MALE INFERTILITY – CAUSES, MANAGEMENT AND THEIR DIAGNOSTIC TESTS: A REVIEW

A.N.Merekar[*1], S.R.Pattan[2], B.S.Kuchekar[3], S.B. Bhawar[4] , R.B. laware[1], S.A.Nirmal[5]. S.K.Parjane [2]and V.M.Gaware[2]

[1]Department of Pharmaceutics, Pravara Rural College of Pharmacy, Pravaranagar, A/P-Loni (413736), Tal- Rahata, Dist.-Ahmednagar, Maharashtra, India.
[2]Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, A/P-Loni (413736), Tal- Rahata, Dist.-Ahmednagar, Maharashtra, India.
[3]Department of Pharmaceutical Chemistry, M.I.T College of Pharmacy, Pune, Maharashtra, India.
[4]Department of Pharmacology, Pravara Rural College of Pharmacy, Pravaranagar, A/P-Loni (413736), Tal- Rahata, Dist.-Ahmednagar, Maharashtra, India.
[5]Department of Pharmacognosy, Pravara Rural College of Pharmacy, Pravaranagar, A/P-Loni (413736), Tal- Rahata, Dist.-Ahmednagar, Maharashtra, India.

Summary

Infertility will be the most common disorder in physiological function, of the body in future. People working at IT, PRO, BPO and other Silicon communication Medias are found be the major affected of infertility of either sex. Male infertility is also the major problem for reproduction and at pregnancy procedures. The infertile couple requires the counseling, effective medical aid and guidance. In this regard we have attempted to review the topic for infertility, the causes and their relative diagnostic tests. The survey is aimed to get the healthy future offspring's of human being.

Key words: Infertility, hyperprolactinemia, variocoele, orchiectomy.

***Address for correspondence** to: Prof.Abhijit.Narayanrao.Merekar, Department of Pharmaceutics, Pravara Rural College of Pharmacy, Pravaranagar, A/P-Loni (413736), Tal- Rahata, Dist.-Ahmednagar, Maharashtra, India. Phone-+919665501229 *E-mail*-anmerekar@yahoo.co.in

Introduction

Infertility is a disease of the reproductive system that impairs one of the body's most basic functions: the conception of children. Conception is a complicated process that depends upon many factors:

1. The production of healthy sperm by the man and healthy eggs by the woman
2. Unblocked fallopian tubes that allow the sperm to reach the egg
3. The sperm's ability to reach the egg
4. The sperm's ability to fertilize the egg when they meet
5. The ability of the fertilized egg (embryo) to become implanted in the woman's uterus
6. A good quality embryo

For the pregnancy to continue to full term, the embryo must be healthy and the woman's hormonal environment adequate for its development. When any one of these factors is impaired, infertility can result. A couple is considered infertile if the woman does not conceive a child after

one year of unprotected, well-timed intercourse or she has been unable to carry a pregnancy to a live birth. The diagnosis is sped up for women over 35 treatments are normally recommended after six months of trying to conceive. Infertility is not a "woman's" problem. It is a medical problem of the male or female reproductive system. In about one third of cases, the cause is traced to the woman, another third of cases are traced to the man. The rest are caused by unknown factors or a physiological incompatibility. Infertility is not only a physical condition--it is an emotional and social condition with accompanying feelings and issues. The infertile couple needs support and consideration from the treatment team, friends, family, and each other.[1]

Infertility History [2]

History of Infertility	**Medical History**	**Gonadotoxins**
Duration Prior pregnancies Present partner Another partner Previous treatments Evaluation and treatment of wife	Systemic illness (i.e., diabetes mellitus, multiple sclerosis Previous/current therapy	Chemicals (pesticides) Drugs (chemotherapeutic, cimetidine, sulfasalazine, nitrofurantoin, alchohol marijuana, androgenic steroids) Thermal exposure Radiation Smoking
Sexual History	**Surgical History**	**Family History**
Potency Lubricants Timing of intercourse Frequency of intercourse Frequency of masturbation	Orchiectomy (testis cancer, torsion) Retroperitoneal injury Pelvic injury Pelvic, inguinal, or scrotal surgery Herniorrhaphy Y-V plasty, transurethral resection of the prostate	Cystic fibrosis Androgen receptor deficiency Infertile first-degree relatives
Childhood & Development	**Infections**	**Review of Systems**
GU congenital anomalies Undescended testes, orchiopexy Herniorrhaphy Y-V plasty of bladder Testicular torsion Testicular trauma Onset of puberty	Viral, febrile Mumps orchitis Venereal Tuberculosis, smallpox (rare)	Respiratory infections Anosmia Galactorrhea Impaired visual fields

Table no.-1 History of Infertility

The Causes of Male Infertility:

Male infertility has many causes--from hormonal imbalances, to physical problems, to psychological and/or behavioral problems. Moreover, fertility reflects a man's "overall" health. Men who live a healthy lifestyle are more likely to produce healthy sperm. The following list highlights some lifestyle choices that negatively impact male fertility--it is not all-inclusive:

1. Smoking--significantly decreases both sperm count and sperm cell motility.
2. Prolonged use of marijuana and other recreational drugs.
3. Chronic alcohol abuse.
4. Anabolic steroid use--causes testicular shrinkage and infertility.
5. Overly intense exercise--produces high levels of adrenal steroid hormones which cause a testosterone deficiency resulting in infertility.
6. Inadequate vitamin C and Zinc in the diet.
7. Tight underwear--increases scrotal temperature which results in decreased sperm production.
8. Exposure to environmental hazards and toxins such as pesticides, lead, paint, radiation, radioactive. substances, mercury, benzene, boron, and heavy metals
9. Malnutrition and anemia.
10. Excessive stress
11. Modifying these behaviors can improve a man's fertility and should be considered when a couple is trying to achieve pregnancy. [3, 4]

Hormonal Problems:

