Review Of Literature
REVIEW OF LITERATURE

Infertility implies apparent failure of couple conceive if a couple fails to achieve pregnancy of her one year of improved and regular intercourse it is an indication to investigate the couple. Due to increasing awareness in the medical community of the fact that subinfertility in the male contributes significantly to being marriage.

"Methews and Duncan" originally defined infertility "if a married couple did not got any issue within 1yr. or marriage". But recent investigations points out infertility as "Inability or failure to conceive within 12 months with regular sexual intercourse". In order to be fertile, the male partner must succeed in depositing his semen intravaginally.

In is now over 300 years since "Anthoni Von Leeuwenhoek" reported his first observation of motile spermatozoa in the human ejaculate in his dramatic letter to Real Society of November 1677 "de Natise semini genitale Animalcules".

In a further letter dated 1685, he went on to speculated that the existence of spermatozoa or animalcules in semen was associated with its fertilizing ability, and moreover that infertility could be caused by either the absence of spermatozoa, or their having reduced function. Charles Bonnet, writing almost 100 years later in 1971 was less certain of role of spermatozoa in semen asking "do they so largely scattered". The first quantitative study on seminal fluid was probably performed by "Lazzaro Spallanzani" in 1780, while the, while the later work of Prevost Dumas and Herwig began to elucidate the mechanism of fertilization establishing that one sperm was necessary to fertilize each egg. The direct quantitavies study of human ejaculate did not began until the early part of the present century when
Benedict, working in New York, published a brief report on counting the spermatozoa in semen using a blood counting chamber, a early as 1902. Not until 1929 was the quantitation of spermatozoa in human semen placed on a scientific footing by Macomber and Sanders who began to evaluate the range of sperm concentrations in semen associated with fertility. This was followed by new classic work of John Macleod who undertook a range of studies of semen quality in groups of fertile and potentially infertile men and in doing so laid the foundation for modern diagnostic andrology.

Even in modern times abnormal semen quality is most common investigation tool arrived in most clinics, thus one of the most important laboratory parameters in an infertile male is **SEmen Analysis**.

Male reproductive tract is an organ complex concerned with ultimate goal of the reproduction of the race. The system includes gonads, the excretory ducts, and several endocrine glands. In the adults, the testis has two main functions, spermatogenesis i.e. the production of germ cells, and steroidogenesis i.e. synthesis and secretion of sex steriod hormones. The epididymes contributes to maturation of sperm. The sex accesory glands provide the bulk of the ejaculate.

Sexual differentiation, development of gonads and of the gential tract continues throughout from the time of birth to puberty; activation of endocrine hypothalamo-pituitary- gonadal axis, appereance of secondary sexual characterstics, and initiation of spermatogenesis. It is only after puberty that male reproductive system is ready for reproduction.

Thus the entire male sexual development dependds on a delicate interplay between anatomic, functional, and regulatory (genetic and hormonal) factors.
The development of the male reproductive tract results from a series of steps in an orderly fashion: the differentiation of the gonad into a testis. The initiation of testicular steroidogenesis and finally, the expression of androgenic activity in target tissues. These three steps are genetically controlled by genes present on both X and Y chromosomes and autosomes. Pericentric region of Y chromosome is implicated in testis determination region of the Yq arm have been associated with spermatogenesis.

Infertility can be brought by gene mutation that causes depression or arrest of spermatogenesis in adult. In men, maturation arrest at various stages of spermatogenesis occurs in some individuals with apparently normal karyotypes and in men with various structural and numerical chromosomal abnormalities.

Probably keeping in mind these early developments it has been suggested the basic laboratory investigations of any patient with infertility should include an adequate semen assessment, chromosomal studies and hormonal assessment.

Therefore, Infertility evaluation should involve a systematic approach using the most non-invasive procedures just and then to proceed for invasive and specialed procedures (testicular biopsy) towards end of evaluation. So we will start with a brief account of the basic anatomy of male genital tract and relevant physiology.

THE HYPOTHALARIC PITUITARY GONADAL AXIS

Steroidogenic function of the testis is gonadotropin dependent regulation of testosterone production is governed by an interplay between the hypothalamus hypophysis and testis. The hypothalamic-pituitary-testicular axis functions in a cybernetic circle in which the role of the common circuit is played by the
hypothalamus (through LHRH secretion). Pituitary secretion can be viewed as regulating the circuit and testicular secretion (sex steroids and inhibin) issue feedback signals, therefore, any disruption of the system or dysfunction may lead to abnormal sexual differentiation, sexual infantilism or infertility.

