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Review Article

Etiology of male infertility: a review

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ABSTRACT

Infertility is one of the major health issues and a socially destabilizing condition for couples often causing marital disharmony. Infertility refers to the biological inability of an individual to contribute to conception over the course of one year of continuous unprotected intercourse. There are numerous factors such as anatomical, physiological, environmental, lifestyle and genetic factors that cause infertility. Male infertility can be diagnosed by different tools, for instance, physical examination, semen analysis, testicular biopsy, hormonal tests, urine test, immunobead test, sperm functional tests, sperm chromatin and abnormal deoxyribonucleic acid (DNA) assays, chromosome and genetic studies. There are diverse treatment options available for male infertility inclusive of hormonal, pharmacological, non-pharmacological, antioxidants, anti-inflammatory therapy, surgical, assisted reproductive technologies (ART), combination and herbal supplement with lifestyle changes. The infertility of known etiology has ample treatment success rate that vary by age, accurate diagnosis and effective therapy along with shared decision-making which can facilitate achievement of fertility goals. Thus, the review summarizes classification, causes, and diagnosis with treatment modalities of male infertility.

Keywords: Male, Infertility, Etiology, Treatments, Reproductive health

INTRODUCTION

Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. Worldwide, around 15% couples are affected by infertility and among them 40-50% cases are attributed to male infertility.[1] Male infertility usually occurs due to acquired or congenital conditions. The cause of infertility in 45% men is unknown (idiopathic infertility). Though, 15-30% of male are infertile due to genetic reasons. Male infertility of known etiology has considerable treatment success rate. However, genetic or idiopathic male infertility has optimized and empirical approach.[2] Male infertility is mainly classified into azoospermia (AS) and coital infertility (CI). Azoospermia (AS) is complete sperm absence in the ejaculate. It is recognized in 15% infertile men and is classified into obstructive infertility (OI) and non-obstructive infertility (NOI).[3] Obstructive infertility means the ejaculate is devoid of spermatozoa and characterized by normal endocrine and exocrine system along with normal spermatogenesis. However, there is an obstruction in the genital tract. It might also occur in any part between ejaculatory ducts and rete testes. Non-obstructive infertility is characterized by abnormal spermatogenesis. It results from primary or secondary testicular failure (TF) or partial or vague testicular failure. Coital infertility is characterized by normal sperm production and genital tract. Yet, the illness is secondary to patient's sexual dysfunction, that effects ejaculation.[4] Sub-fertility can be either primary or secondary. Primary

sub-fertility means delay for a couple who have had no previous pregnancies; and, secondary sub-fertility means delay for a couple who have conceived previously, although the pregnancy may not have been successful, for example, miscarriage, and ectopic pregnancy.[4]

CAUSES

Pubertal growth

Ejaculatory duct obstruction (EDO)

Ejaculatory duct obstruction (EDO) is an eminent but occasional cause of obstructive infertility; it may be acquired or congenital. Congenital cases are characterized by stenosis or atresia along with cystic lesions. Acquired reasons might be inflammation or trauma with calculus and stenosis following prostatic transurethral resection. Typical EDO is characterized by acidic ejaculate, normal hormones, dilated ejaculatory ducts and seminal vesicles, dysuria, painful ejaculation, prostatic calcification or cysts and hematospermia. Obstruction may be complete or partial; complete duct obstruction presents total absence of sperm in the ejaculate and partial duct obstruction have reduced number of sperms in the ejaculate.[5]

Epididymal obstruction

About 30-67% of AS cases suffer from epididymal obstruction which is usually caused by infections in epididymis. Epididymal surgery, for instance cyst removal may result in azoospermia. Moreover, distal obstruction leading to epididymal obstruction should also be considered while treating seminal.[6]

Cryptorchidism

Cryptorchidism is an inability of testes to descend down into scrotum, reported in about 2-6% newborns and nearly, 10% infertile individuals suffer from cryptorchidism. In bilateral cryptorchidism (BCr), both testes remain in abdominal cavity that eventually causes complete sterility. However, in unilateral cryptorchidism (UCr), one testis remains in abdominal cavity and other remains normal and descends down to scrotal sac. The normal one performs steroidogenesis and spermatogenesis in usual way, however at reduced level. There are 13-34% chances of developing azoospermia, even after treatment of both types of cryptorchidism.[7]

Testicular torsion (TT)

