A Review On Male Infertility

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Abstract:

Male subfertility is common, and it causes significant distress to couples. The most common cause of male subfertility is idiopathic failure of spermatogenesis, Compared to reproductive specialists, endocrinologists may see a population of men that have a higher prevalence of treatable causes of subfertility including sexual disorders, endocrinopathies, obesity, drugs, and ejaculatory dysfunction. Seminal fluid analysis is the most important diagnostic study, and at least 2 samples should be analyzed. All patients with sperm concentrations < 10 million/mL due to idiopathic spermatogenic defects should be referred for genetic counseling and karyotyping; most experts also recommend that these patients be tested for Y chromosomal microdeletions. For most men with low sperm concentrations due to gonadotropin deficiency, gonadotropin therapy effectively increases spermatogenesis. The endocrinologist must recognize when to use medical therapy to stimulate spermatogenesis and when to refer for consideration of assisted reproductive technology.

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Introduction:

Reproduction is a simple and natural experience for most couples. However, for some couples it is very difficult to conceive. Infertility is defined as a failure to conceive within one or more years of regular unprotected intercourse. Male infertility is diagnosed when, after testing of both partners, reproductive problems have been found in the male partner. The term 'subfertility' may be preferable to infertility, as many of the bars to conception are relative rather than absolute and in about 30% of cases no cause is found.

People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within one year if:

- the woman is aged under 40 years; and
- they do not use contraception; and
- they have regular sexual intercourse.

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Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%).[1]

Infertility may be due to problems with one or both partners. Although it has been traditionally accepted that fertility is more related to the age of the female than that of the male partner, recent literature suggests trends that increased paternal age is also associated with lower fertility.[2]

Epidemiology:

According to the National Institutes of Health, male infertility is involved in approximately 40 percent of the more than 2 million infertile married couples in the United States. One-half of these men experience irreversible infertility and cannot father children, and a small number of these cases are caused by a treatable medical condition. In American men, the risk of having low sperm count correlates to approximately 1 in 25. Low sperm counts, poor semen quality, or both account for 90% of cases; however, studies of infertile couples without treatment reveal that 23% of these couples conceive within 2 years, and 10% more conceive within 4 years. Even patients with severe oligospermia (< 2 million sperm/mL) have a 7.6% chance of conception within 2 years.[3]

Comorbidities:

Many patients who present with infertility as their primary symptom have a serious underlying medical disease, such as pituitary adenomas, hormonally active tumors, testicular cancer, liver and renal failure, and cystic fibrosis (CF). Evaluating patients for life-

threatening or life-altering conditions during the workup is important.

In addition, the risk of cancer appears to be increased in infertile men. In a study,it was shown that male infertility was associated with an increased risk of developing cancer in comparison with the general population.[4,5] Overall, 29 men developed some type of cancer, including 10 (2.2%) with azoospermia and 19 (1.1%) without azoospermia.[5] Compared with the general population of Texas, infertile men had a higher risk of overall cancer (standardized incidence ratio [SIR], 1.7; 95% confidence interval [CI], 1.2-2.5).

The men who developed cancer in the study developed a variety of malignancies, including prostate cancer, brain and central nervous system cancer, melanoma, and stomach cancer, as well as testicular cancer.[7]

Causes of male infertility"

Since the discovery of spermatozoon by Anton van Leeuwenhoek in 1677, there has been an ever increasing understanding of its role in reproduction. Many factors adversely affect sperm quality, including varicocele, accessory gland infection, immunological factors, congenital abnormalities, and iatrogenic systemic and endocrine causes, such as diabetes mellitus, obesity, metabolic syndrome, and smoking. The mechanisms responsible for the association between poor sperm parameters and ill health may include oxidative stress, low-grade inflammation, low testosterone, and low sex-hormone-binding globulin.

i. General health

Even in the absence of systemic illness, poor general health will impair fertility.

