible. The hyperprolactinemia is caused by a lactotroph adenoma. It should be treated with a dopamine agonist, such as cabergoline or bromocriptine. The process of spermatogenesis normally takes 3 months. As a result, restoration of a normal sperm count usually does not occur for at least 3 and sometimes 6 months or more after the serum prolactin and testosterone concentrations have returned to normal.

In some patients, who have a lactotroph macroadenoma, the hypogonadotropic hypogonadism appears to be the result of permanent damage to the gonadotroph cells by the mass effect of the adenoma. Gonadotropin treatment should be instituted for these patients.

- **Gonadotropin therapy**: Treatment is initiated with human chorionic gonadotropin (hCG), 1,500–2,000 IU three times per week subcutaneously or intramuscularly for at least 6 months. hCG has the biologic activity of LH. The hCG dose should be adjusted upward according to symptoms of hypogonadism, serum testosterone concentrations, and semen parameters.

Some patients with acquired hypogonadotropic states can be stimulated with hCG alone to produce sufficient sperm. If after 6–9 months the patient remains azoospermic or severely oligospermic, then human menopausal gonadotropin (hMG) or recombinant FSH should be added.

- **Pulsatile GnRH treatment**: Pulsatile subcutaneous or intravenous treatment with GnRH has also been successfully used to treat gonadotropin deficient patients.

GnRH has to be delivered in pulses using a portable pump with an attached catheter and needle for many months or years; most patients find it inconvenient to use GnRH therapy for so long.
and avoidance of environmental toxins and medications that may cause sterility.

Other possible future developments include identification and avoidance of environmental toxins and medications that may adversely affect reproductive function.

Sperm Autoimmunity

Continuous or intermittent high doses of prednisone (from 40 mg/day to 80 mg/day) for up to 6 months have been shown in placebo-controlled trials to improve cumulative pregnancy significantly in partners of men with sperm autoantibodies.27,28 However, many patients cannot tolerate this regimen because of the adverse effects of high-dose corticosteroid therapy. As a result, most couples prefer to try an assisted reproductive technique, such as ICSI, as primary treatment for sperm autoimmunity.

Potential Treatments in the Future

Mammalian (mouse) germ cells can initiate organized, normal spermatogenesis when transplanted to mice depleted of germ cells due to genetic mutation or after chemotherapy, and can result in normal progeny after successful mating with females.29,30

These observations suggest that germ cell transplantation or cultured testicular stem cells may become a treatment for male infertility and for genetic diseases in men that can be corrected and eradicated in germ cell lines. This possibility raises serious ethical, social, and moral issues.29,30

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REFERENCES