In normal adults, a fall in testosterone secretion results in an increased release of LH which, in turn, stimulates testosterone secretion in such a way that testosterone levels are maintained rather constant except of slight day-night variations and biologic rhythms. LH is secreted in successive spikes at a frequency of approximately one per hour. Negative feedback control of LH secretion is exerted by both sex steroids testosterone and $E_2$, but their short term effects and site of action differ. In long term, androgens diminishes the response of LH to LHRH altering little that of FSH, while estrogens potentiate both FSH and LH release. Besides $E_2$, another substance secreted by the testis, named inhibin, specifically inhibits FSH, testosterone having little effect on its secretion. Inhibin is produced by sertoli cells and acts not only at pituitary level but also on the hypothalamus and the testis.

The role of prolactin in male reproduction is not well understood. Prolactin alone has little action on the male reproductive tract but it potentiates the effect of LH on the Leyding cell and that of testosterone on the prostate and seminal vesicle. Prolactin is able to increase the androgen receptor complex which is transferred to nucleus in target tissues. However, the mechanisms by which, the hyperprolactonemic men, lead to decreased reproductive function is unknown. Prolactin is thought to produce impotence independently of its lowering action on testosterone secretion.
The main action of LH is stimulate testosterone, a secretion by Leydig cells. FSH stimulates sertoli cells, protein synthesis ABP and inhibin secretions and the aromatization of testosterone to E2. The pulsatile pattern of gonadotropin secretion results from pulsatile secretion of LH-RH. Gonadal and gonadotropic function undergo subsequent periods of activation and depression throughout life. It is becoming evident that the CNS mediates those "maturationa; changes' by modulating the synthesis and or release of LHRH.  

**THE TESTES:**

Testosterone is secreted episodically from leydig cell in response to LH pulses and has a diurnal pattern, with peak level in the early morning and the through level in the late afternoon or early evening. In the intact testis, LH receptors decreases or down regulate after exogenous LH administration. Testosterone; the primary inhibitor of LH secretion in males. Testosterone may be metabolized in peripheral tissue to potent androgen dehydrottestosterone or the potent estrogen estradiol.

Large dosed of Gn RH or its analogs can reduce the number of LH receptors and therefore inhibit LH secretion. This has been applied clinically to cause medical castration in men with prostate cancer. Estrogen inhibits some enzymes in the testosterone synthesis pathway and therefore directly affects testosterone production. There also appears to be an intra-testicular ultrashort loop feedback such that exogenous testosterone will override the effect of LH and inhibit testosterone production. In normal male only 2% of testosterone is free 44% bound to testosterone-estradiol binding globulin or TeBG, called sex hormones binding globulin. 54% of testosterone is bound to albumin and other
proteins. These steroid binding proteins modulate androgen action. 
TeBG has higher affinity for testosterone than for estradiol and 
changes on TeBG alter or amplify the hormonal milieu. TeBG 
levels are increased by estrogens, thyroid administration and 
cirrhosis of liver and may be decreased by growth hormone and 
obesity. The biological actions of androgens are exerted on the 
target organs that contain specific androgen receptor proteins. 
Testosterone leaves the circulation and enters the target cells 
where it is converted to the more potent androgen 
dehydrotrestosterone by an enzyme 5 alpha-reductase. The major 
functions of androgens in target tissue include regulation of 
gonadotropin secretion by hypothalamic-pituitary axis, initiation 
and maintainence of spermatogenesis, differentiation of internal 
and external male gential system during fetal development and 
promotion of sexual maturation at puberty.