A small percentage of male infertility is caused by hormonal problems. The hypothalamus-pituitary endocrine system regulates the chain of hormonal events that enables testes to produce and effectively disseminate sperm. Several things can go wrong with the hypothalamus-pituitary endocrine system:

1. The brain can fail to release gonadotrophic-releasing hormone (GnRH) properly. GnRH stimulates the hormonal pathway that causes testosterone synthesis and sperm production. A disruption in GnRH release leads to a lack of testosterone and a cessation in sperm production.
2. The pituitary can fail to produce enough lutenizing hormone (LH) and follicle stimulating hormone (FSH) to stimulate the testes and testosterone/sperm production. LH and FSH are intermediates in the hormonal pathway responsible for testosterone and sperm production.
3. The testes' Leydig cells may not produce testosterone in response to LH stimulation.
4. A male may produce other hormones and chemical compounds which interfere with the sex-hormone balance. [4, 5, 6]

The following is a list of hormonal disorders which can disrupt male infertility:

Hyperprolactinemia	Elevated prolactin--a hormone associated with nursing mothers, is found in 10 to 40 percent of infertile males. Mild elevation of prolactin levels produces no symptoms, but greater elevations of the hormone reduce sperm production, reduces libido and may cause impotence. This condition responds well to the drug Parlodel (bromocriptine).[7]
Hypothyroidism	Low thyroid hormone levels--can cause poor semen quality, poor testicular function and may disturb libido. May be caused by a diet high in iodine. Reducing iodine intake or beginning thyroid hormone replacement therapy can elevate sperm count. This condition is found in only 1 percent of infertile men.[8, 9]
Congenital Adrenal Hyperplasia	Occurs when the pituitary is suppressed by increased levels of adrenal androgens. Symptoms include low sperm count, an increased number of immature sperm cells, and low sperm cell motility. Is treated with cortisone replacement therapy. This condition is found in only 1 percent of infertile men.[10]
Hypogonadotropic Hypopituitarism	Low pituitary gland output of LH and FSH. This condition arrests sperm development and causes the progressive loss of germ cells from the testes and causes the seminiferous tubules and Leydig (testosterone producing) cells to deteriorate. May be treated with the drug Serophene. However, if all germ cells are destroyed before treatment commences, the male may be permanently infertile.[11]
Panhypopituitafism	Complete pituitary gland failure--lowers growth hormone, thyroid-stimulating hormone, and LH and FSH levels. Symptoms include: lethargy, impotence, decreased libido, loss of secondary sex characteristics, and normal or undersized testicles. Supplementing the missing pituitary hormones may restore vigor and a hormone called hCG may stimulate testosterone and sperm production.[12]

Table no.-2 Hormonal disorders which can disrupt male infertility

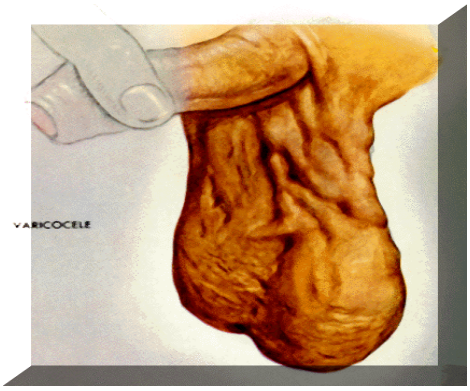
Physical Problems:

A variety of physical problems can cause male infertility. These problems either interfere with the sperm production process or disrupt the pathway down which sperm travel from the testes to the tip of the penis. These problems are usually characterized by a low sperm count and/or abnormal sperm morphology. The following is a list of the most common physical problems that cause male infertility:

Variocoele	A varicocele is an enlargement of the internal spermatic veins that drain blood from the testicle to the abdomen (back to the heart) and are present in 15% of the general male population and 40% of infertile men. These images show what a variocoele looks like externally and internally.A varicocele is an enlargement of the internal spermatic veins that drain blood from the testicle to the abdomen (back to the heart) and are present in 15% of the general male population and 40% of infertile men. These images show what a variocoele looks like externally and internally.[13, 14]
Damaged Sperm Ducts	Seven percent of infertile men cannot transport sperm from their testicles to out of their penis. This pathway may be blocked by a number of conditions: A genetic or developmental mistake may block or cause the absence of one or both tubes (which transport the sperm from the testes to the penis). Scarring from tuberculosis or some STDs may block the epididymis or tubes. An elective or accidental vasectomy may interrupt tube continuity.[15]
Torsion	Is a common problem affecting fertility that is caused by a supportive tissue abnormality which allows the testes to twist inside the scrotum which is characterized by extreme swelling? Torsion pinches the blood vessels that feed the testes shut which causes testicular damage. If emergency surgery is not performed to untwist the testes, torsion can seriously impair fertility and cause permanent infertility if both testes twist.[16]
Infection and Disease	Mumps, tuberculosis, brucellosis, gonorrhea, typhoid, influenza, smallpox, and syphilis can cause testicular atrophy. A low sperm count and low sperm motility are indicators of this condition. Also, elevated FSH levels and other hormonal problems are indicative of testicular damage. Some STDs like gonorrhea and chlamydia can cause infertility by blocking the epididimis or tubes. These conditions are usually treated by hormonal replacement therapy and surgery in the case of tubular blockage. [17]
Klinefelter's Syndrome:	Is a genetic condition in which each cell in the human body has an additional X chromosome--men with Klinefelter's Syndrome have one Y and two X chromosomes? Physical symptoms include peanut-sized testicles and enlarged breasts. A chromosome analysis is used to confirm this analysis. If this condition is treated in its early stages (with the drug hCG), sperm production may commence and/or improve. However, Klinefelter's Syndrome eventually causes all active testicular structures to atrophy. Once testicular failure has occurred, improving fertility is impossible.[18]

