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A REVIEW ON MALE INFERTILITY

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ABSTRACT
The first blessing given by the Lord to the mankind is "Be fruitful and increase in number" Infertility signifies a severe emotional and common problem in the social order where importance is emotionally involved to have offspring. Infertility is viewed as 'male factor' when an alteration in sperm concentration and/or motility and/or morphology is present in at least one sample of two sperm analyses, collected between one to four weeks apart. Recently male infertility has been a focus of interest because of decline in the semen quality amongst young healthy men in worldwide; extensive public awareness and psychological health. The causes includes disarray in the control mechanism which includes pre-testicular; testicular and post-testicular factors. This review article states the anatomy/physiology of the male reproductive organ, aetiology, pathogenesis, diagnosis, laboratory tests, treatment and preventive measures of male infertility.

KEYWORDS: Male Infertility, Sperm Concentration, Motility, Morphology, Semen Quality, Testicular.

INTRODUCTION
"Be fruitful and increase in number" this was the first blessing given by the Lord to the mankind.[1] Ever since the commencement of documentation of history, the human has positioned a great importance on fertility.[2] Reproduction, continuity, maintenance through the descendants and the desire for self protection forms the fundamental need of family unit. Infertility represents a severe emotional and common problem in the social order where importance is emotionally involved to have offspring.[3] 50 to 80 million general populations suffer due to infertility on world level. The World Health Organization (WHO) has estimated about 8 to 10% of couples goes through this problem.[4] Male part is exclusively accountable with reference to 20% of unfruitful couples and contributory factor in 30 – 40%.[5] **"**Infertility is regarded as 'male factor' when an alteration in sperm concentration and/or motility and/or morphology is present in at least one sample of two sperm analyses, which comply with the World Health Organization (WHO) 1999 guidelines, collected between one to four weeks apart."[6] Infertility (clinical definition): "A disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse."[7] "A male who do not have biological offspring and presents for reproductive evaluation is labeled as "primary infertility," and one who is incapable to impregnate his partner but already has biological children is defined as "secondary infertility".[8]

Recently male infertility has been a focus of interest because of decline in the semen quality amongst young healthy men in worldwide; extensive public awareness and psychological health.[9] Significant among male infertility are the low sperm concentration (oligozoospermia); poor sperm motility (asthenozoospermia); abnormal sperm morphology (teratozoospermia). The causes includes disarray in the control mechanism which includes pre-testicular; testicular and post-testicular factors.[10] This article discuss about the anatomy and physiology of the male reproductive organ, aetiology, pathogenesis, diagnosis, laboratory tests, treatment and preventive measures of male infertility.

Table. 1: Nomenclature related to semen quality.[11]

Oligozoospermia	Total number of sperm below 15 $\times 10^6$ million / ml
Asthenozoospermia	Percentage of PR (progressively motile) sperm below 32 ml
Teratozoospermia	Percentage of normal morphological sperm below 4%
Aspermia	No semen (or retrograde ejaculation)
Azoospermia	No sperm in the ejaculate
Cryptozoospermia	Sperm absent in fresh preparations however observed in centrifuged pellet
Haemospermia	Presence of erythrocyte in ejaculate
Leukospermia	Presence of leukocyte in ejaculate beyond the threshold value
Necrozoospermia	Low percentage of live and high percentage of immotile sperm

Anatomy and Physiology

Reproductive organs[3]

The principal reproductive organs / gonads of the males are the testis, which produce sperm and as well secrete testosterone the male sex hormone. Prostate gland, seminal vesicles and bulbourethral glands are the accessory secretory glands which are involved in the secretion of seminal fluid.

Spermatozoa[3]

Spermatozoa are formed in the seminiferous tubules of the testis. Seminiferous tubules have many germ cells - spermatogenic cells and majority are in various stage of division. The outer most layer of spermatogenesis is in contact with the membrane which surrounds each seminiferous tubule and these are termed as spermatogonia (undifferentiated germ cells) which divides mitotically and provides source of germ cells constantly. Spermatogonia that move about from the membrane will increase distinctly in size. These large cells are termed as primary spermatocyte which undergoes meiotic division and form 2 secondary spermatocytes, which consecutively divide in to 2 spermatids. Spermatids ultimately transform into spermatozoa (sperm). Semen in general contains about hundred million sperms per milliliters, even if it takes one sperm only to fertilize an ovum. Length of the normal spermatozoa is about 50-70 µm. Head being oval shape with acrosomal cap which measures about 3 to 5 × 2 to 3 µm, a middle piece (short) and a thin long tail (length which is about 45 µm).

Semen[3]

Semen is composed of fluids from the seminal vesicles, vas deferens, prostate gland and bulbourethral glands (mucous glands). Major bulk of the fluid is from seminal vesicle (60%) which is last to ejaculate and also serves to wash the spermatozoa out of the ejaculatory duct and urethra. The protein concentration in seminal plasma is 35 to 55 mg/ml.

Sperm Quality and Semen Quality[12]

Sperms go throughout the ejaculatory ducts and mix with the fluids. Fructose secreted by the seminal vesicle is specially rich in semen and provide nutritonal energy to the spermatozoa. Seminal plasma is fundamental since it provides protective and nutritive environment for sperm to survive, mainly during the passage through the reproductive tract of female which direct to the fertilization. Most mammalian seminal plasma and sperm are greatly rich in zinc which is derived from the prostate. In addition to fructose, semen contains high level of Ca (calcium), Mg (magnesium) and Cu (copper) and they are bounded in ionic form.