It is characterized by twisty spermatic cord, with decrease or blocked blood supply, causing severe pain, testicle ischemia/infarction and may consequently result in testicle loss. Infertile males represent long term outcomes; acquired anorchia, testicular atrophy, oligoasthenoteratozoospermia, oligozoospermia, and non-obstructive infertility of the disease at young age than with the acute testicular torsion (TT) itself.[8]

Varicocele

Varicocele is a dilation of testicular veins within pampiniform plexus of spermatic cord that holds up testicles. It is characterized by scrotal swelling and pain. The mechanisms which may cause varicocele include hypoxia, testicular venous hypertension, increased spermatic vein catecholamine, increased testicular temperature and increased oxidative stress.[9]

Penile deformities

Person with abnormal position of urethra meatus or with congenital penile curvature can have problem in vaginal penetration and sperm discharge. Penile abnormalities include phimosis, hypospadias, penile deviation and epispadia. Infertile patients suffering from these abnormalities might have decreased fertility or coital infertility.[10]

Ejaculatory disorders

Retrograde ejaculation (ReE)

In retrograde ejaculation (ReE), there is partial or complete sperms ejaculation into bladder instead of urethra and penis. When sperms mix up with urine, they don't survive very long. It results from anatomic, neurogenic and pharmacological factors. Pharmacologically it is attributable to alpha blockers and psychotropic drugs. Neurogenic reasons include lesions of spinal cord, retroperitoneal surgery and neuropathies.[11]

Anejaculation (AnE)

It is an inability to ejaculate even with normal erection. Anejaculation (AnE) is characterized by lack of retrograde ejaculation or antegrade ejaculation, owing to failure of releasing semen from ejaculatory ducts, prostate and seminal vesicles into urethra. True AnE, accompanying normal sensation of orgasmic is associated with drugs and nervous system dysfunction. It may be caused by neurological disorders including spinal cord injury (SpCI). Primary AnE may results from psychosexual or neurological factors such as decreased genital organs sensitivity or high ejaculatory reflex threshold. Secondary AnE may follow surgeries of abdomen or pelvis that originate sympathetic chain injury. It may occur in diabetic autonomic neuropathy and in other types of autonomic neuropathy.[12]

Testicular trauma and cancer

Testicular trauma is characterized by swelling and dislocation or disruption of testicles, which can result from some accident or injury to the testicles. Injury to testicles

can result in bleeding and formation of antisperm antibodies which can eventually lead to infertility.[13] Testicular cancer is an abnormal growth on testes which appears as a painless lump on the surface of testes. However, males having testicular cancer have lower fertility. It is a treatable cancer, with 95% survival rate. It causes infertility because of ejaculatory dysfunction as a consequence of pelvic plexus. In such patient's fertility is further affected by exposure to chemotherapy or radiotherapy. Contra-lateral testes size is small in infertile individuals suffering from testicular cancer. In these patients if there is obstructive infertility and non-obstructive infertility, fertilization is characterized by sperm extraction.[14]

Viral mumps orchitis

This is mainly due to lack of the measles, mumps and rubella (MMR) vaccine in children during the early 1990s. About 25% of the adults who get mumps will develop orchitis, out of these; one-third will have bilateral disease. The infection damaged directly to the seminiferous tubules through severe intratesticular swelling. Testicular atrophy may occur from 1 to 6 months after the infection.[15]

Genetic and chromosomal defects

Genetic and chromosomal causes account for 10-15% of severe male infertility, including chromosomal abnormalities, autosomal gene mutation, polymorphism and epigenetic errors. It may alter spermatogenesis, impair normal development of the genital tract and decrease sperm motility and fertilization capacity. Recent work showed that azoospermia factor (AZF) of the human Y chromosome microdeletions result from homologous recombination between almost identical blocks in this gene region. These microdeletions are a frequent molecular genetic cause of spermatogenetic failure leading to male infertility.[16] Polymorphisms of several genes that are associated with the human azoospermic population are genetic risk factors for the patients with azoospermia. Noonan syndrome caused by genetic mutation can lead to cryptorchidism and spermatogenesis deficiency due to elevated FSH level in men.[17]

Translocations occur in 3% of patients with severe oligozoospermia. Autosomal inversions are eight times more frequent in infertile men, although these rearrangements are balanced, in some cases leading to severe oligoasthenoteratozoospermia or azoospermia. Some gene mutations with pathological syndromes can be associated with infertility, such as congenital bilateral absence of the vas deferens (CBAVD), which cause obstructive azoospermia in 80 to 90% of cases, which is caused by a mutation in the cystic fibrosis transmembrane regulator (CFTR). Primary ciliary defects are an autosomal recessive heterogeneous defect caused by a lack of normal eyelash function and present in half of men with asthenospermia.[18]