Retrograde Ejaculation	Is a condition in which semen is ejaculated into the bladder rather than out through the urethra because the bladder sphincter does not close during ejaculation. If this disorder is present, ejaculate volume is small and urine may be cloudy after ejaculation. This condition affects 1.5 percent of infertile men and may be controlled by medications like decongestants which contract the bladder sphincter or surgical reconstruction of the bladder neck can restore normal ejaculation.[19, 20]

Table no.-3 Physical Problems of infertility



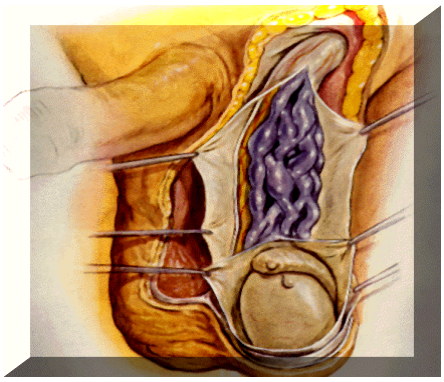


Figure no. – 1& 2 Enlargement of Variocoele

Psychological/Physical/Behavioral Problems:

Several sexual problems exist that can affect male fertility. These problems are most often both psychological and physical in nature: it is difficult to separate the physiological and physical components.

Erectile Disfunction (ED)	Also known as impotence, this condition is common and affects 20 million American men. ED is the result of a single, or more commonly a combination of multiple factors. In the past, ED was thought to be the result of psychological problems, but new research indicates that 90 percent of cases are organic in nature. However, most men who suffer from ED have a secondary psychological problem that can worsen the situation like performance anxiety, guilt, and low self-esteem. Many of the common causes of impotence include: diabetes, high blood pressure, heart and vascular disease, stress, hormone problems, pelvic surgery, trauma, venous leak, and the side effects of frequently prescribed medications (i.e. Prozac and other SSRIs, Propecia). Luckily, many treatment options exist for ED depending on the cause--these will be discussed in the treatment section.[21, 22]
Premature Ejaculation	Is defined as an inability to control the ejaculatory response for at least thirty seconds following penetration. Premature ejaculation becomes a fertility problem when ejaculation occurs before a man is able to fully insert his penis into his partner's vagina. Premature ejaculation can be overcome by artificial insemination or by using a behavioral modification technique called the "squeeze technique" which desensitizes the penis.[23, 24]

Ejaculatory Incompetence:	This rare psychological condition prevents men from ejaculating during sexual intercourse even though they can ejaculate normally through masturbation. This condition sometimes responds well to behavioral therapy; if this technique does not work, artificial insemination can be employed using an ejaculate from masturbation.[25, 26]

Table no. - 4 Psychological/Physical/Behavioral Problems of infertility

Effect of cell phones on male fertility:

Fertility rates among men who regularly use mobile phones could be as much as 30% lower, vastly reducing chances of conception, according to new research. The study - the first to indicate that mobile phones have a negative effect on sperm counts - found that men most affected were those who kept their phones in their trouser pocket, or in a belt holster. "The prolonged use of cell phones may have a negative effect on spermatogenesis and male fertility that deteriorates both concentration and motility." A new study shows a worrying link between poor sperm and the number of hours a day that a man uses his mobile phone. Those who made calls on a mobile phone for more than four hours a day had the worst sperm counts and the poorest quality sperm. Doctors believe the damage could be caused by the electromagnetic radiation emitted by handsets or the heat they generate. The findings suggest millions of men may encounter difficulties in fathering a child due to the widespread use of mobile phones and offers another possible explanation for plummeting fertility levels. Men who used a mobile for more than four hours a day had a 25 per cent lower sperm count than men who never used a mobile. The men with highest usage also had greater problems with sperm quality, with the swimming ability of sperm - a crucial factor in conception - down by a third. They had a 50 per cent drop in the number of properly formed sperm, with just one-fifth looking normal under a microscope. "It is just like using a toothbrush but mobiles could be having a devastating effect on fertility. It still has to be proved but it could have a huge impact because mobiles are so much part of our lives." The main finding was that on four measures of sperm potency - count, motility, viability and morphology, or appearance - there were significant differences between the groups. The greater the use of mobile phones, the greater the reduction in each measure. The WHO says a normal sperm count is above 20 million per millilitre of seminal fluid. "There was a significant decrease in the most important measures of sperm health with cell phone use and that should definitely be reflected in a decrease in fertility".[27]

Diagnostic Test:

Acrosome Reaction	Assesses the ability of sperm to penetrate an egg. In the fertilization process, sperm must first fuse to, then penetrate, the female egg in order to fertilize it. Typically fusing to the egg is not an issue, but penetrating the egg's hard shell (zona pellucida) can be difficult for sperm. For this reason, sperm cells go through a process known as acrosome reaction. Shortly before penetration of the egg, the tip of the head of a sperm cell (the cap) will rupture releasing enzymes responsible for breaking down the eggs hard shell in order to gain access to the egg and fertilize it. In cases where sperm fail to undergo the acrosome reaction, they typically have a severely reduced chance of penetrating an egg. This information may be used to help determine the most appropriate ART (Assisted Reproductive Technology) procedure.[27]
Anti-sperm antibody	This test looks for antibodies in semen that can damage or kill sperm resulting in reduced motility, interfering with egg fertilization or even infertility. Normally, the testes contain a natural barrier that acts as a protective layer by preventing immune cells from gaining access to sperm within the male reproductive tract. However, the barrier can be broken when testicles are physically injured, after a surgery (biopsy or vasectomy) or after a prostate gland infection. This allows sperm to come into contact with the immune system resulting in the production of the antibodies. If a high number of sperm antibodies come into contact with a man's sperm, it may be hard for the sperm to fertilize an egg.[28, 29]
Chromosome Analysis Karyotyping	One or both of the parents may be the carrier of an abnormal chromosome. Karyotyping is the analysis of the number and shapes of chromosomes in individual cells. Abnormal karyotypes are a significant cause of recurrent miscarriage, or infertility. Chromosomal abnormalities include: extra or missing chromosomes, alterations to the normal structure of specific chromosomes or cases where sections of one chromosome will be relocated to another chromosome where it does not belong (translocation). A chromosome analysis can identify these abnormalities and determine the anatomical, physical and physiological problems associated with it.[30, 31]
Estradiol	A small amount of estradiol is produced by the male testes. It has been reported that high levels of estradiol in men is associated with infertility characterized by low sperm production and quality.[32]
Follicle Stimulating Hormone (FSH-male)	a hormone produced by the pituitary gland that is located in the brain. It plays a key role in the development and release of sperm in the testes. If the reason for the azoospermia is testicular failure, then this is reflected in a raised FSH level. This is because, in these patients, the testis also fails to produce a hormone called inhibin (which normally suppresses FSH levels to their normal range). A high FSH level is usually diagnostic of primary testicular failure, a condition in which the seminiferous tubules (a coiled mass of tubes which makes up the bulk of the testes) in the testes do not produce sperm normally, because they are damaged.[33]