- In those who are overweight (BMI 25-30kg/m^2) and obese (BMI >30kg/m^2), there is a relationship between the degree of excessive weight and poor quality and quantity of sperm.[4] Obesity and male infertility have increased in the last decades; therefore, a possible association between these pathologies has been explored. Studies inform that obesity may affect fertility througth different mechanisms, which alltogether could exert erectile dysfunction and/or sperm quality impairment. These include: 1) hypothalamic-pituitary-testicular (HPG) axis malfunction: obese hormonal profile is characterized by reduction of testosterone, gonadotrophins, SHBG and/or inhibin B concentrations and hyperestrogenemy. 2) increased release of adipose-derived hormones: leptin increase could be responsible for some of the alterations on the HPG axis and could also exert direct deleterious effects on Leydig cells physiology, spermatogenesis and sperm function; 3) proinflammatory adipokines augmentation, higher scrotal temperature (due to fat accumulation in areas surrounding testes) and endocrine disruptors accumulation in adiposites, all of these responsible for the increase in testes oxidative stress and 4) sleep apnea, frequent in obese patients, suppresses the nocturnal testosterone rise needed for normal spermatogenesis. In summary, although obesity may impair male fertility by some/all of the described mechanisms, the fact is that only a small proportion of obese men are infertile, probably those who are genetically predisposed or morbidly obese. Nevertheless, it is likely that because the incidence of obesity is growing, the number of men with reduced fertility will increase as well.[7]

- The adverse effects of smoking on male fertility are well documented.[8]Smoking is reported to cause Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) dysfunction in the airway, and is also associated with pancreatitis, male infertility, and cachexia, features characteristic of CF and suggestive of an etiological role for CFTR.[7] The mechanisms according to which tobacco affects spermatozoa are poorly understood. Some of the studies focused on the relation between cigarette smoking and the principal semen analysis, variable such as concentration, morphology and motility. In A study by Davar R, the sperm parameters were compared between smokers and non-smokers. There were no significant differences among groups according to sperm concentration , morphology and motility. Also there were no significant relationship between sperm parameters and the amount of cigarettes people had used (based on pack/year scale).[9]

- Although there is an association between elevated scrotal temperature and reduced semen quality, it is still uncertain whether wearing loose-fitting underwear improves fertility. Hu JT et al [10] showed in their study that high temperature (> 36°c) inhibited

the proliferation of rat Sertoli cells in vitro, and decreased the expression of OCLN, which suggests that a higher temperature above 36°c may reduce male fertility by affecting the proliferation of Sertoli cells and integrity of the tight junction among Sertoli cells or Sertoli cells and other cells.

- Excessive alcohol consumption also impairs fertility.[11] This has been reported to be associated with hypotestosteronemia and low-normal or elevated gonadotropin levels suggesting a combined central and testicular detrimental effect of alcohol. Nevertheless, alcohol consumption does not seem to have much effect on fertility either in in vitro fertilization(IVF) programs or population-based studies.
- Stress and anxiety also had shown negative impact on semen parameters. A study carried out by Vellani E et al showed that increased levels of both state and trait anxiety were associated with lower semen volume, sperm concentration and count, reduced sperm motility, and increased sperm DNA fragmentation of IVF patients, thus influencing seminal parameters at the macroscopic and cellular or subcellular levels. [13]
- Anabolic androgenic steroids, marijuana, opioid narcotics, cocaine and methamphetamines have an adverse impact on male fertility, and adverse effects have been reported on the hypothalamic-pituitary-testicular axis, sperm function and testicular structure.[14]

ii. Genetic defects

- Yq microdeletions are the leading genetic cause of male infertility and its detection is clinically relevant for appropriate genetic counseling. The frequency of Yq microdeletions is lower in Indian population as compared to Western counterparts. There is no major association of Yq microdeletions with seminal parameters or cause of infertility.[15]
- Azoospermia factor (AZF) microdeletions are the most frequent genetic cause of male infertility after Klinefelter's syndrome.[16]

iii. Disorders of the testis and spermatogenesis

These may be structural or hormonal.