Klinefelter's syndrome is a genetic mutation where the male has XXY instead of the usual XY chromosomes depicts with the most typical symptoms, i.e., bilateral atrophic or hypertrophic testes, reduced muscle mass, scant body and facial hair, and gynecomastia. Klinefelter's syndrome is the most common diagnosed cause of primary hypogonadism, leading to infertility.[18,19]

Endocrinal disorders

Any fluctuation in luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone can affect spermatogenesis in males. High FSH level or lack of typical spermatogenesis due to testicular histology in azoospermia is evidence of non-obstructive infertility. Level of testosterone is decreased in old age and in obese persons, which causes erectile dysfunction and low sex drive. Studies have demonstrated that hypothyroid is decreases the level of serum testosterone and gonadotropins (GTs) which ultimately affect spermatogenesis.[20] Prolactinoma is a condition where prolactin gets elevated and suggested a possible prolactin-secreting pituitary tumour. Such tumours may cause infertility, hypogonadism, gynecomastia, galactorrhea, and a reduction of the peripheral visual fields. Dopamine agonists are generally used as medical therapy to suppress prolactin secretion, and many men will then normalize their testosterone levels and sperm counts. Surgical therapy with a trans-sphenoidal resection of the prolactinoma is successful in 80% to 90% of cases, but the tumours often recur.[21]

Vasectomy

Ideally, vasectomy is characterized by reversible azoospermia and lack of adverse effects. It is a leading cause of obstructive infertility and may damage functions of epididymal epithelium with epididymal obstruction. It may result in 20-40% decrease in spermatids count, after 1 to 20 years of the procedure. However; 2-6% males undergo vasectomy reversal procedure (vasovasostomy) within 10 years, desiring to develop fertility again.[22]

Other causes

Older individuals have anomalous sperm morphology, i.e., less normal sperm forms with decreased vitality along with supplementary cytoplasmic droplets. Erectile dysfunction (EDF) is also common in aged men.[23] Different types of viral and bacterial infections through *S. aureus* and *E. coli* can influence male fertility by reducing sperm viability. Moreover; mycoplasmas and urea plasmas might colonize urethra and infect semen. *Ureaplasma urealyticum* (UU) is pathogenic and induces leukocytospermia which lead to decrease sperm counts, sperm damage and invariably impaired sperm motility. Herpes simplex virus (HSV) found in semen may cause low sperm count; reduce sperm motility and sperm damage.[24] Sexually transmitted diseases (STD) are caused by bacteria, viruses and parasitic microorganisms. These diseases are syphilis,