Hyaluronan Binding Assay (HBA)	Hyaluronan is a naturally occurring protein found in all human cells, including the gel layer surrounding the oocyte (egg). This test is based on the ability of mature, but not immature, sperm to bind hyaluronan. A low level of sperm binding to hyaluronan indicates a low proportion of mature sperm in the sample. The results of the HBA assay may provide information as to the most appropriate ART (Assisted Reproductive Technology) procedure.[34]
Inhibin B (Male)	A hormone test used to assess the reproductive capacity of males. This hormone is a direct product of the testes and is found to be higher in those men with normal fertility and lower in those who have abnormal sperm production. Inhibin B levels can be used to distinguish between obstructive (normal levels) and non-obstructive (low levels) causes for a lack of sperm. In the case of an obstruction, men typically have normal sperm production but their pathway is blocked due to some physical obstruction. In non-obstructive cases there is no physical obstruction; sperm production is simply low or nonexistent. Non-obstructive lack of sperm is typically due to some type of genetic abnormality.[35]
LH (Luteinizing Hormone - male)	In the man LH is necessary for spermatogenesis (sperm production) and stimulates the testicles to produce testosterone (Leydig cell function). Low levels of LH indicate a hormonal cause for low sperm production.[36, 37]
Prolactin	Hormone involved in the production of testosterone. Too much of this hormone in the blood stream can cause infertility by: interfering with the pituitary production of FSH and LH, adversely affecting the function of testicles, causing decreased testosterone levels, or causing abnormal sperm. High prolactin levels can be caused by tumors or certain medications. Prolactin levels are used with other tests, to help: Diagnose prolactinomas (tumors of the pituitary gland that produce prolactin), investigate potential infertility issues and erectile dysfunction in males.[38]
Semen Analysis	The examination of semen under the microscope. The purpose of this assessment is to measure the volume of semen, approximate number (sperm count), morphology (shape of the sperm) and motility (how well they swim). White blood cells are also measured to detect any possible infection.[39, 40]
Sperm DNA Decondensation (SDD)	Used to assess how well a population of sperms DNA functions once it has fertilized an egg. Once a sperm has fertilized an egg, there are several processes its DNA goes through in order for it to pair up with the egg's DNA. There are many factors that may impair this process. An abnormal results indicates the general sperm populations DNA will not act normally once inside the egg. This test may provide useful information that will direct couples to the most appropriate ART (Assisted Reproductive Technique) procedure.[41,42]
Sperm DNA Fragmentation (SDFA)	A test used to assess the quality of DNA in sperm by measuring the amount of “breaks” or “fragmented” DNA in a sample. These DNA “breaks” are indicative of damaged DNA. Significant DNA damage may indicate the general sperm populations reduced ability to fertilize an egg.

	It also may provide information as to the most appropriate ART (Assisted Reproductive Technique) procedure to be selected.[43]
Sperm Penetration Assay (SPA, Hamster Test)	Test of the ability of sperm to penetrate a hamster egg that has been stripped of the Zona Pellucida (outer membrane of the egg). This is another test used to examine the relative health, fitness and fertilizing ability of sperm.[40]
Testosterone	This hormone is produced by the testicles and is responsible for the development and release of sperm, secondary physical characteristics and sex drive. It is present in two forms: free and bound to Sex Hormone Binding Globulin (SHBG). The amount of testosterone in a man's body is controlled by the pituitary gland. At low levels, the pituitary gland typically releases luteinizing hormone (LH), which tells the testicles to make more testosterone. In cases where this process is impaired, consistently low testosterone levels can lead to low sperm counts and quality. There are several reasons for low testosterone levels including: hypothalamic or pituitary disease, damage to the testes (such as alcoholism, physical damage, or viral diseases), genetic diseases, or testicular failure. Total testosterone measurement does not indicate a problem until end stage testicular failure is reached. Free testosterone is an earlier indicator and more informative. [44, 45]
Y Chromosome Micro deletion	Mainly used for men who have very few (oligospermia) or no (azoospermia) sperm present in a semen sample and do not have any type of physical obstruction. This test identifies small missing segments of DNA from specific genes located on the Y chromosome.[46] The functionality of these genes has been linked to male infertility. There are 3 basic deletions: AZFa – is rare and the most severe. There is no chance of being able to produce sperm, AZFb – there have been no documented cases of finding mature sperm with surgical procedures, AZFc – is the most common deletion. Successful extraction of sperm with surgical procedures occurs in ~ 2/3 of cases.[47]

Table no. – 5 Diagnostic Test for infertility

Sperm Function Tests:

A number of tests of sperm function are available to examine the human fertilization process (Fig. 3). These are only performed in specialist laboratories. If simpler approaches or active preparations of zona pellucida (ZP) or sperm receptor proteins become available, they will be widely used to improve the assessment of human sperm. IVF has permitted many conventional and new tests of sperm function to be examined. Groups of sperm variables that are independently significantly related to the proportion of oocyte that fertilize in vitro can be determined by regression analysis. This approach has confirmed the importance of sperm morphology in the ability of sperm to interact with the coverings of the oocyte. [48]

Human Sperm-Oocyte Interaction:

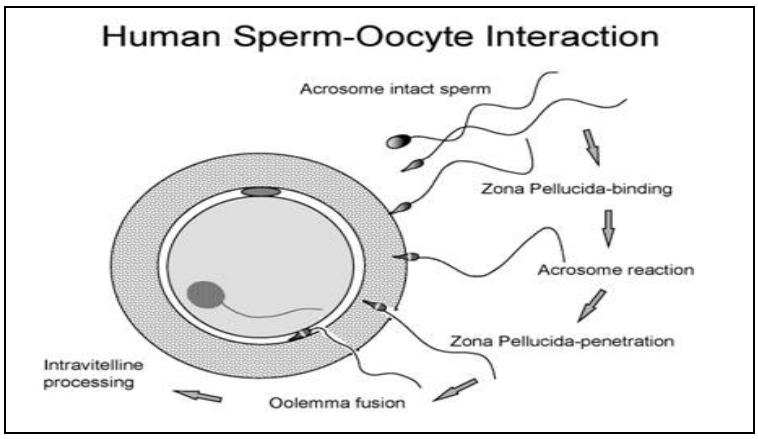


Figure no. - 3 Stages of human fertilization. Spermatozoa swim through the surrounding medium and cumulus mass (not shown) and bind to the surface of the zona pellucida. The acrosome reaction is stimulated by zona proteins and the acrosome reacted sperm penetrates the zona, enters the perivitelline space and binds to the oolemma via the equatorial segment. Oocyte processes surround the sperm head and it enters the ooplasm and decondenses. Infertility could result from defects of any of these processes. For example, abnormal sperm particularly with defective head morphology bind poorly to the zona.

Human Sperm–Zona Pellucida Binding Ratio Test	It is difficult to determine the number of sperm penetrating the ZP when many sperm are bound to the surface.[48] The sperm bound to the surface of the ZP can be sheared off by repeatedly aspirating the oocyte with a pipette with an internal m). The sperm penetratingμdiameter less than the diameter of the oocyte (120 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.[49]
Zona Pellucida–Induced Acrosome Reaction Test	Sperm dislodged from the ZP can be stained with a fluorescein-labeled lectin such as pisum sativum agglutinin or an antibody specific for the acrosomal contents to determine the proportion that are acrosome reacted. This test is useful for diagnosis of disordered ZP-induced acrosome reaction.[48]
Human Sperm–Oolemma Binding Ratio Test	Sperm-oolemma binding has been studied in a similar way to the sperm-ZP binding test, using oocytes that have had the ZP removed. Variations in Semen Volume and Appearance.Low semen volume suggest incomplete collection, short duration of abstinence from ejaculation before the test, absence or obstruction of the seminal vesicles, or androgen deficiency. High semen volume (>8 mL) may be seen in association with oligospermia but is of little practical significance. Hemospermia is usually the result of minor bleeding from the urethra, but serious conditions, such as genital tract tumors, must be excluded. Other discoloration of the semen may indicate inflammation of accessory sex organs.[49] The semen may be yellow with jaundice or salazopyrine administration. Defects of liquefaction and viscosity are relatively common and presumably result from malfunction

	of the accessory sex organs. Although these may cause problems with semen analysis and preparation of sperm for assisted reproductive technology (ART), they are probably of little relevance to fertility. Sperm agglutination is common with sperm autoimmunity but can also occur for other reasons[50].
Azoospermia	The total absence of sperm from the semen needs to be confirmed in repeated tests with vigorous centrifugation of the semen and careful examination of the pellet. Rarely, an illness or difficulty with collection will cause transient azoospermia; however, this can also occur for unexplained reasons. With severe spermatogenic disorders and some obstructions, sperm may be present in the semen intermittently. If any live sperm can be found, these can be cryopreserved for intracytoplasmic sperm injection (ICSI).[51]
Oligospermia	Sperm concentrations of less than 20 million/mL is classified as oligospermic. This figure probably derives mainly from the work of MacLeod and Gold, who found that only 5% of fertile men had sperm concentrations less than 20 million/mL.[51] Recent studies of fertile men generally support 20 million/mL as a clinically useful figure although the new edition of the WHO semen analysis manual will suggest lowering the cutoff to 14 million/mL and also lower values for sperm motility and normal morphology. There is a correlation between sperm concentration and other aspects of semen quality. Both motility and morphology are usually poor with oligospermia.[52]
Asthenospermia	Asthenospermia is defined as less than 50% sperm motility or less than 25% with rapid progressive motility. Spurious asthenospermia caused by exposure of sperm to rubber (particularly condoms), spermicides, extremes of temperature, or long delays between collection and examination, should be excluded. Low sperm motility is a frequent accompaniment of oligospermia, and is often also associated with a mixed picture of morphologic defects suggesting defective spermiogenesis.Specific ultrastructural defects of the sperm can be evaluated by electron microscopy when there is zero sperm motility or extreme asthenospermia (less than 5% motile sperm).[53] Absent dynein arms, other axonemal defects, mitochondrial abnormalities, disorganized fibrous sheath or outer dense fibers, or normal ultrastructure may be found. Standard semen analyses usually show normal sperm concentrations and morphology but there may be tail abnormalities: short, straight, or thick tails, or midpiece defects. Viability tests help to distinguish this group of patients from those with necrospermia. Patients with structural defects in the sperm may be able to be treated by ICSI. Asthenospermia may also be associated with sperm autoimmunity. The causes of other motility defects of moderate degree are unidentified.[54]
Necrospermia	It is important to distinguish necrospermia from other types of severe asthenospermia because some patients produce pregnancies despite the low sperm motility. Necrospermia is characterized by usually less than 20% to 30% total motility, less than 5% progressive motility, and a viability test