To take in to concern six main criteria (Sperm volume, concentration, vitality, motility, morphology, and pH) as defined by WHO (world health organization – 2010) in grouping a semen into normal / subnormal.

Table. 2: Lower reference limits for normal semen (fifth centiles and 95% confidence intervals).[11]

Volume	**1.5 ml**
Concentration	>39million sperms/ejaculate > 15 million/ ml of semen
Vitality	> 58 %
Progressive motility **Total motility**	> 32% > 40%
Morphologically normal forms	> 4%
pH	> 7.2
Peroxidase positive leukocytes	(106/ mL) < 1.0
MAR test (motile spermatozoa with bound particles	< 50 %
Immunobead test (motile spermatozoa with bound beads	< 50 %
Zinc	> 2.4 (µmol per ejaculate)
Fructose	> 13 (µmol per ejaculate)
Neutral glucosidase	> 20 (mU per ejaculate)

Endocrine Interplay[13]

The complete and successful germ cell (male) growth depends on the balanced endocrine interaction of hypothalamus – pituitary - testis. Hypothalmus secretes gonadotropin releasing hormone (Gnrh) and bring forth the release of gonadotrophins FSH and LH from pituitary gland.FSH bind with receptors present in sertoli cells and will stimulate spermatogenesis. LH will stimulate the steroidogenesis (testosterone productio) in leydig cells which will act on sertoli cells and peritubular cells in seminiferous tubules and will stimulate spermatogenesis. Failure of pituitary in secreting FSH and LH may result in disturbance in testicle function which will lead to infertility. Testosterone, inhibin and estradiol will control the gonadotrophins secretion through feedback mechanism.

Primary hypogonadism is the disorder which directly affects the gonads. Secondary hypogonadism is due to defective secretion of pituitary gonadotropin. Testosterone, FSH and LH are the principal regulators of germ cell growth. Quantitative production of sperm generally needs the presence of these principal regulators. FSH directly acts on the seminiferous tubules while LH indirectly stimulate spermatogenesis via testosterone.FSH acts a key role in the stimulation of meiotic and mitotic DNA production in spermatogonia. Androgen receptors are sited on sertoli cells and peritubular myoid cells. The signal has to be transduced by these cells, mainly in sertoli cells, since these receptors are not expressed on germ cells.

Spermatogenesis[12]

Spermatogenesis is exactly an organized development by which diploid cells transform into spermatozoa which take place inside the seminiferous tubules. Three distinctive phases may be divided in the development of spermatogenesis and they are, **Profileration**: Increase in diploid spermatogonia; **Meiosis**: Spermatocytes into haploid spermatids and **Differentiation:** Round haploid spermatids are differentiated into elongated sperm with mid piece and tail at final stage of spermiogenesis.

Table. 3: Micronutrients function during Spermatogenesis.[12]

Calcium	Its important in sperm motility, acrosomal reaction and metabolism
Magnesium	Found in high concentration in the prostrate and is necessary for correct ejaculation
Potassiumand sodium	Have great role in acrosome reactions
Zinc	Involves in the ribonuclease activity and is highly active in the mitosis of spermatogonia and in meiosis of spermatocytes
Selenium [Antioxidant]	The high Selenium concentration in spermatogenesis is linked to its protective properties and to its related enzymes, like mitochondrial capsule protein in spermatozoa. If the Selenium content in seleno-proteins is low it likely decreases the chance of fertilization.
Folate	Folate has the antioxidant property which possibly inhibit apoptosis that results after DNA oxidative damage in spermatozoa
Nickel	Deficiency reduces the production of sperm in testis, count in epididymis and motility
Manganese	Manganese is suggested as the stimulator of pubertal growth

Table. 4: Functions of Vitamins during Spermatogenesis.[12]

Vit B12	Involves in DNA and RNA synthesis and will promote healthy development of seminiferous tubule
Vit B9	Promotes healthy spermatozoa and seminiferous tubule growth
Vit A	Differentiation of spermatogonia and in spermatid regulation
Vit C	Protects spermatozoa from the oxidative stress
Vit E	Improves the mitochondrial function

Table. 5: Biomolecules in Sperm Function.[12,14]

Lipids	Maintains sperm maturity, viability, function and fertility
Arginine	Precursor in the production of spermine, spermidine, putrescine and necessary in sperm motility
L-carnitine	Progression of sperm development, maturation and the maintenance of the quality
Tyrosine	Scavanges free radicals and improve the motility
Hyaluronan	Its the main protein derivative found to be in reproductive fluids and is involved in sperm motility and penetration
HSP-A1/A2 & A3	Concerned in the management of sperm motility and in sperm-oocyte binding
MCP- CD46	It is the complement regulatory protein and have role in protecting sperm from lysis in female reproductive tract and in interaction of sperm and oocyte
Neurotrophins (group of protein)	Plays role in the spermatogenesis and in the post- ejaculatory functions like motility, capacitation and acrosomal-exocytosis
Cholesterol	Secreted from the prostrate gland and is important in the protection of the sperm membrane integrity from environmental shocks by the chemicals/pollutants

Functions of Sertoli Cells and Leydig Cells.[12]
Sertoli cells, specifically nurse cell, lines the inner walls of the tubules and participate partially in the differentiation process and provide nutritional and structural support for developing germinative cells. Secretion of the sertoli cells facilitates the transportation of non-motile sperm from testis in to the efferent duct. Leydig cells (interstitial cells) are interspersed within the seminiferous tubule which is the main site of steriodogenesis that produce testosterone in testes and also play vital role in the maturation of sperm.