chlamydia, gonorrhea, chancroid and trichomoniasis. Human papillomavirus, lymphogranuloma venereum and HSV also cause STD.[25] Prolonged starvation and excessive exercise can affect sperm count, motility and even can stop sperm production. Excessive restriction in food intake can reduce the level of Zn, vitamin C, vitamin A, vitamin E, selenium (Se), folic acid and other nutrients that are necessary for proper functioning of body and spermatogenesis.[26] In males, psychological stress increases glucocorticoid level which suppresses testosterone concentration in testes that rigorously affecting spermatogenesis. Stress may also induce structural and meiotic changes in sperm and make it difficult to target ovum. Infertility may result in stress, depression, low self-esteem, negative thoughts and marital problem.[27] Some therapeutic drugs are also involved in causing male infertility. Sulfasalazine is a disease anti-rheumatic drug, which is known to reduce male fertility. Methotrexate is an immunosuppressive drug that alters semen quality and is responsible for the inhibition of dihydrofolate reductase enzyme which is important for folate synthesis. Folate is required for the synthesis of thymidine which is an important component of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) protein synthesis. Methotrexate also induces germ cell apoptosis by increasing the level of Bax/Bcl-2. Use of beta blockers and some psychotropic drugs can cause impotence in males. Other drugs with high risk of infertility are; cyclophosphamide, chlorambucil, melphalan, procarbazine, bleomycin and dactinomycin.[28] Some heavy metals including lead, chromium, copper and cadmium adversely affect sperm and male reproductive system. The magnitude of effect is directly associated with concentrations and exposure duration. Pesticides are another contributing factor in male infertility that can cause testicular cancer; reduce sperm quality and erectile dysfunction by blocking the activity of hormones.[29] Testicular hyperthermia can cause the genital heat stress leading to the production of low-quality spermatozoa. Heat exposure can lead to many abnormalities in the testis including; dilatation of smooth endoplasmic reticulum, degeneration of mitochondria and wider spaces in spermatid cells. Heat stress leads to damage DNA, autophagy and apoptosis of germ cells due to generation of reactive oxygen species and breakage of strands. Testicular temperature can be influenced by excessive exercise, frequent bike riding, cycling, tight clothing and keeping laptops or mobiles on their legs.[30] Male fertility is also affected by today lifestyle factors. There is high concentration of free radicals in the seminal fluid of smokers which causes sperm damage and production of high concentration of malformed sperms.[31] Excessive intake of alcohol in men causes shrinkage of testes and impairs production of testosterone, hence resulting in infertility, impotence, decreased libido and reduction of secondary sexual characteristics. Obesity affects fertility of men by changing hormonal profile, increasing scrotal temperature and altered semen parameters. In addition with excessive air pollution in men also changes the natural sperm shape and reduces sperm motility.[31] Reactive oxygen species (ROS) are necessary for the performance of normal physiological functions of a cell. Increased H_2O_2 concentration causes immobilization of sperms by decreasing ATP level and lipid peroxidation. ROS are also associated with DNA damage and apoptosis inside the sperms by disruption of mitochondrial membrane that causes the release of cytochrome-C hence, leading to apoptosis and DNA fragmentation inside cell nucleus.[32]

DIAGNOSIS

Physical examination and semen analysis

It involves patient questioning, genital examination including prostate, anal sphincter tone and bulbocavernosus reflex evaluation. Semen analysis is performed to analyze the shape, movement and number of sperms under microscope as well as sperm production. Staining of seminal smear permits quantitative assessment of both normal and abnormal morphological forms of sperm in the ejaculate. The volume of the semen sample, approximate number of total sperm cells, sperm motility, viability and percentage of sperm with normal morphology are measured.[33,34]

Hormone tests

The test is limited in determining the levels of testosterone, LH and FSH. It is performed in individuals with possibility of hypogonadism. The differentiation between obstructive infertility and non-obstructive infertility is a significant factor in male infertility. In obstruction there is normal level of FSH with bilaterally standard testicular volume. Yet, 29% individuals having normal FSH are characterized by defective spermatogenesis or spermatogenic arrest.[35]

Testicular biopsy (TBO)

Bilateral testicular biopsy (TBO) is recommended while diagnosing male infertility. It is predominantly useful for investigation of oligospermia and azoospermia (AS) with normal endocrine activity. Though, Sertoli cell only (SCO) histology is a common pattern in individuals with AS, small testes, primary infertility and primary testicular failure.[36]

Immunobead test

The immunobead test (IBT) with beads binding to more than 50% of motile sperm is regarded as positive, but there is usually more than 70-80% immunoglobulin A (IgA) bead binding with clinically significant sperm autoimmunity. The indirect IBT, in which normal donor sperm are exposed to test serum or seminal plasma, can be used when there are too few motile sperm for the direct IBT. Sperm-mucus penetration tests can be performed by postcoital examination of sperm in cervical mucus collected at mid-cycle or after estrogen treatment to produce mucus of equivalent quality. *In vitro* capillary

mucus penetration (Kremer) tests are particularly important for evaluating the significance of sperm auto antibodies.[37]

Sperm functional tests

A hypo-osmotic swelling (HOS) test that indicates membrane integrity and viability of spermatozoa; acrosomal intactness (AI) test that indicates the functional status of the sperm acrosome and its ability to penetrate the oocyte; nuclear chromatin decondensation (NCD) test which indicates the ability of the sperm chromatin to undergo decondensation following fertilization and sperm mitochondrial activity index (SMAI) test that indicates motility disorders and flagellar and mitochondrial defects are available to examine the human fertilization process. Capacitation and sperm penetration assay are also performed where a sperm defect is suspected. Presence of inhibin B level determined acrosomal activity, where a high inhibin B level may be caused by seminiferous tubular disorders or ductal obstruction and can lead to sperm self-destruction.[38] The human sperm-zona pellucida **(**ZP) interaction tests have been developed using oocytes that failed to fertilize *in vitro*. The sperm bound to the surface of the ZP can be sheared off by repeatedly aspirating the oocyte with a pipette. The sperm penetrating the ZP or perivitelline space can then be counted easily, and the results of this test are the most predictive of fertilization rates with standard IVF.[39] Sperm dislodged from the ZP can be stained with a fluorescein-labeled lectin to determine the proportion that are acrosome reacted. This test is useful for diagnosis of disordered ZP-induced acrosome reaction. Sperm-oolemma binding has been studied in a similar way to the sperm-ZP binding test.[39]