	less than 30% to 40%, indicating a high proportion of dead sperm. Other causes of severe asthenospermia such as sperm autoimmunity and collection problems must be excluded.[55] Necrospermia may fluctuate in severity, particularly with changes in coital frequency. Characteristic of necrospermia is an improvement of sperm motility with increased frequency of ejaculation. The condition may be caused by defective storage of sperm in the tails of the epididymides or stasis in the genital tract and it also occurs with chronic spinal cord injury and with adult polycystic kidney disease associated with cysts in the region of the ejaculatory ducts. There are ultrastructural features of degeneration in the ejaculated sperm but normal structure of late spermatids in testicular biopsies. Treatment with antibiotics may have a beneficial effect, but this is not proved. The couple should have intercourse once or twice every day for 3 to 4 days up to the time of ovulation.[56]
Teratospermia	Teratospermia is a reduced percentage of sperm with normal morphology assessed by light microscopy. It is important to distinguish mixed abnormalities of sperm morphology from those in which all or the majority of sperm show a single uniform defect, such as spherical heads with absence of the acrosomes (globospermia) and pinhead sperm. Pinhead sperm result when the centrioles from which the sperm tails develop are not correctly aligned opposite the developing acrosome. On spermiation, the sperm heads are disconnected from the tails and absorbed during epididymal transit so that there are only sperm tails in the ejaculate, the cytoplasmic droplet on the midpiece giving the pinhead appearance. Both these conditions cause sterility but are extremely rare.In general, human spermatozoa are very variable in appearance and the microscopic assessment of sperm morphology is highly subjective and difficult to standardize between laboratories. Only a small proportion (<25%) of the motile sperm from fertile men are capable of binding the ZP in vitro, and this zona binding capacity is closely related to the morphology of the sperm head. The morphometric characteristics of the sperm that bind to the ZP may be useful as a standard for sperm morphology. Various histological assessments of morphology have been used.[57] The simplest is to record as normal only those sperm that have no shape defects in head, midpiece or tail, regions. In the strict morphology approach, although size measurements are set, the sperm are assessed by eye and those marginally abnormal are assigned abnormal. Automated methods involving image analysis by computer have been developed that could overcome the between-laboratory variability and greatly improve the predictive value of semen analysis for natural conception.Before the introduction of ICSI, the percentage of sperm with normal morphology assessed by strict criteria after washing the sperm and adjusting the concentration to 80 million/mL, provided one of the most useful predictors of fertilization rates with standard IVF. There was a progressive reduction in oocytes fertilized from 60% to 20% as abnormal morphology increased from less than 70% to more than 95%.[79] Patients with high proportions of sperm with abnormal

	morphology are now treated by ICSI because of the risk of failure of fertilization with standard IVF. ICSI results are independent of sperm morphology.[58]

Table no. – 6 Sperm Function Tests

World Health Organization (WHO) Criteria:

For Normal Semen Values [58]

Volume	>/= 2.0 cc or greater
pH	7.2-7.8
Sperm concentration	>/= 20 million/cc
Total sperm count	>/= 40 million
Motility	>/= 50% with normal morphology
Morphology	> 30% normal forms

Management of infertility:

History taking from the man [59, 60]

- Past history

1. Mumps
2. Operations (hernia, hydrocoele)
3. RTI or STIs.

- Habits

1. Smoking, alcohol or drug intake.
2. Exposure to heavy metals/lead.

- Coital history

1. Frequency
2. Number of partners
3. Severe premature ejaculation
4. Other coital abnormalities

Examination:

- General examination (personal history, age, occupation)
- Obesity
- Distribution of hair
- Undecended testicles
- Size of testicles, varicocoele
- Hypospadius

Semen analysis:

- **Instructions should emphasize:**

1. Sexual abstinence for three days is required.

2. All the ejaculate should be collected by masturbation in a wide container.

3. If sample taken at home, it should be carried in outside pocket (at ordinary temperature) and brought immediately to laboratory within one hour.

4. If any abnormality is detected, no treatment should be started until semen analysis is repeated, preferably,two weeks from the first.

- **Normal semen picture: according to WHO standards, normal semen should be as follows:**

1. Spermatozoa concentration:
2. More than 20 millions per ml
    - Motility either:
        - More than 25% grade (A) motility
        - More than 50% grade (A) and (B) motility.
    - Morphology: more than 30% normal head forms.
    - Less than 10% of motile spermatozoa are antibody coated and no agglutination.
3. Seminal plasma:
    - Volume: more than 2.0 ml
    - Normal appearance and consistency
    - pH between 7.2 and 7.8
    - Biochemistry: normal
    - White blood cells: normal
    - Culture: negative, i.e, less than 1000 bacteria per ml.

Hospital Investigations:

If all the previous findings are normal, refer the wife to hospital for the following investigations:

- Hormonal analysis
- Ovulation test
  - Monitoring by ultrasound.
  - Premenstrual endometrial biopsy.
  - Recording the basal body temperature.
- Tubal patency test, e.g, by hysterosalpingography
- Laparoscopy and hysteroscopy may be needed in certain cases in order to be able toreach a definite diagnosis.

Conclusion

The present review is aimed to find out the history of infertility, causes and diagnostic tests. Medical and Pharmaceutical science is so androne that Man's efforts are honoured with fruitful to get the effective treatment and proper guidance to get rid of infertility. In the present work we have listed out of all probable causes responsible for male's infertility. Hormonal imbalancement can be rectified and spermatogenesis can be promoted by minor Vericocele surgery or testicular surgery. Review has classified male's infertility. Ever set back has the remedy. Male's infertility can be readily treated with their proper diagnosis. In this regard we have attempted to review the causes, diagnosis and management of male's infertility for their treatment in future.