Seminiferous tubules

The séminiferous tubules contains all the germ cells at 
various stages of maturation and their supporting sertoli cells. 
These account for 85 to 90% of the testicular volume. Sertoli 
cells are a fixed population of non dividing cells. They rest on 
the basement membrane of the seminiferous tubules. They are 
linked by tight junctions. These tight junctions coupled with the 
close approximation of the myoid cells of the pertibular contractile 
cell lyayers serves to form the blood testes barrier. This barrier 
provides a unique micro-enviornment that facilitates spermatogenesis 
and maintains isolation is important because spermatozoa are 
produced during puberty, long after the period of self recognition 
by the immune system. If these developing spermatozoa were no 
immunologically protected, they would recognized as foriegn and 
attacked by the body’s immune system. Sertoli cells appear to
be involved with the nourishment of the developing germ cells as well as the phagocytosis of damaged cells. Spermatogonia and young spermatocytes are lower down in the basal compartment of the seminiferous tubules, whereas matured spermatocytes and spermatids are sequestered higher up in the adluminal compartment. The germinal cells or the spermatogenic cells are arranged in an orderly manner from the basement membrane up to the lumen. Spermatogonia lie directly on the basement membrane, and next in order, progressing up to the lumen, are found the primary spermatocytes, secondary spermatocytes and spermatids. Spermatogenesis is a complex process whereby primitive stem cells or spermatogonia, either divide to reproduce themselves for stem cell renewal or they divide to produce daughter cells that will later become spermatocytes. The spermatocytes eventually divide and give rise to mature cell lines that eventually give rise to spermatids then undergo a transformation into spermatozoa. This transformation include nuclear condensation, acrosome formation, loss of most of the cytoplasm, development of a tail and arrangement of the mitochondria into the middle piece of the sperm which basically becomes the engine room to power the tail. Groups of germ cells tend to develop and pass through spermatogenesis together. This sequence of developing germ cells is called a generation. These generations of germ cells are basically in the same stage of development. There are six stage of seminiferous epithelium development. The progress from stage 1 through stage 6 constitutes 1 cycle. In humans the duration of each cycle is approx. 16 days and 4.6 cycles are required for a mature sperm to develop from early spermatogonia. Therefore, the duration of entire spermatogenic cycle in humans is 4.6 cycles times 16 days equals 74 days.
Hormonal control of Spermatogenesis.

An intimate structural and functional relationship exists between the two separate compartment of the testis, i.e. the seminiferous tubule and the interstitium between the tubule and the interstitium between the tubules. LH affects spermatogenesis indirectly in that it stimulates androgenous testosterone production. FSH targets sertoli cells. Therefore, testosterone and FSH are the hormones that are directed at the seminiferous tubule epithelium. Androgen-binding protein which is a sertoli cell product carries testosterone intracellularly and may serve as a testosterone reservoir within the seminiferous tubules in addition to transporting testosterone from the testes into the epididymal tubule. The physical proximity of the leydig cells to the seminiferous tubules and the elaboration by the sertoli cells of the androgen-binding protein, cause a high level of testosterone to be maintained in the micro enviroment of the developing spermatozoa. The hormonal requirements for initiation of spermatogenesis. For spermatogenesis to be maintained like for instance after a ituitary obliteration, only testosterone is required. However, if spermatogenesis is to be re-initiated after the germinal epithelium has been allowed to regress completely, then both FSH and testosterone are required.

Transport- maturation-storage of sperm.

Although the testis is responsible for sperm production, the epididymus is intimately involved with the maturation, storage and trasport of spermatooa. Testicular spermatozoa are non-motile and were felt to be incapable of fertilizing ova. Spermatozoa gain progrrssive motility and fertilizing ability after passing through the epididymis. The coiled seminiferous tubules terminate within the rate testis, which in turn coalesce to form the ductuli efferents. These ductuli efferents conduct testicular fluid and spermatozoa
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coagulating substrate. A recognized function of the seminal plasma is its buffering capacity on the acidic vaginal enviornment. The coagulum formed by the ejaculated semen liquified within 20 to 30 minutes as a results of prostatic proteolytic enzymes. The prostate also adds zinc phospholipids, spermine, and phosphate to the seminal fluid. The first portion of the ejaculate characteristically contains most of the spermatozoa and most of the prosatic secretions, while the second is composed primarily of seminal vesicle secretions and fewer spermatozoa.

Fertilization normally takes place within the uterine tubes after ovulation has occurred. During the menstrual mid cycle, the cervical mucus changes to become more abundant, thinner and more watery. These changes serve to facilitate entry of the sperm into the uterus, and to protect the sperm from the highly acidic vaginal secretions. Physiologic changes in the spermatozoa known as capacitation occur within the female reproductive tracts in order for fertilization to occur. As the sperm interacts with the egg, there is initiation of new flageller movement call hyperactive motility and morphologic changes in the sperm that result in the release of lytic enzyme and exposure of part of the sperm structure known as the acrosoma reaction. As a result of these changes, the fertilizing sperm cell is able to reach the oocyte, traverse its various layers and become incorporated into the ooplasm of the egg:

**Causes of male infertility**

Causes may be:-

1. pretesticular of mainly endocrinal.
2. Testicular or defective sperm production.
3. Post testicular or defective sperm delivery.