- Persistent azoospermia is incompatible with fertility: Whilst oligospermia is a poor prognostic feature, and the lower the count the worse the prognosis, it is not totally incompatible with fertility.
- Klinefelter's syndrome with karyotype XXY is associated with hypogonadism and disorders of spermatogenesis. [17]
- Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility. Additionally, there is an increased risk of testicular neoplasia in the form of carcinoma in situ (CIS) cells.[18] Early orchidopexy (6-12 months of age) might be beneficial for testicular development in adulthood.[19]
- Androgen insensitivity syndrome (AIS), the end-organ resistance to androgens,is an X-linked disorder caused by mutations in the androgen receptor (AR) gene. Precise diagnosis requires clinical, hormonal and molecular investigation and is of great importance for appropriate gender assignment and management in general. More than 400 different AR gene mutations have thus far been reported but the receptor structure-function relationship and its phenotypic outcome is not yet fully understood. [20]
- Patients with cancer are at risk of loss of gonadal function due to the cancer treatment. Chemo- and radiation therapy are known to induce gonadal failure in both men and women and especially treatment with alkylating agents and/or abdominal or testicular radiation therapy poses a high risk. Methods exist to preserve fertility and these should be discussed with and offered to the patient if necessary and possible. For men, cryopreservation of semen is simple, non-invasive and low-cost. [21] Garolla A et al [22]showed in their study that patients with testicular cancer had frequently altered sperm parameters and higher prevalence of Human Papilloma Virus semen infection that were worsened after radio and chemotherapy.
- Accumulating evidence suggests that varicocele, long associated with male infertility, is a risk factor for low testosterone levels. The exact pathophysiology of the negative effects of varicocele on testicular function is not well understood, but theories include venous stasis, increased testicular temperature, oxidative stress, and resulting toxic environment. While prior studies

report conflicting effects of non-microsurgical varicocelectomy on testosterone level, recent literature demonstrates that microsurgical varicocelectomy improves testosterone levels in men with varicocele and low testosterone preoperatively.[23] Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility.[19]

- Trauma can cause testicular damage.

iv. Disorders of pituitary and hypothalamus

- Prolactinoma is the most common cause of hyperprolactinemia, which is a common cause of infertility in males and females. They can also present with decreased libido. So clinical diagnosis of prolactinoma in male patients is late, which can lead to misdiagnosis of microprolactinoma in male patients.
- Hyperprolactinemia causes infertility in around 11% of oligospermic males. Hyperprolactinemia inhibits the pulsatile secretion of the gonadotrophin releasing hormone, which causes decreased pulsatile release of follicle stimulating hormone, luteinizing hormone, and testosterone, which in turn causes spermatogenic arrest, impaired sperm motility, and altered sperm quality. It later produces secondary hypogonadism and infertility. Hyperprolactinemia also directly influences spermatogenesis and steroidogenesis . It is seen that oligospermic or azoospermic patients with normal serum levels of gonadotrophins show relatively higher serum levels of prolactin, proving a role of prolactin in gametogenesis, which is independent of gonadotrophins. There are many studies suggesting that hyperprolactinemia has a definite role in the male infertility, and is one of the reversible causes of infertility[24].Hyperprolactinaemia must be severe - e"735 mU/L (usually due to a pituitary tumour) - to have an effect on sexual function.[25]
- Hypogonadism in men is defined as a complex of signs and symptoms due to testosterone deficiency or inappropriate production, which occurs in about 1-2%. The most common causes of primary hypogonadism is Klinefelter's syndrome, while secondary—pituitary tumors. "Peripheral" hypogonadism results from androgen receptor polymorphism. [27]

v. Disorders of the genital tract

- Failure of adequate differentiation of the embryonic testis can cause failure of proper development of the spermatic ducts.
- Congenital urogenital abnormalities such as hypospadias can cause problems. It tends to deposit the semen in the acid environment of the vagina rather than near the friendlier environment of the cervix.

History

The patient's smoking, alcohol and drug (including any illicit drugs) history should be recorded.