References

1. Gnoth C, Godehardt E, Frank-Herrmann P, *et a l* Definition and prevalence of subfertility and infertility. Hum Reprod ,2005:1144-1147.
2. Sigman, Lipshultz, L.I, and Howards, S.S.: Evaluation of the subfertile male. In: Infertility in the Male, 3rd edition. Edited by L.I. Lipshultz and S.S. Howards. St.Louis: Mosby-Year Book, 1997:174.
3. Crowley WF, Whitcomb RW,Gonadotropin-releasing hormone deficiency in men: diagnosis and treatment with exogenous gonadotropin-releasing hormone. Am J Obstet Gynecol; 1990, 163: 1752-58.
4. Zarate A, Valdes-Vallina F, Gonzales A, et al.Therapeutic effect of synthetic luteinizing hormone-releasing hormone (LH-RH) in male infertility due to idiopathic azoospermia and oligospermia. Fertil Steril; 1973,24:485-486.
5. Büchter, D, Behre, H.M, Kliesch, S. and Nieschlag, E. Pulsatile GnRH of hCG/hMG as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. Eur. J. Endocrinol, 1998,139, 298–303.
6. Glazener, C.M.A, Kelly, N.J. and Hull, M.G.R. Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle. Br. J. Obstet. Gynaecol, 1987, 94, 535–538
7. Johnson, A, Bassham, B, Lipshultz, L.I, *et al.*A quality control system for the optimized sperm penetration assay. Fertil. Steril, 1995, 64(4),.
8. Puri, P, Barton, D, OíDonnell, B.: Prepubertal testicular torsion: Subsequent fertility. J. Pediatr. Surg, 1985, 20:598,.
9. Strohmer, H, et al.: Agricultural work and male infertility. Am. J. Ind. Med, 1993 24:587.

10. Finkel DM, Phillips JL, Snyder PJ. Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. N Engl J Med 1985; 313:651-655.
11. Schopohl J, Mehltretter G, von Zumbusch R, Eversmann T, von Werder K. Comparison of gonadotropin-releasing hormone and gonadotropin therapy in male patients with idiopathic hypothalamic hypogonadism. Fertil Steril 1991; 56:1143-1150.
12. Kass, E.J, and Belman, A.B.: Reversal of testicular growth by varicocele ligation. J. Urol, 1987, 137:475.
13. Saypol, D.C, Lipshultz, L.I, and Howards, S.S.: Varicocele. In: Infertility in the Male, 1st Edition. Edited by L.I. Lipshultz and S.S. Howards. New York: Churchill Livingstone, 1983, 6:213-232.
14. Nilsson, S, Edvinsson, A, and Nilsson. B, Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: Fact or fiction? Br. J. Urol, 1979. 51:591.
15. Charny CW. The use of androgens for human spermatogenesis. Fertil Steril 1959; 10:557-570.
16. Rao, M, and Rao, D.: Cytogenetic studies in primary infertility. Fertil. Steril, 1998,197, 28:209.
17. Griffin, J.E, and Wilson, J.D.: Disorders of sexual differentiation. In Walsh, P.C, *et al.*(eds.): Campbellís Urology, Volume 2. Edited by P.C. Walsh, *et al.*Philadelphia: W.B. Saunders, 1992, 5:123-12.
18. Beckerman H, Becher J, Lankhorst GJ. The effectiveness of vibratory stimulation in anejaculatory men with spinal cord injury. Paraplegia 1993;31:689-699
19. Jequier, A.M, Crich, J.P, and Holmes, S.C.: Incomplete obstruction of the male genital tract: A cause of oligozoospermia. Br. J. Urol, 1983, 55:545.
20. Brindley GS. Reflex ejaculation under vibratory stimulation in paraplegic men. Paraplegia 1981;19:299-302
21. Kruger, T.F, et al.: Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil. Steril, , 1988, 49:112.
22. Denil J, Ohl DA, McGuire EJ, and Jonas U. Treatment of anejaculation with electroejaculation. Acta Urol Belg 1992; 60:15-25.
23. Niederberger, C.S, Lamb, D.J, Glinz, M, Lipshultz, L.I, and Scully, N.F.: Tests of sperm function for evaluation of the male: Penetrak and Tru-Trax. Fertil. Steril, 1993,60:319n323.
24. van der Linden PJ, Nan PM, te Velde ER, *et al.*Retrograde ejaculation: successful treatment with artificial insemination. Obstet Gynecol 1992; 79:126-128.
25. Smith, R.G, et al.: Functional tests of spermatozoa. Sperm penetration assay. Urol. Clin. North Am, 1987, 14:451.
26. Research Center for Wireless Technology, by JENNY HOPE on 23rd October 2006.
27. Auger J, Kunstmann JM, Czyglik F, Jouannet P. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 1995;332:281-285
28. Collins JA, Burrows EA, Yeo J, YoungLai EV. Frequency and predictive value of antisperm antibodies among infertile couples. Hum Reprod 1993;8:592-598
29. Hendry WF, Hughes L, Scammel G, Pryor JP, Hargreave TB. Comparison of prednisolone and placebo in subfertile men with antibodies in spermatozoa. Lancet 1990; 335:85-88.
30. Krausz C, Degl'Innocenti S: Y chromosome and male infertility: Update, 2006. Front Biosci , 2006,11:3049-3061.