Capacitation and Fertilization.[12]
Spermatozoa have to be activated priorly to obtain the competence to fertilize the oocyte and this process of activation is defined as capacitation. The eventual organization of capacitation is within sperm membrane. Glycocalyx the outer surface of the membrane undergoes various biochemical alterations.Preprogrammed cellular derepression takes place which hyperactivate the sperm. The alterations include modifications in lipid and protein composition. Oviduct the microenvironment provides higher levels of bicarbonate than the epididymis and permits sperm capacitation. The capacitation needs electrolytes, metabolic energy sources (Ca2+) and protein sources like BSA (bovine serum albumin). To achieve fertilization perfectly and efficiently, it is essential for sperm to be progressive motile and the membranes should be intact.

AETIOLOGY

Y-chromosome micro-deletions.[14]
Microdeletions in long arm of Y chromosome leads in to failure of spermatogenesis and ejaculation. Paternal lineage Y chromosome are related with low count and motility. Deletions of the regions that underline the heterochromatin in Y chromosome lead to the morphological abnormalities.

Chromosomal abnormalities.[14]
Klinfelter's Syndrome is the common genetic abnormality found to be in 5% to 10% oligozoospermia peoples and is associated with failure of testicle and low count.

Anti-sperm antibodies (ASA).[14]
Anti-Sperm Antibodies are small proteins identified to deteriorate the fertility and semen quality through reducing acrosomal reaction, sperm motility, lysis of sperm, inhibiting the sperm penetration in to the cervical mucus and its capacitation.

Hormonal Disruption and Hormonal Imbalance.[4]
Testicular dysgenesis syndrome (TDS) - Congenital derangement in seminiferous tubulule structure and its function inextricably associated to inappropriate concentration of hormones (sex) at various stages of the life cycle which leads to male infertility.Testosterone deficiency will lead to the clinical condition hypogonadism. Abnormalities like reduced production of sperm and inhibition in the capability in fertilization take place in the male reproductive structure due to unbalanced action of the androgen during maturity. Copious amount of the circulating estrogens will suppress spermatogenesis and will adversely have an effect on male fertility.

Table. 6: Anatomical Abnormalities in male reproductive system.[4, 15]

Cryptorchidism	The testicles fails to descend into the scrotal sacs prior to birth.Abdominal testicles are not capable to maintain spermatogenesis since it needs the temperature less (2^{o}C) than the normal temperature of human for maturation of the spermatozoa to be functional, viable and fertilizable.
Varicocele	Collection of unusually swelled, dilated spermatic veins which drains the testicle. It may arise on both the side and most frequently on the left side. Varicocele will lower sperm quantity and quality and even shrinkage of the testicles.
Congenital anomalies	May be either rare with the localized defect in the vas deferens (proximal part) or with an complete abnormal growth
Epispadias	It is a congenital defect with abnormal curvature, shorter and wider size (penis) which will make the intercourse difficult.
Anomalies of the seminal vesicles	Abnormalities in number (fusion and agenesis), maturation (hypoplasia) and canalization (cyst)
Hypospadias	Uro-genital birth defect with abnormal urethral opening and it's the part of TDS which includes male infertility.

Alcoholism, Smoking[4,16]
Heavy and chronic alcohol toxication will have slow and progressive harmful impact. Will lead to moderate teratozoospermia which will be followed by the oligoasthenoteratospermia (OATS), then severe cryptozoospermia and finally azoospermia.

Smoking and the passive inhalation of cigarette smoking will reduce the spermatozoa count, morphology, motility, viability and fertilizing capacity by increasing the seminal-oxidative stress and DNA damage. Nicotine, the major constituent in smoke has the considerable impact on morphology and count. Burning up of more than twenty cigarettes per day showed elevation in seminal Cd (cadmium) level in smokers.

Club Drug[4,17]

MDMA (Ecasty), GHB (gamma-hydroxybutyrate), methamphetamine, ketamine, morphine, heroin, marijuana, rohypnol, caffeine, cocaine and poppers. These addictions are accountable for the deleterious effect on complete sperm structure. Chronic addiction to cocaine has deleterious impact on spermatogenesis and eventually fertility. Caffeine intake, probably through sperm DNA damage, might negatively affect the male reproductive function

Lifestyle[4,18,19]

Decline in fertility with the age is related with a decrease in the testicular weight, spermatozoa production and level of testosterone. Obesity and overweight will end in hypogonadism, higher scrotal temperature, defective spermatogenesis, decline in sperm concentration and motility and increased DNA damage of sperm. Mild to severe psychological stress and psycho pharmacological agents will decrease the testosterone and probably disrupt the spermatogenesis.

Table. 7: Pollution and Radiation[4]

Air pollution	Reduces sperm motility.
Textile dye	Decrease the weight of the reproductive organ
Pulp/paper-mill	Reduces testis weight, count, motility and testosterone.
Ozone (Oxidant)	Reduce the sperm density by means of oxidative damage pathway.
Radio-frequency electromagnetic waves (RF-EMW)	Leads to oxidative stress in semen that negatively affects sperm and impairs fertility.
Chemotherapies and radiation	Utilized in the cancer treatment will severely affect sperm production

Diseases.[4]

Mumps, sexually transmitted diseases, tuberculosis and febrile illness will cause temporary sperm decline.