The search for the cause of infertility or subfertility should be systematic and led by clinical features, not a blind screening process for everything:

- Coitus must be satisfactory and occurring on a frequent basis, preferably two to three times a week:
  - There may be periods of time when one of the partners is away.
  - Physical or emotional problems may be present.
  - Erectile dysfunction can occasionally present as a complaint of infertility.
- Ejaculatory problems - particular attention must be paid to the characteristics of micturition and ejaculation:
  - Presence of nocturnal emission.
  - Ejaculatory ability in given circumstances.
  - Primary or acquired disorder.
  - Consider psychosexual aspects (eg, features of affective relationship, pre-existent psychological trauma, previous psychological therapy).
- Current guidelines recommend that patients should be asked about:
  - Haematospermia.
  - Post-ejaculatory pain.
  - Previous or present urethritis or prostatitis.
  - Obstructive or irritative urinary symptoms.
  - Previous scrotal enlargement or pain or surgery.
  - Previous inguinal herniorrhaphy or trauma.
  - Chronic sinopulmonary infection.

- Mumps after the age of puberty may have caused orchitis.
- Previous treatment for malignancy:
  - In men about to receive chemotherapy, the question of sperm banking needs to be considered. Retention of fertility for prepubertal boys with malignancy is a growing field.[28]
- Cryptorchidism:
  - Paternity in men with unilateral cryptorchidism is almost equal to that in men without cryptorchidism. However, bilateral cryptorchidism significantly reduces the likelihood of paternity.
- Torsion of the testis may be relevant, as failure to reduce it swiftly can compromise blood supply and cause lasting damage.
- Sexually transmitted diseases can cause infertility.
- Drug and medication history. Legal drugs taken for legitimate purposes may cause problems:
  - Phenothiazines and the older typical antipsychotics as well as metoclopramide increase levels of prolactin.[28]
  - Oral and rectal sulfasalazine impair spermatogenesis. This is reversible when the drug is withdrawn or switched to mesalazine.
  - Immunosuppressants - eg, for autoimmune disease or after transplantation.

Examination[19]

- It is prudent to record the patient's blood pressure, weight and height (to calculate their BMI).
- Men with ejaculatory disorders should have their fasting glucose performed to exclude diabetes mellitus.
- A comprehensive andrological examination is indicated if semen analysis shows abnormalities compared with reference values.
- The patient should be examined for age-appropriate development of male secondary sex characteristics, gynaecomastia or hirsutism.
- Testicular site, consistency and volume should be noted.
- Examine for the presence of a varicocele, epididymal thickening or scrotal swelling.
- Examine for inguinal lymphadenopathy in those with symptoms to suggest an STI or in those with risk factors for an STI.

Investigation[19]

In the male, semen analysis in the only necessary initial investigation:

- The specimen should be produced by masturbation (and not into a condom, as they contain spermatocides) and after three days of abstinence from sexual activity.
- The specimen should be kept warm and sent to the laboratory for examination, ideally within an hour from production, although in practice this is difficult to achieve. Prior arrangement with the laboratory may be necessary to ensure that they are able to deal with the specimen on the same day as collection.
- Normal results based on World Health Organization (WHO) criteria are given below. Figures shown are lowest acceptable result (5th percentile) and 95% confidence limits in brackets:
  - Semen volume (mL): 1.5 (1.4-1.7)
  - Total sperm number (10^6 per ejaculation): 39 (33-46)
  - Sperm concentration (10^6 per mL): 15 (12-16)
  - Total motility (%): 40 (38-42)
  - Progressive motility (%): 32 (31-34)
  - Vitality (live spermatozoa, %): 58 (55-63)
  - Sperm morphology (normal forms, %): 4 (3.0-4.0)
- Repeat confirmatory tests should ideally be undertaken three months after the initial analysis, to allow time for the cycle of spermatozoa formation to be completed. However, if a gross spermatozoal deficiency (azoospermia or severe oligozoospermia) has been detected, the repeat test should be undertaken as soon as possible.
- After a second unsatisfactory result, an FSH level should be taken.
- It is important to differentiate between the following:
  - Oligozoospermia: <15 million spermatozoa/mL
  - Asthenozoospermia: <32% motile spermatozoa
  - Teratozoospermia: <4% normal forms

- Impaired spermatogenesis is often associated with elevated FSH concentration.
- Other laboratory tests that may be helpful include the following:
  - § Antisperm antibody test
  - § Hormonal analysis-S. FSH, S.LH, S. testosterone, S.prolactine.