Sperm chromatin and abnormal DNA assays

A variety of flow cytometric and other assays to measure sperm chromatin integrity, DNA fragmentation, antisperm antibody, sperm apoptosis or nuclear integrity have been developed. The usefulness of these tests for prediction of fertility remains controversial.[40]

Chromosome and genetic studies

Karyotypes are performed in men with clinical evidence of primary testicular failure and small testes to confirm a clinical diagnosis of Klinefelter's syndrome. The extra Y chromosome is deleted early in gametogenesis because the sperm, embryos, and children generally have normal karyotypes. However, an increased rate of sex chromosomal and autosomal aneuploidy has been noted in studies of sperm from XXY and XYY men. Some Y chromosome abnormalities, such as an isochromosome of two short arms, are associated with absences of spermatogenesis. An increased frequency of autosomal abnormalities is found with defective spermatogenesis, particularly balanced autosomal translocations which may be transmitted in unbalanced form to their offspring.[41] Microdeletions in the long arm of the Y chromosome (AZF regions) have been found in 3-15% of men with severe primary spermatogenic disorders. Polymorphisms of the promoter region of the estrogen receptor gene have been shown to be related to sperm production. Androgen receptor defects have also been found in some men with unexplained primary spermatogenic disorders. Mutations in the gene impairing androgen receptor activity produce androgen insensitivity, which has a variable phenotypic expression from testicular feminization to otherwise normal males with gynecomastia or hypospermatogenesis and oligospermia.[41,42]

Other investigations

Ultrasonography is useful to check for tumors in the testes, particularly when the testes are difficult to palpate because of a tense hydrocele. It can also be used to measure testicular size and confirm the presence and nature of cysts or other abnormalities in the scrotum. Doppler blood flow assessment is valuable in assessing a painful swollen testis for torsion or inflammation and for evaluating varicoceles. Other tests of a varicocele, including thermography, technetium scans, and venography may be performed but, as pointed out later, the value of treating varicoceles to improve fertility is uncertain. Rectal ultrasound may demonstrate cysts in the prostate, enlarged seminal vesicles, or dilated ejaculatory ducts associated with distal genital tract obstructions. Clinical suspicion of the presence of a pituitary tumor should be followed up by appropriate radiology. Abdominal imaging is also necessary to check the position of impalpable testes.[43]

TREATMENT OPTIONS

Hormonal

Gonadotrophin releasing hormone (GnRH) stimulates the release of LH and FSH by estrogen receptors blockade in hypothalamus. Pulsatile treatment with GnRH, substitutes GnRH deficiency in infertile individuals suffering from hypogonadotropic hypogonadism (HH) and lack of hypothalamus secretions. High estrogen levels can also impair male fertility by suppressing gonadotropin secretion and thereby diminishing intratesticular androgen levels.[44]

Human chorionic gonadotropin (rec-hCG recombinant), recombinant LH (rec-hLH), FSH (rec-hFSH) and purified urinary gonadotropins (GTs) recombinant is used for the treatment of infertile men with pituitary inefficiency. GTs are self-administered via subcutaneous injections. Combined therapy of (hCG), LH, FSH, GnRH and human menopausal gonadotropin (HMG) also found quite successful. Also, combination therapy with hCG and FSH for a period of couple of years increased testicular size, improved spermatogenesis and increased pregnancy rates to about 50%.[45] Dopamine agonists (bromocriptine and cabergoline) treat male infertility caused by hyperprolactinemia. Cabergoline has more ability to

normalize prolactin levels than bromocriptine. There is earlier improvement of sexual and gonadal function in men with prolactinoma, by cabergoline than bromocriptine.[46] Estrogen receptor antagonist and aromatase inhibitors (AInh) delay epiphysial maturation and increase testosterone levels. Clomiphene and tamoxifen are two most commonly used anti-estrogens for male infertility. Clomiphene increases the serum level of FSH, LH and testosterone. Both anti-estrogens and AInh affect estrogen's negative feedback and increase LH and FSH levels which then increase steroidogenesis and spermatogenesis. Excessive androgens result in feedback inhibition on gonadotropin secretion and suppression of steroids that consequently recovers spermatogenesis. Testosterone replacement therapy is also beneficial for the sexual parameters. Nasal testosterone gel is a testosterone replacement supplement that has minimal effect on semen parameters, unlike other testosterone replacement therapy.[45,46]