Table. 8: Antispermatogenic Plants.[4, 20]

Azadirachta indica	Leaves are powerful spermicide
Carica papaya	Seeds affect cauda epididymis sperm motility, count and viability
Momordica charantia	Seeds have antisteroidogenic, antispermatogenicand androgenic properties
Embelia ribes	Spermicidal anti- androgenic activites.

Infections[3,20,21]**:** Antisperm antibodies presence is regarded as the indicator of chronic infections. *Chlamydia trachomatis* is the general cause of prostatitis and epididymitis. *E.coli* in the semen lowers the motilty of the sperm. *Candida albicans* exert its inhibition in sperm motility. *Ureaplasma urealyticum* have a negative effect on male fertility. *Mycoplasma hominis will* cause sperm tail abnormalities.

Table. 9: Occupation and chemicals[4,20,22,23]

Lead workers	Showed decreased spermatozoa count and decreased motility
Welders	Exposed to chromium and will have reduced sperm quality.
Exposure to copper	Associated to oligo/terato/ astheno- zoospermia
Professional drivers	Impairment of spermatogenesis
Pesticide/agricultural workers	1-2-dibromo-3-chloropropane and nematocide may affect spermatogenesis.
Formaldehyde	Leads to male sterility
Boric acid	Reproductive toxicant that reduces the testosterone
Aluminium	Reduces the weight of the reproductive organs and will impair fertility
Ammonium metavanadate	Toxic effect on reproduction

Table. 10: Diet Factors.[4,20]

Gossypol	The toxic residue in cotton seeds inhibits sperm function and being examined as male birth control pill.
Estrogen and diethyl-stilbestrol	Broadly used in poultry, livestock and dairy industries.Increased exposure is responsible for prenatal testicular damage, post-natal testicular function depression and spermatogenesis.
Soyabeans-(isoflavone-phytoestrogens)	Long term use willl have adverse effect on the growth and function of male reproductive system will result in decrease count and fertility

Scrotal temperature[20]**:** Sperm needs temperature for about 3 to 4°C less than the normal temperature of the body for active production. This aspect is supported by the decrease sperm count in the pathologies like cryptorchidism, varicocele, patients constrained to wheel chair as in paralysis, drivers and in prolonged sauna exposure.

Table. 11: Therapeutic drugs[4,20]

Antineoplastic agents	Chlorambucil cyclophosphamide, busulphan and methotrexate
Drugs-Schizophrenia	Phenothiazines like thioridazine and chlorpromazine causes hypospermatogenesis, hyperprolactinaemia and impotence
Anti-bacterial drugs	Furacin and nitro furantoin significantly affect the spermatogenesis. Sulfasalazine causes oligozoospermia and reduced sperm motility Tetracycline derivatives will cause decrease sperm index Macrolide group – Neomycin, erythromycin and spiramycin affect fertility Penicillin group- Ampicillin, penicillin-G and dicloxacillin causes spermatogenic arrest. Aminoglycosides (gentamycin and neomycin) will alter the testicular functions..
Anti-malaria drugs	Quinine, chloroquine and quinacrine will inhibit leydig cell and steroidogenesis. Chloroquine will reduce the sperm motility. Pyrimethamine (prophylactic drug) causes spermatogenic arrest. Quinine causes morphological change in the testis and will suppress the spermatogenesis.
High blood pressure monitoring drugs	CCB (calcium channel blockers) and CNS depressant drugs will suppress the spermatogenesis
Drugs-Gastric problems	Will interfere in the production sperm and ejaculation
Chemotherapeutic agents	Will causes oligozoospermia and even will lead to azoospermia

Oxidative stress[24,25,26]

Among various causes, oxidative stress (OS) has been attributed to have an effect on the fertility status and physiology of spermatozoa.Many pathological conditions such as cryptorchidism, infections in the male reproductive tract, varicocele, exposure to drugs, environmental factors, aging and smoking have oxidative stress as a common component. The time durability of spermatozoa in epididymis is longer in oligozoospermia which results in higher exposure to reactive oxygen species.

Pathogenesis[14,4,20,19,27]

Condensation of sperm chromatin may be changed by exposure to the OP (organophosphorus) with higher susceptibility to denaturation of DNA and will affect the reproductive system adversely through protein phosphorylation mechanism.Klinefelter's syndrome (47 XXY) is the common chromosomal disorder that affects the growth of the testicle. Chromosomal abnormalities may interrupt cell division and the sperm production. Spermatogenic break-down will result due to Y chromosome (related to spermatogenesis) microdeletion. Genes required for the process of spermatogenesis are situated in azoospermia factor (AZF) region of Y chromosome. In azoosperimia deletion are related to the six azoospermia factor regions. In oligozoospermia deletions doesn't takes place inside AZF region and it takes place outside the region of deletion. Robertsonian translocations the major sex chromosomal aberration affects the structure and count in the semen and also several degrees of variation in the sperm. This take place when the two chromosome (acronetic) mingle together to form single chromosome. This will result in the abnormal dicentric chromosome formation which will modulate the count, motility and morphology. Reciprocal translocations are a mutual exchange of information between the two chromosomes. This leads to the unbalanced sperm and their morphology. This results in severe oligozoospermia and azoosperimia in males.