An abnormal postcoital test result is observed in 10% of infertile couples. Indications for performing a postcoital test include semen hyperviscosity, increased or decreased semen volume with good sperm density, or unexplained infertility.

If the test result is normal, consider sperm function tests, such as the following:

- Capacitation assay
- Acrosome reaction assay
- Sperm penetration assay
- Hypoosmotic swelling test
- Inhibin B level
- Vitality stains
- Testicular biopsy is indicated in azoospermic men with a normal-sized testis and normal findings on hormonal studies to evaluate for ductal obstruction, to further evaluate idiopathic infertility, and to retrieve sperm. Spermatozoa are found in about 60% of patients with non-obstructive azoospermia (NOA).
- Ultrasound (Transrectal ultrasonography ,Scrotal ultrasonography) and magnetic resonance imaging are first-line, noninvasive imaging techniques that provide accurate definition of anatomical causes of infertility. This illustrates normal imaging anatomy and various causes of male infertility, and focuses on congenital and acquired testicular abnormalities and post-testicular obstruction, such as congenital absence of the vasa deferentia, seminal vesicle cysts, prostatic utricle cysts, Mullerian cysts, ejaculatory duct cysts (Wolffian cysts), and epididymal obstruction.[28]
- People undergoing IVF treatment should be offered testing for HIV, hepatitis B and hepatitis C. Those people found to test positive for one or more of HIV, hepatitis B, or hepatitis C should be offered specialist advice and counselling and appropriate clinical management.[1]

Management of male infertility:

Treatment approaches for male infertility varies greatly, depending on the severity of the sperm problem. Any fertility treatment may be expected to have an effect on semen quality roughly three months after it is started, as this is the length of time required for a single cycle of spermatogenesis, or sperm production. If neither surgical nor medical therapy is appropriate, assisted reproductive technologies are possible.

Lifestyle:

Patients should be encouraged to stop smoking cigarettes and marijuana and to limit environmental exposures to harmful substances and/or conditions.

Stress-relief therapy and consultation of other appropriate psychological and social professionals may be advised.

Infections should be treated with appropriate antimicrobial therapy.

The optimal timing to perform intercourse for conception is every 2 days at mid cycle.

The use of spermatotoxic lubricants should be avoided.

Dietary supplements and vitamins

- Safarinejad et al found a statistically significant increase in sperm concentration, motility, and strict morphology in subjects who received ubiquinol compared to those who received placebo, and these effects gradually returned to baseline levels during the off-drug time period. While pregnancy rates were not tracked or reported, the study does appear to support the use of ubiquinol in men trying to achieve a pregnancy based on improvement in semen parameters.[29] A diet high in antioxidants such as vitamin C and vitamin E has been proposed to improve the quality of sperm by decreasing the number of free radicals that may cause membrane damage.
- Additionally, the use of zinc, fish oil, and selenium has been shown to be of benefit in some studies.[30]

Specific Therapy:

Medical treatment

The most successful medical therapy for male infertility involves reversing chemical, infectious or endocrine imbalances. This is called specific therapy, and it is usually successful because treatment is based on the correction of well-defined problems.

Examples of this include:

- The replacement of the pituitary hormones — follicle stimulating hormone (FSH) and leutinizing hormone (LH) - for radiation or surgically induced pituitary disease. Gonadotropin and testosterone therapy is available in treatment of hypogonadism in men. The treatment strategy depends on the age of patient and the goals of therapy (restore of fertility and/or produce and maintain of virilization). The gonadototropins and GnRH are useful in spermetogenesis stimulation. The testosterone replacement therapy is efficacious and safe. Testosterone esters and gels are widely applied.[25]
- Hyperprolactinaemia- It can be managed medically with simple medication, such as bromocriptine and cabergoline, which normalizes serum prolactin levels, restoration of gonadal function, reversing infertility caused by hyperprolactinemia and induces reduction in the prolactinoma size in the majority of patients.[24]
- The administration of testosterone in men with hypoandrogenic hypogonadism. Testosterone supplementation, which should be initiated if the testosterone concentration drops below 12 nmol/L and should be given as directed in the guidelines for the treatment of hypogonadism. This recommendation is made even though there have not been any randomized controlled trials documenting the efficacy of testosterone therapy in adolescents or young adults. [17]
- Retrograde ejaculation

Imipramine or alpha-sympathomimetics, such as pseudoephedrine, may help close the bladder neck to assist in antegrade ejaculation. However, these medicines are of limited efficacy, especially in patients with a fixed abnormality such as a bladder neck abnormality occurring after a surgical procedure.