Pharmacological

To reduce the level of oxidative stress in infertile male different enzymatic and non-enzymatic antioxidants are used, that improves fertility by decreasing the production of ROS. Glutathione peroxidase (GP) is a significant agent in seminal enzymatic antioxidant pathway. It causes hydroperoxides reduction by glutathione. It combats oxidative attack, as its particular inhibition by mercapto-succinate results in enhanced sperm lipid peroxidation. Superoxide dismutase (SOD) inhibits lipid peroxidation in plasma membrane by catalyzing superoxide into HO and oxygen and thus increases sperm motility. It conjugates with GP and catalase prevents it from damaging the sperm.[47] Non-enzymatic antioxidants as vitamin C is found in the human seminal plasma, where it protects the spermatozoa against endogenous damage from ROS.[48] Vitamin E is a lipid soluble vitamin which increases motility of sperm by decreasing the level of malondialdehyde to normospermic level.[49] Inside mitochondria, carnitine facilitates the transportation and utilization of free fatty acids. It also decreases fatty acid oxidation by restoring the phospholipids composition of mitochondrial membrane. It provides energy to spermatozoa and directly involved in maturation and motility of sperms.[50] Selenium (Se) plays a vital role in normal spermatogenesis, testicular development and sperm motility. It protects DNA of sperm from oxidative damage.[51] Decreased levels of both CoQ-10 and ubiquinol in spermatozoa and seminal plasma are found in idiopathic infertile males and asthenospermia. Oral administration of CoQ-10 recovers fertility by inhibiting the production of hydrogen peroxide inside seminal fluid and improving sperm motility.[52] Zinc (Zn) has a significant role in normal sperm motility and production of adequate semen concentration. Its concentration is higher in seminal plasma as compared to other tissues, where it stabilizes cell membrane and sperm chromatin.[53] Clomiphene is an anti-estrogen can increase gonadotropins (FSH and LH) and stimulate spermatogenesis in idiopathic cases of male infertility. It works by inhibiting the estradiol negative feedback response to the hypothalamus, which results in a higher release of LH, causing higher testosterone levels but also resulting in higher estradiol levels.[54]

Surgical treatments

Surgical techniques are classified in to microsurgical, laparoscopic and conventional open methods. Meanwhile, others are inguinal, retroperitoneal, scrotal and sub-inguinal approaches according to access level. Radiological treatment is alternatively used with less invasiveness and significance to control small collaterals which are not detected while surgery. Laparoscopic varicocelectomy is an effective technique for the disease. Robotic surgery is another varicocelectomy option that has recently introduced.[55] Vasoepididymostomy (VE) and vasovasostomy (VV) are challenging microsurgeries as its success level depends on experience and skills of the surgeon. Improved fertility rates occur with VV compared to VE, a shorter time period from the original obstructive surgery, finding sperm at the time of vasovasostomy and if the nature of the original obstructive event was surgical rather than infectious. Men with increased FSH levels may require additional assisted technologies to achieve a pregnancy even after successful surgery.[56] Microsurgical epididymal sperm aspiration/testicular sperm extraction (MESA/TESE) is implemented with ICSI when it's not likely to perform VV. Testicular biopsy is performed if MESA is unable to produce spermatozoa or produce a very small spermatozoa count. MESA is a quick process without suturing or microsurgical dissection. In obstructive infertility patients, sperm can be retrieved from testis or epididymis while in non-obstructive infertility, TESE is the only useful technique. Midline prostatic and ejaculatory duct cysts are present in about 10.2% of all infertile men, suspected with low ejaculate volume, azoospermia or severe oligozoospermia, normal hormonal screening, normal secondary sexual characteristics, and dilated seminal vesicles on transrectal ultrasound examinations. Cysts are identified from a transrectal ultrasound and can be treated either with transurethral resection or by cyst puncture with aspiration with transrectal ultrasound.[57]

Assisted reproductive technologies (ART)