Mast cells release inflammatory mediators which directly inhibit sperm motility in potential reversible mode.Excess sugar in the blood will affect the quality of sperms directly and will gradually cause male infertility. In chronic diabetes, autonomous nervous system function gets damage which will result in the problems related to ejaculation and erection. It will directly effect fertility by causing sperm DNA damage. Germ cell tumors will produce β-HCG (β–human chorionic gonadotropin) and AFP (α-fetoprotein). The increased β-HCG of the intra-testicular production of estradiol decreases/ inhibits spermatogenesis in contra-lateral testis and increased AFP will cause oligozoospermia. Mumps, TB (tuberculosis) and STD (sexually transmitted diseases) may affect production of sperm through inflammation and male genital tract obstruction. *Chlamydial* infection may damage sperm parameters, acrosome reaction capacity and proportion of the DNA fragmentation, which will affect male fertility adversely. ASA (anti sperm antibodies) will impair fertility and quality of semen through impairing acrosomal reaction, the complement cascade will be invoked which will result in sperm lysis, motility inhibition, inhibits sperm penetration and capacitation. Sperm antibodies will impede the reproductive function and depends on where the antibodies are found as well as where the corresponding antigen located on sperm surface.

Lead and cadmium are considered to decrease the gonadotrophin binding which diminish the hormone secretion and will reduce the quality of the semen. Bisphenol A (BPA) the toxicant released in the environment in the period of industrialization affected the spermatogenesis by modifying the gene expression that is predient to the formation of sperm and also affects steroidogenesis by changing the effect of the epigenetic.

Estrogen, its derivatives and diethylstilbestrol (synthetic analogs) are responsible for depression of spermatogenesis. Exogenous estrogens have impact on fetal growth by inhibiting the sertoli cell development which will determine the life long capability for sperm production. Smoking has negative correlation with cadmium in the blood and density of sperm. Smokers show the presence of elevated estradiol in serum, more leucocytes in semen, low sperm density, higher DNA fragmentation in sperm and decrease sperm penetration. Nicotine modifies the hypothalamic pituitary axis function which will affect the growth hormone, vasopressin, cortisol, oxytocin release then inhibits the luteinizing hormone and prolactin release which have negative impact on spermatogenesis. The testis is extremely susceptible to ethanol since it crosses the blood testis barrier and will depress the spermatogenesis. Cocaine will induce injury in the testicle which could be associated to apoptosis and will involve the mitochondria-associated pathway or fasmediated pathway.

Cocaine exposure will cuase the cytochrome release from mitochondria and following activation of caspase 9 and 3 in the testes and will play a important role in the cocaine induced germ cell loss or apoptosis in the testicle. There will be increase in the DFI (sperm DNA fragmentation index) with age. In obesity SHBG (sex hormone binding globulin) will be decreased and free testosterone will be increased and results in the conversion of testosterone to estradiol in the adipose tissue. Decrease in the testosterone estradiol ratio will contribute to the spermatogenesis impairment. HPA (hypothalamus-pituitary-adrenal) axis controls spermatogenesis and reported to be involved in stress which raises the cortisol hormone levels and which will result in the involution of the testicle followed by fall in the testosterone. Stress is related to enhance ROS generation.

Oxidative Stress as a common component of pathophysiological mechanisms[7,24]

Imbalance between the reactive oxygen species production and ability of the biological system to detoxify/repair the damage due to the reactive intermediates is known as oxidative stress.The production of reactive oxygen species by sperm is the normal physiological process. The imbalance between this ROS production and the scavenging activity is unfavorable to the sperm and is related with male infertility. The main source of production of ROS in semen is immature sperms and leukocytes. Spermatids and matured sperm are considered to be extremely sensitive to reactive oxygen species because sperm membranes are chiefly rich in the poly-unsaturated lipids. Inhibition in spermatogenesis will lead to abnormal sperm and give way to more ROS and which may overpower and reduce the antioxidant defense mechanism and end in oxidative stress. Overload in free radical generation will frequently cause an error in the spermiogenesis which results in release of sperm from germinal epithelium with abnormal high level of the cytoplasmic retention: ROS alters the membrane integrity and will harm sperm morphology and motility and will lead in sperm death. The concentration of the marker lipid peroxidation MDA (malondialdehyde) was found to be twice as high in spermtozoa pellet suspension in asthenozoospermic and oligoasthenozoospermic males.

Diagnosis

Fertility History[28]

Infertility duration; childhood illness and problem in the development; diabetes, cancer, respiratory infections and previous surgery; sexually transmitted diseases; exposure to toxins, chemicals and radiation; medication history and family history related to reproductive problem.

Developmental History[29]

Cryptorchidism; orchiopexy (to treat cryptorchidism); testicular trauma or torsion; pubertal development timing and mumps.

Medical History[29]

Diabetes; fever/viremia; prostatitis or pyospermia; primary ciliary dyskinesia (immotile cilia syndrome); chronic upper respiratory infections (affects sperm motility); hormonal abnormalities-thyroid disorder, elevated estrogen and hyperprolactinemia; urinary tract infectionsand sexually transmitted disease

Past Surgical History and Cancer Treatments[29]

Retroperitoneal and pelvic surgery will impair ejaculation. Testicular cancer may be present with male infertility before or after the treatment.50 percentage of testicular cancer will affect sperm density before chemotherapy. Chemotherapy in lymphoma, sarcoma and leukemia will cause permanent sterility after treatment.

Physical examination[28,29,30]

Cremaster reflex: Intact reflex indicates integrity of sensory and the motor nerves.