Alternatively, sperm may be recovered from voided or catheterized postejaculatory urine to be used in assisted reproductive techniques. The urine should be alkalinized with a solution of sodium bicarbonate for optimal recovery.

More recently, the injection of collagen to the bladder neck has allowed antegrade ejaculation in a patient who had previously undergone a V-Y plasty of the bladder neck and for whom pseudoephedrine and intrauterine insemination had failed.[31]

Surgical Treatment:

Varicocelectomy

Various techniques for varicocelectomy have been proposed and used, each with advantages and disadvantages.

The retroperitoneal approach may be performed as an open procedure or laparoscopically. The inguinal and subinguinal microscopic approach allows for ligation of individual veins with decreased risk of inadvertent arterial damage.

Successful varicocelectomy results in improvement in semen parameters in 60-70% of patients. The repair also typically halts further testicular damage and improves Leydig cell function.

Results from a prospective, randomized controlled trial from Saudi Arabia compared subinguinal microsurgical varicocele repair to observation. In treated men, the mean of all semen parameters significantly improved in follow-up compared with baseline ($p < 0.0001$). This study provided an evidence-based endorsement of the superiority of varicocelectomy over observation in infertile men with palpable varicoceles and impaired semen quality.[32]

Vasovasostomy or vasoepididymostomy:

These microsurgical techniques are performed in patients with known epididymal or vasal obstruction, both congenital and acquired (eg, due to surgery, trauma, infection). Improved surgical techniques and the use of the operating microscope have improved the outcomes in patients requiring vasectomy reversal or those with primary vas obstruction.[33] In a study by Fenig et al, the timing of a reversal along with a sperm granuloma identified during the patient's physical examination have been identified as predictors of the need for epididymovasostomy.[34]

Transurethral resection of the ejaculatory ducts:

Patients with a known or suspected obstruction of the ejaculatory ducts may be eligible for transurethral resection of the ejaculatory ducts (TURED), which durably improves semen quality in patients with ejaculatory duct obstruction.

Sperm retrieval techniques:

Testicular sperm extraction (TESE) is performed at the time of testicular biopsy or as a separate procedure using the same technique.[35]

Testicular sperm aspiration (TESA) is less invasive that TESE but yields fewer sperm and is suboptimal in cases of nonobstructive azoospermia.[35]

Microsurgical epididymal sperm aspiration (MESA) involves directly retrieving sperm from the epididymis. Sperm in the epididymis are more mature than that in the testis. Using a microscope, the epididymis is uncovered and incised to express sperm. Epididymal fluid is aspirated into a tuberculin syringe primed with human tubal fluid (HTF).

Percutaneous epididymal sperm aspiration (PESA) involves direct sperm aspiration from the epididymis. This procedure can be performed under local anesthesia in the office setting. While effective in sperm retrieval, this does not allow sampling from multiple sites and is associated with an increased risk of epididymal and testicular injury and secondary epididymal obstruction.

Electroejaculation:

Under general anesthesia, an unlubricated Foley catheter is placed in the bladder and a buffer (ie, HTF) is instilled through the catheter. A rectal probe is inserted with its electrodes positioned against the posterior seminal vesicles. Electrical stimulation is begun at 3-5 volts and increased as necessary.

Electroejaculation achieves up to a 90% sperm retrieval rate.

The penile vibratory stimulator has been shown to be a useful alternative to electroejaculation in select patients.