Male infertility can be managed by ART including ICSI, *in vitro* fertilization (IVF) and intra-uterine insemination (IUI). Most ART centres use ICSI as priority option for infertility. In ICSI, oocytes in metaphase-II phase are prepared by removal of corona radiata and cumulus mass with hyaluronidase. Then one sperm from epididymis, ejaculate or testis is injected by a micropipette into oocyte cytoplasm, which has already been immobilized under oil. During injection the cytoplasm is aspirated and injected, to activate oocyte and improve fertilization. As spermatozoa influences oocyte activation, spermatozoa immobilization is persuaded via distorting sperm tail between injection micropipette and petri dish bottom.[58] IVF includes

retrieval of multiple mature eggs from a woman and fertilized with a man's sperm outside the womb in a laboratory. Then, the fertilized embryos are implanted in the uterus after three to five days of fertilization. In zygote intra-fallopian transfer (ZIFT), the fertilized egg is directly transferred into the fallopian tube; whereas, in gamete intra-fallopian transfer (GIFT) a mixture of sperms and eggs is placed in the fallopian tube and fertilization occurs there. The ultimate ART currently available, ICSI, is similar to the IVF, but involves the use of a microscope and micropipette to inject a single sperm taken from the male partner directly into an egg from the female partner that has been surgically extracted. The fertilized eggs are implanted into the uterus of the female partner. IVF with ICSI (IVF/ICSI) also allows couples to become fertile. Literature has published offspring safety of IVF/ICSI. However, more study is required to determine risks associated with ART offsprings.[58]

Ethno-pharmacological treatment

Medicinal plants treat male infertility empirically as decoctions, extracts, fractions and semi-purified compositions. These products treat sperm, erection and libido dysfunctions. Various studies have reported pharmacological properties of different plants *in vitro* on cell lines and *in vivo* in animals. Ashwagandha (*Withania somnifera*), Kapikacchu (*Mucuna pruriens*), Shatavari (*Asparagus racemosus*), Bala (*Sida cordifolia*), Vidarikandha (*Ipomoea digitata*), Shilajit (Asphaltum), Pippali (*Piper longum*), *Buteasuperba*, *Curculigo orchioides*, *Cynomorium coccineum*, *Chlorophytum borivilianum*, *Epimedium koreanum*, *Eurycoma longifolia*, *Tribulus terrestris*, etc. are few examples of studied plants.[59,60] There is still requirement of clinical trials to explore molecular and cellular mechanism of these medicinal plants. Research on validation of these plants will expose a new approach in treating male infertility.

Lifestyle changes

Healthy lifestyle changes should be recommended with all male infertility patients, which include avoiding smoking, limiting or eliminating alcohol intake, adopting nutritious diet, weight loss measures, increased exercise, avoiding toxic lubricants during intercourse, reducing stress, eliminating drug use, avoiding exposure to pesticides and heavy metals (such as lead, mercury, boron, and cadmium), and eliminating any unnecessary chemical exposures. Other possible factors may also influence extent of infertility such as low body weight which overcomes by protein supplements, clothing selection that alter scrotal temperature, hot water, mobile telephone use, occupation options, pollution, life events (war and earthquake) and many more. Thus, modification of lifestyle may help couples to obtain better quality of life and improved possibility to conceive spontaneously or optimize their chances of conception.[31]

CONCLUSION

Etiological pattern of infertility varies in different parts of world. Male and female factors both are responsible for infertility. So, the partners should be counseled and investigated properly. Therefore, it is needed to look into the factors which are leading to such an alarming rise in male fertility and attempts should be made to control such factors in the near future. Male infertility needs to be studied and researched to truly understand its magnitude and prevalence to get a better insight into its etiology and treatment. Male infertility drastically affects a couple's social and psychological behavior. Therefore, it is essential to recover their reproductive health. There are different medical, social, genetic and environmental factors that cause male infertility. Pharmacological treatment is effective only when etiology of infertility is known. Based on literature, hormonal treatment is generally not used extensively for treating idiopathic infertility because of doubtful efficacy. In case of treatment failure and idiopathy, patients are recommended to try assisted reproductive technologies. Researchers have explored pharmacological properties of different medicinal plants against male infertility. However, they are not recommended by physician due to inadequate clinical data on their safety, efficacy and adverse effects. Thus, action is needed to improve national and international collaborative research in the field of male reproductive health to resolve the many remaining queries.

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