Inspecting the Pubis: Hair will be more/less abundant. Triangular shape pattern with no vertical extension will indicate hormonal disorder.

Inspecting the Penis

Size, symmetry, color and hair distribution; skin lesion, excoriations, warts, abrasions and tumors; **Phlebitis** - Tender/inflamed/nodular veins; **Peyronie disease** - Penile curvature in erection; Ulcer (Balanitis, granuloma inguinale, chancroid, herpes genitalis, primary syphlis or penile carcinoma); **Urethral meatus:** Erythema, discharge, vesicles, plaques, pustules and intraurethral warts; Urethritis or blockage in urethra (incontinence, dribbling) which will indicate urethral carcinoma or stricture and **Hypospadias** (incorrect position of urethral opening).

Inspecting the Scrotum
Size and configuration; fungal or bacterial infections and skin lesion; swollen area in the scrotum due to hernia in which peritoneum or portion of bowel will protrude into inguinal canal/scrotum which causes asymmetry; asymmetrical swelling may also be a sign of a varicocele, tumour and hydrocele and Scrotal thermography test to see the scrotal temperature.

Palpating the Scrotal Contents
Srotum (each half) should be checked for the presence of testicle (large ovoid mass); Epididymis (Ridge of tissue that lies vertically on postero-lateral surface of ovoid mass) and Spermatic cord (Firm, non-tender column of the blood vessel and tissue ascends through and leaves the scrotal sac near to the groin).

Testicle
Examination for cryptorchidism; Examination for normal size - 2.5 to 5 cm, consistency, contour and tenderness; Nodular, very firm, or tender testis indicate cancer; Small and abnormal soft testis will indicate testicular atrophy or endocrine disorder; Testicle could be measured with orchidometer. Detrioration in spermatogenesis frequently accompanied with small volume testicle. Normal volume is 20 ml and Smaller size and soft testis along with low sperm count strongly related with problem in sperm formation. Normal testis with low count may suggest probable obstruction.

Epididymis
Acute epididymitis: Enlarged and tender epididymis when compared with the other side; **Epididymo orchitis:** Testis and epididymis could not be distinguished from each other in palpation. They are very tender and scrotum is generally inflamed; chronic and painless induration of epididymis will indicate schistosomiasis (bilharzia), tuberculosis, or non-specific chronic epididymitis; cystic mass near to the upper pole of testis which are separated from the testis and epididymis are generally spermatoceles that contain milky, thin fluid and sperm.

Spermatic cord: Swollen region in the spermatic cord will be cystic (hernia or hydrocele); Solid (rare connective tissue tumour or lipoma); filariasis- Diffuse swelling/ induration; varicocele and absence of vas deferens or Tuberculosis

The rectal examination
Warts, hemorrhoids, lesions, scars from trauma, mucous discharge and anal bleeding; tenderness in the prostate will indicate acute or chronic prostatitis and prostate gland nodules (Cancer or BPH)

Laboratory Tests
Semen analysis[11]
Collection of semen for diagnostic or research purposes: The sample is supposed to be taken through masturbation and should be ejaculated into a wide mouthed, clean, glass or plastic container (non-toxic for sperm). The container must be in ambient temperature of 20°C - 37°C. The container must be placed on the bench or incubator (temp-37°C) when the semen liquefies. Incomplete sample especially the first which is rich in sperm will be missing. And in that case second sample must be taken, again after 2-7 days abstinence period.

Liquefication: At room temperature the sample will normally liquefies within 15 mts, though rarely it will take up to 60 mts or more. Normally liquefied sample will contain jelly like granules (i.e- gelatinous bodies) which will not liquefy but these do not show any clinical significance. Presence of the mucus strands will interfere with the semen analysis.

Semen viscosity: High viscosity will interfere with sperm motility, concentration, biochemical markers and detection of antibody coated sperm.

Appearance of the ejaculate: Normal semen after liquefication will have homogeneous, grey and opalescent in appearance. It will be less opaque when the concentration of sperm is very low and also the colour will be different. In haemospermia the colour will be red-brown; and yellow colour in jaundice or taking certain drugs and certain vitamins.

Semen volume: Semen volume is contributed principally by seminal vesicles and prostate gland and a small amount from bulbourethral glands/epididymides. Low volume is the feature of ejaculatory duct obstruction or congenital absence of vas deferens (bilateral), this is the condition in which seminal vesicles are developed poorly. Low volume may also be due to collection problem, retrograde ejaculation (partial) or androgen deficiency. High volume will be a sign of active exudation in active inflammation of accessory organs.

Semen pH
The pH exposes the balance between the values (pH) of different accessory gland secretions (alkaline seminal vesicular and acidic prostatic secretion). pH less below 7.0 with low semen volume and low sperm count will denote obstruction in the ejaculatory duct or congenital absence of vas deferens (bilateral), this is the condition in which seminal vesicles are developed poorly.

Aggregation of spermatozoa: The adherence of immotile sperms to each other or motile sperms to mucus strands or non sperm cell or debris.

Agglutination of spermatozoa
Agglutination in particular refers to the motile sperms which stick to each other (head to head, tail to tail or mixed way). Agglutination implies the presence of anti sperm antibodies. Severe agglutination may affect the evaluation of sperm motility and sperm concentration.