Empiric Therapy:

Empiric therapy, attempts to correct rather ill-defined conditions. The use of clomiphene citrate, tamoxifen or ProXeed for low sperm density or motility are examples of this form of therapy. Aromatase inhibitors are relatively expensive pharmaceutical agents and may be steroidal (testolactoma) or nonsteroidal (anastrozole, letrozole and exemestane). Anastrazole represents the fourth generation of aromatase inhibitors. The drug is safe and well-tolerated and can be administered orally in men with idiopathic oligozoospermia. One indication for treatment is an abnormal testosterone/estrogen ratio. However, normal ratio ranges have not yet been standardized. Serum testosterone, estrogen concentrations and seminal parameters are followed at regular intervals. In addition, serum liver function tests should be performed because transaminase elevations are common but tend to resolve after therapy is stopped .[36]

In choosing a treatment plan, consideration should be given to each couple's long-term goals, financial constraints, and the results of the female partner's evaluation in addition to male factor findings.

Few disorders have become subjects of rational treatment of the infertile male, even though, as examples, hypogonadotropic hypogonadism is treatable by gonadotropins and obstructive azoospermia by reconstructive surgery. Early treatment of maldescended testes and sexually transmitted diseases can prevent infertility. Similar pregnancy rates from patients with varicocele following surgery or counseling demonstrate the important role of the physician in the treatment of infertility. In the age of evidence-based medicine, most empirical treatments have been demonstrated to be ineffective. Instead, symptomatic treatment by assisted reproductive techniques has become a central tool to overcome otherwise untreatable male infertility.[37]

Artificial insemination:

Artificial insemination (AI) involves the placement of sperm directly into the cervix (ie, intracervical insemination [ICI]) or the uterus (ie, intrauterine insemination [IUI]). AI is most useful for couples in whom the postcoital test indicated no sperm, those who have very low sperm density or motility, or those who have unexplained infertility.

IUI allows the sperm to be placed past the inhospitable cervical mucus and increases the chance of natural fertilization. This results in a 4% pregnancy rate if used alone and a pregnancy rate of 8-17% if combined with superovulation. Both processes require semen processing.

Patients in whom IUI has failed 3-6 times should consider proceeding to IVF.

Assisted reproduction techniques:

Patients with severe oligospermia, azoospermia, unexplained infertility, or known defects that preclude fertilization by other means are candidates for assisted reproduction techniques(ART). ART use donated or retrieved eggs that are fertilized by the male partner's sperm or donor sperm. The fertilized embryos are then replaced within the female reproductive tract. These techniques result in a 15-20% delivery rate per cycle and may eventually be successful in 50% of cases. However, the high cost and technical difficulty of the

procedures generally preclude their routine use as first-line therapy.

In vitro fertilization:

IVF involves fertilization of the egg outside the body and reimplantation of the fertilized embryo into the woman's uterus. Indications for IVF include previous failures with IUI and known conditions of the male or female precluding the use of less-demanding techniques.

IVF generally requires a minimum of 50,000-500,000 motile sperm. Harvesting eggs initially involves down-regulating the woman's pituitary with a GnRH agonist and then performing controlled ovarian hyperstimulation.

Follicular development is monitored by ultrasonographic examination and by checking serum levels of estrogen and progesterone. When the follicles are appropriately enlarged, a transvaginal follicular aspiration is performed.

A mean of 12 eggs are typically retrieved per cycle, and they are immediately placed in an agar of fallopian-tube medium. After an incubation period of 3-6 hours, the sperm are added to the medium using approximately 100,000 sperm per oocyte. After 48 hours, the embryos have usually reached the 3- to 8-cell stage.2 to 4 embryos are usually implanted in the uterus, while the remaining embryos are frozen for future use. Pregnancy rates are 10-45%.

Overall, IVF is a safe and useful procedure. Risks include multiple pregnancies and ovarian hyperstimulation syndrome. Additionally, an increased risk of hypospadias occurs in boys (1.5% vs 0.3%), probably because of the increased maternal progesterone used for egg harvesting.[38]

Finally, the use of this technology has led to many ethical issues, such as the fate of embryos after divorce.

Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT)

These procedures allow the placement of semen (GIFT) or a fertilized zygote (ZIFT) directly into the fallopian tube by laparoscopy or laparotomy. Success rates have been estimated to be 25-30% using these techniques. Unfortunately, these procedures require general anesthesia and have associated risks. Fertilization and implantation within the uterus are not guaranteed, and these procedures cannot be performed in patients with fallopian tube obstruction. GIFT and ZIFT are rarely used as a therapeutic option.

Intracytoplasmic sperm injection

ICSI involves the direct injection of a sperm into an egg under microscopy (see image below).

ICSI is indicated in patients who have failed more conservative therapies or those with severe abnormalities in which no other treatment would be effective, including patients with sperm extracted directly from the epididymis or testicle.

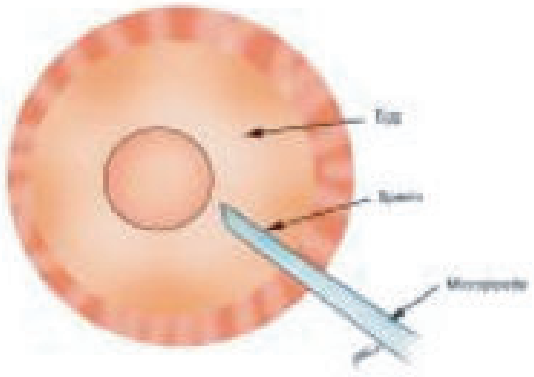

Fig.-1: *Technique of intracytoplasmic sperm injection (ICSI). A micropipette is used to inject a single sperm directly into an egg.*

Oocytes are processed with hyaluronidase to remove the cumulus mass and corona radiata. A micropipette is used to hold the egg while a second micropipette injects the sperm. The oocyte is positioned with the polar body at the 6-o'clock or 12-o'clock position, and the sperm is injected at the 3-o'clock position to minimize the risk of chromosomal damage in the egg.

After incubation for 48 hours, the embryo is implanted in the woman. Van Steirteghem et al (1993) reported a 59% fertilization rate and a 35% pregnancy rate using ICSI in 1409 oocytes.[39]

Fresh or cryopreserved sperm appear to have similar success rates.[40]

In a study spanning 15 years, testicular sperm extraction (TESE) from men with azoospermia followed by cryopreservation was more effective at fertilization than fresh sperm from biopsies.[41,42] In males with all diagnoses, the researchers found a significant difference in fertilization rate between frozen (62%) and fresh (47%) sperm. The fertilization rate was also greater in men with obstructive azoospermia (66%) compared with those

with nonobstructive azoospermia (43%).[41,42] In addition, the testicular sperm recovery rate was greater among patients with cancer (70%) and obstructive azoospermia, paralysis, and other causes of infertility (100%) than in men with nonobstructive azoospermia (31%). Moreover, although male diagnosis did not affect clinical pregnancy rates, men with obstructive azoospermia who underwent IVF had higher delivery rates (62%) than men with nonobstructive azoospermia (20%).[41,42]

The investigators also noted that female partners of men with infertility who have diminished ovarian reserve may also affect the success of TESE in men undergoing IVF with intracytoplasmic sperm injection (ICSI).[41,42] In their cohort of women who underwent egg retrievals involving TESE/ICSI cycles, the clinical pregnancy rate was reduced in women with diminished ovarian reserve (7.4%) relative to women with other diagnoses (endometriosis, tubal factor, polycystic ovary syndrome, ovulatory dysfunction) (44%).

The potential complications, ethical issues, and high costs of ICSI need to be considered and individualized.

Conclusion:

Prognosis of a patient with infertility depends on the underlying cause of infertility. The appropriate workup must be performed, and then the appropriate intervention may be used. Prognosis is individualized depending on these results. Numerous advances have been made in reproductive medicine in the last few years. Infertile couples who previously were considered untreatable now have a chance at genetic paternity. ART provide a great opportunity to families with infertility, and their used has become routine in the treatment of infertile couples. Sometimes male fertility problems can't be treated, and it's impossible for a man to father a child. Consideration should be given on either using sperm from a donor or adopting a child.

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