31. Reijo R, Lee TY, Salo P, et al: Diverse spermatogenic defects in humans caused by y chromosome deletions encompassing a novel RNA-binding protein gene. Nat Genet, 1995, 10:383-393.
32. Thomas, A.J, Jr, and Howards, S.S.: Microsurgical treatment of male infertility. In: Infertility in the Male, 3rd Edition. Edited by L.I. Lipshultz and S.S. Howards. St. Louis: Mosby Year Book, 1997, 371-384
33. Hayes, F. J, Pitteloud, N, DeCruz, S, et al.Importance of Inhibin B in the Regulation of FSH Secretion in the Human Male. J. Clin. Endocrinol. Metab, 2001,. 86: 5541-5546.
34. Gnessi, L, Fabbri, A, Spera, G. Gonadal Peptides as Mediators of Development and Functional Control of the Testis: An Integrated System with Hormones and Local Environment. Endocr. Rev. 1997, 18: 541-609.
35. Lisek, E.W, and Levine, L.A.: Percutaneous technique for extraction of sperm from the epididymis and testicle. Tech. Urol, 1997, 3(2):81-86.
36. Aulitzky W, Frick J, Hadziselimovic F. Pulsatile LHRH therapy in patients with oligozoospermia and disturbed LH pulsatility. Int J Androl 1989;12:265-272
37. Zarate A, Valdes-Vallina F, Gonzales A,*et al.*Therapeutic effect of synthetic luteinizing hormone-releasing hormone (LH-RH) in male infertility due to idiopathic azoospermia and oligospermia. Fertil Steril 1973; 24:485-486.
38. Baker HWG, Pepperell RJ: Lack of effect of bromocriptine on semen quality in men with normal or slightly elevated prolactin levels. Aust N Z J Obstet Gynaecol, 1980 20:158-161.
39. Chia, S.-E, Lim, S.-T. A, Ho, L.-M, Tay, S.-K. Monthly variation in human semen quality in male partners of infertile women in the tropics. Hum Reprod 2001,16: 277-281
40. Garrett C, Liu DY, Clarke GN, et al: Automated semen analysis: 'zona pellucida preferred' sperm morphometry and straight-line velocity are related to pregnancy rate in subfertile couples. Hum Reprod, 2003, 18:1643-1649.
41. Alvarez JG, Sharma RK, Ollero M, et al: Increased DNA damage in sperm from leukocytospermic semen samples as determined by the sperm chromatin structure assay. Fertil Steril, 2002, 78:319-329.
42. Liu DY, Baker HW: Human sperm bound to the zona pellucida have normal nuclear chromatin as assessed by acridine orange fluorescence. Hum Reprod, 2007, 22:1597-1602.
43. Aitken RJ, De Iuliis GN: Origins and consequences of DNA damage in male germ cells. Reprod Biomed Online, 2007, 14:727-733.
44. Wang C, Chan CW, Wong KK, Yeung KK. Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. Fertil Steril 1983; 40:358-365.
45. Tohda, A, Okuno, T, Matsumiya, K,*et al.*Restoration of Spermatogenesis and Fertility in Azoospermic Mutant Mice by Suppression and Reelevation of Testosterone Followed by Intracytoplasmic Sperm Injection. *Biol. Reprod,* 2002, 66: 85-90.
46. Skakkebaek, N.E, et al.: Quantification of human seminiferous epithelium. III. Histological studies in 44 infertile men and controls with normal chromosome complements. Acta Path. Microbiol. Scand, 1973, 81:97.

47. Najmabadi H, Huang V, Yen P, et al: Substantial prevalence of microdeletions of the Y-chromosome in infertile men with idiopathic azoospermia and oligozoospermia detected using a sequence-tagged site-based mapping strategy. J Clin Endocrinol Metab, , 1996, 81:1347-1352.
48. Liu DY, Garrett C, and Baker HW: Clinical application of sperm-oocyte interaction tests in in vitro fertilization--embryo transfer and intracytoplasmic sperm injection programs. Fertil Steril, 2004, 82:1251-1263,.
49. Burkman LJ, Coddington CC, Franken DR, et al: The hemizona assay (HZA): development of a diagnostic test for the binding of human spermatozoa to the human hemizona pellucida to predict fertilization potential. Fertil Steril, 1988, 49:688-697.
50. Clarke G, Baker H: Immunological evaluation of male infertility. In Kandeel F (ed): Male reproductive function pathophysiology and treatment, New York, Informa, 2007, 293-300.
51. WHO: World health organization laboratory manual for the exmination of human semen and sperm-cervical mucus interaction. In Editor (eds), Cambridge, Cambridge University Press, 1999.
52. Ombelet W, Bosmans E, Janssen M, et al: Semen parameters in a fertile versus subfertile population: A need for change in the interpretation of semen testing. Hum Reprod , 1997,12:987–993.
53. Zariwala MA, Knowles MR, Omran H: Genetic defects in ciliary structure and function. Annu Rev Physiol, 2007, 69:423-450,.
54. Wilton LJ, Temple-Smith PD, Baker HWG, et al: Human male infertility caused by degeneration and death of sperm in the epididymis. Fertil Steril, 1988, 49:1052-1058.
55. Fang S, Baker HWG: Male infertility and adult polycystic kidney disease are associated with necrospermia. Fertil Steril , 2003,79:643-644.
56. Correa-Perez JR, Fernandez-Pelegrina R, Aslanis P, et al: Clinical management of men producing ejaculates characterized by high levels of dead sperm and altered seminal plasma factors consistent with epididymal necrospermia. Fertil Steril , 2004 81:1148-1150.
57. Garrett C, Baker HWG: New fully automated system for the morphometric analysis of human sperm heads. Fertil Steril , 1995,63:1306-1317.
58. Francavilla S, Cordeschi G, Pelliccione F, et al: Isolated teratozoospermia: A cause of male sterility in the era of ICSI? Front Biosci, 2007, 12:69-88.
59. Gilbert, B.R, *et al*.: Semen analysis in the evaluation of male factor subfertility. AUA Update Series, Lesson 32, VolumeXI, 1992.
60. Standards of Practice for Integrated MCH/RH Services: First Edition, June 2005, Chapter 18 Management of Infertility.