Sperm motility

Progressive motility (PR): Actively moving sperm, linearly or in large circle, and with regardless speed; **Non-progressive motility (NP):** Other type of motility with absence in progression, e.g. flagellar force that hardly displacing the sperm head, or once a flagellar beat will be observed and swims in small circles; **Immotility (IM):** No motility and **Total motility:** Progressive motility (PR) + Non-progressive motility (NP)

Sperm vitality

It is clinically essential to identify whether immotile sperms are dead or alive. Vitality results must be evaluated with motility results. Presence of large percentage of vital but immotile sperm cells will indicate flagellum structure defect. High proportion of immotile / non viable sperm cells (necrozoospermia) will indicate epididymal pathology related sperm numbers.

Sperm concentration

Sperm concentration: Number of sperms per unit volume of the semen and **Total sperm number**: Total number of sperms in the entire ejaculation

The concept of normal spermatozoa

Sperm consist of head (with neck) and tail (with mid and principal piece). For a sperm to be referred normal, both the head and the tail should be normal.

Classification of abnormal sperm morphology

- **Head defects:** Large/small, pyriform, tapered, round, vacuolated, double heads, amorphous or any of this in combination.
- **Neck and midpiece defects:** Insertion (asymmetrical) of midpiece into head, abnormal thin thick or irregular, sharp bent or any of these combination.
- **Principal piece defects:** Mutiple, short, smooth hairpin bends, broken, sharply angulated bends, coiled, irregular width or any of this combinations.

Cellular elements other than spermatozoa

Epithelial cells from genito-urinary tract and leukocytes and immature germinative cells, and the latter two is together referred as round cells. Germ cells may comprise of round spermatids, spermatocytes, and rarely spermatogonia. Non sperm cells in ejaculation may indicate damage in the testicle (immature germ cells), efferent duct pathology (ciliary tufts) or accessory gland inflammation (leukocytes).Increased leukocytes (pyospermia, leukocytospermia) is related to infection and poor quality of sperm. Leukocytes may impair motility and DNA integrity by means of oxidative attack.

Test for antibody coating of spermatozoa[11,28]

Sperm antibodies may also be present without agglutination; likewise agglutination may be caused other than spermtozoa antibodies. Anti-sperm antibodies belong to two immunoglobulin - IgA and IgG. Blood test for antisperm antibodies may be carried out in man with reversed vasectomy and yet cannot impregnate the women or semen analysis showing clumping of sperms. ASA's will also be developed after injury to testis or genital infection. The two recognized test to assess the presence of antisperm antibodies are: The Immunobead test and Sperm Mar test.

Biochemical assays[11]

Secretory capacity of the prostate: Zinc, acid phosphatase and citric acid

Secretory capacity of the seminal vesicles: Fructose and prostaglandin

Secretory capacity of the epididymis: L-Carnitine, neutral glucosidase and GPC

Low fructose is the feature of ejaculatory duct obstruction, partial retrograde ejaculation, congenital absence of vas deferens (bilateral) and androgen deficiency.

Hormonal Levels[28, 29]

FSH, LH, testosterone, PRL and estradiol (E2)

Hormone test are specified particularly when sperm concentration is below 10 million per milliliter.

Testosterone and FSH levels are generally assesed first. When level of testosterone is low then LH is measured.

Other sperm function tests[28]

Post-Ejaculatory Urine Sample: Urine sample is asessed to identify sperm following the ejaculation which will indicate retrograde ejaculation and also can be used to test infections.

Postcoital Test (Cervical mucus penetration test)

To evaluate the effect of woman's cervical mucus to man's spermatozoa.

Ultrasound[28]

To find out the testis size or to detect tumors, cysts, tumors, varicocele or abnormal blood flow

Genetic Testing[28]

Tested in men with severe sperm deficient and with no obstruction.

Testicular biopsy[28,29]

To distinguish between maturation arrest and obstruction. When mature sperms are identified in biopsy it can be cryopreserved for IVF/ICSI cycle.

Sertoli one syndrome (sperm producing cells in testis is found to be absent).

Fertilization Tests[28]

- **The Hamster Test (Micro-penetration assay test):** Sperm samples are used to fertilize the hamster eggs in which covering will be removed to allow sperm penetration. It is used to determine the best ART options for infertility men.
- **The Human Zona Penetration Test:** The test makes use of spermtozoa to fertilize the dead human eggs,

usually taken from the ovary. Results will give the same suggestion like hamster test.

- **Acrosome Reaction Test:** Induces the capability of the spermatozoa enzyme rich acrosome covering to dissolve.

Investigative Tests[28]

Additional sophisticated lab test to measure the sperm function can also be carried out. They will assess the factors like level of cell damaging oxidants and computer aided sperm motility analysis.

Table. 12: Differential Diagnosis.[29]

Oligozoospermia Defect in sperm count	In count below 10 million /mL, FSH and testosterone should be assessed. In count below 5 million sperm per mL, karyotype or Y chromosome microdeletion test will be considered. Elevated FSH will signify primary testicular defect. Varicoceles are general cause of less sperm density.
Asthenozoospermia Defect in sperm motility	Varicocele and antisperm antibodies will be the cause for this defect.
Teratozoospermia Defect in sperm morphology	The major cases are idiopathic.Varicoceles and temperature influence to spermatogenesis is also potential cause**.**
Azoospermia Lack in sperm production	Non-obstructive azoospermia indicates lack in sperm production Obstructive azoospermia indicates failure in delivering the sperm to ejaculate, due to ductal obstruction. The information on size of testis and presence of vas deferens indicates the diagnosis. CBAVD (Congenital bilateral absence of the vas deferens) an obstructive azoospermia will be diagnosed through physical examination.
MultipleSemenAbnormalities Oligoasthenoteratozoospermia The defect in sperm count, motility and morphology	Most general cause is varicocele. Additional causes include environmental toxins, medications and cryptorchidism. In extreme cases (< 1 millionsperms/mL) there is increased occurrence of obstruction of male genital tract or genetic abnormalities.
Defects in Isolated Semen Parameters (Aspermia) No seminal fluids	May be due to retrograde ejaculation. Common causes include neurogenic abnormalities (spinal cord injury), multiple sclerosis, diabetes and use of α-blockers. Retroperitoneal surgery which includes the pelvic surgery and retroperitoneal lymph node dissection, may also cause impaired ejaculation.

Treatment

Antioxidants[11,20,31,32]

Antioxidants like vitamin C and E, lycopene, β-carotene, zinc, folic acid, selenium, lactoferrin, papaya and lipophilic diet will improve sperm parameters.Carnitine (water-soluble antioxidant) obtained from human diet will protect DNA of sperm from free radical damage and apoptosis and will provide primary fuel for its motility. Polyunsaturated fatty acid, chiefly omega-3 fatty acids-docosahexanoic acid may be the most important sperm membrane fluidity determinant. Coenzyme Q10 plays potential rolein managing male infertility (significant improvements in sperm concentration, sperm motility).

Hormone therapy[28,33]

In hypogonadism and gonadotropin deficiency GnRH (Gonadotropin-releasing hormone) will be useful. GnRH may also be helpful in restoring the sperm production following to chemotherapy treatment.Sperm production rarely respond to the low doses of testosterone; estrogen and testosterone; clomiphene citrate (Clomid); menotropins (Repronal, Pergonal), human follicle-stimulating hormone (Gonal-F, r-hFSH) and human chorionic gonadotropin (hCG). An enzyme, aromatase inhibitors block aromatase, is the main source of estrogen which present in various main body tissues. They are letrozole. (Femara) and anastrozole (Arimidex) whih will be helpful in male infertility related to unusual testosterone-to-estrogen ratios. Goal is to optimize the LH level to stimulate Testosterone production from Leydig cells; FSH level to stimulate the sertoli cells-spermatogenesis and eliminate any excess estrogen.

Nonhormonal Agents[28]

Bromocriptine – Parlodel is given in male infertility related with excess prolactin harmone. Infections that affect male fertility will be treated with the antibiotics. Men with less count will be treated with antihistamines which will block mast cells.

Treatment for Antisperm antibodies[28]

IUI (intrauterine inseminations) to avoid the cervical mucus or IVF (In Vitro Fertilization) in any case of antibody type. Antisperm antibodies can be treated with steroids.

Surgical Procedures[28]**:** Ejaculatory duct obstruction may be treated by scraping or excising the part where prostate gland enclose the urethra and through reconstructing the duct. Undescended testicles (in young boy) will be repositioned through surgery to prevent later on infertility.

Table. 13: Assisted Reproductive Technologies.[34,35,36]

Artificial/Assisted Insemination	Sperm by concentrating before insemination or by sperm donation is introduced in to the uterus. Used to treat male infertility with weak sperm, low count or total testicular failure to produce sperm.
In vitro fertilization (IVF)	Fertilization takes place outside the body. Used in when fallopian tubes of the women is blocked or man producing too little sperms.Women are treated with the drugs that will cause to produce multiple eggs from the ovaries and once matured, eggs will be removed. Eggs are put in to the dish in a lab along sperm for fertilization. Later than 3-5 days, healthy embryos will be implanted in to the uterus.
Zygote intrafallopian transfer (ZIFT) or Tubal Embryo	Transfer is alike to IVF. Fertilization takes place in the lab. Very young embryo will be transferred in to the fallopian tube.
Gamete intrafallopian transfer (GIFT)	Transferring of sperm and eggs in to the fallopian tube. Fertilization takes place inside the woman's body.
Intracytoplasmic sperm injection (ICSI)	Used in men with serious sperm problems or older couples or in failed IVF efforts.A single sperm will be injected in to the matured egg. After that the embryo will be transferred to uterus/fallopian tube
Donation of Gamete and Embryo	In assisted insemination or IVF or its variants, the issue of egg, sperm or embryo donation becomes applicable. Sperm, eggs and embryos may be frozened through cryopreservation and these will be thawed later and will be offered for use to anybody who needs them, predominantly women or men with diminished egg/sperm.

Lifestyle Changes[28]

Smoking should be avoided; overweight men can make an effort to reduce weight; Should take adequate rest; regular and moderate exercise; Stress reduction techniques will develop fertility; tight underwear cause no hazard to fertility, however there will be no harm in looser clothing and avoid hot showers and steam rooms to prevent over heating to testis

Preventive measures[3]

Sex education, public health and hygiene; control of STD (sexually transmitted diseases); rectification of nutritional deficiencies; early on treatment for abnormal conditions; prevention of the damage from chemical, trauma,. heat and x-ray exposure and cotton seed oil, hydrogenated oils, saturated fats, trans-fatty acids, palm and coconut oil should be avoided.

CONCLUSION

The manuscript discussed about the anatomy/physiology of the male reproductive organ, aetiology, pathogenesis, diagnosis, laboratory tests, treatment and preventive measures of male infertility. This review article will be useful for researchers to figure out male infertility and to initiate with further research.

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