1. Pretesticular causes :-
Mainly constitutes endocrinal, other causes are stress.
The various endocrinal defect leading to infertility are-

A. Hypothalamic diseases:
   * Isolated gonadotropin deficiency (Kallmans' syndrome)
   * Isolated LH deficiency ("Fertileunch")
   * Isolated FSH deficiency
   * Congenital hypogonadotropic syndromes.

B. Pituitary diseases:
   * Pituitary insufficiency (Tumors, infiltrative processes, operation, radiation)
   * Hyperprolactinemia.
   * Hemochromatoses- Approximately 80% of these men have testicular dysfunction.
   * Exogenous hormones (estrogen-androgen excess, glucocorticid excess, hyper and hypothyroidism.
   * Hypothalamic diseases.

**Hypogonadotropic state of male infertility**
Depressed levels of gonadotrophins, in concert with subnormal level of testosterone and absent spermatogenesis, characterize the clinical state of hypogonadotropic hypogonadism.

Causes of hypogonadotropic state:

1. Idiopathic
2. Aquired

*AQUIRED*

A. Defect in pituitary:
   * Tumors of supporting structure
   * Pituitary adenoma
   * Anurysm of ICA
   * An infiltrative process
   * Radiation or operative.

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B. Defect in hypothalamus:

1. Primary and metastatic tumours
2. Infiltrative processess
3. Trauma
4. Infection.

**In Idiopathic**

1. Isolated gonadotrophin deficiency (Kallman’s syndrome)
   * Familial disease having autosomal dominant transmission
   * Generally presentation in adolescence with failure to progress through puberty. However patients with partial deficency present in adult life with partial virilization with infertility and initial evaluation will reveal depressed LH, FSH and testosterone level.

2. Congenital hypogonadotrophic hypogonadism syndromes include Laurence-Moon-Biedl syndrome, the Prader-Villi syndrome
   * Moebius syndrome. All are associated with sexual infantilism secondary to hypogonadotrophic defects, but their presentation are not those of infertile males.

Two additional nutritional states resulting in hypogonadotrophic hypogonadism are malnutrition or severe illness. In these gonadotrophic level fall with concomitant decrease in serum testosterone and spermatogenesis. Prolonged starvation leads to testicular histologic changes. Alcoholism: in addition to its direct toxic effect on testicle; also leads to altered estrogen metabolism leading intially to depressed gonado trophin levels, followed by decreased testosterone levels and spermatogenesis.
Hyperprolactinemia

Indicators of pituitary-hypothalamic function that are reported to abnormal in hyperprolactemia are -
  * Loss of periodicity of LH secretion.
  * Loss of response to LRH.
  * Abnormal secretion of LRH and normal response to LHRH.

Hyperprolactinemia has been demonstrated to have a direct effect on testicular function resulting in gonadal refractoriness to gonadotrophin stimulation present with impotence.

(2) Those with nondetectable sites of hyperprolactin secretion who present with infertility. This latter group seems to be an extremely rare one.

THE THYROID

The thyroid gland exerts its influence on the testis in several ways -

  a) Increases sensitivity of gonads to gonadotrophins.
  b) Thyroid hormone can affect testicular metabolism.
  c) Additionally, the thyroid has the ability to affect the rate of production of hypothalamic releasing factor and ant. pituitary hormones.

Alteration in thyroid function lead to decreased fertility. Hyperthyroidism in man will lead to a constellation of manifestations of increased estrogen production, but the effect on fertility has not been investigated.

Hypothyroidism may lead to abnormal spermatogenesis with decreased total sperm count and decreased motility. Generally these patients complain of loss of libido which usually is not
accompanied by any alteration in sexual function. It seems that hypothyroidism exerts its effect on spermatogenesis via reduced gonadotrophin release.

Thus, patients presenting for evaluation of infertility do not require investigations of their thyroid status unless there are overt clinical signs or symptoms of thyroid dysfunction. Subtle alternation in thyroid function seem not be related to fertility in man.

THE ADRENAL GLAND

The two pathologic adrenal status which have been implicated as potential cause of male infertility are -

1. Congenital adrenal hyperplasia
2. Cushing's syndrome.

1) **Congenital adrenal hyperplasia**

Excessive adrenal androgens would lead to gonadotrophin suppression and lead to infertility.

2) **Cushing's syndrome.**
   *
   Five times more common in females than in males.
   *
   Patient reported with Cushing's syndrome are found to have normal serum LH levels in face of decreased testosterone levels. This is due to decreased responsiveness of leydig cells due to high serum glucocorticoid levels in these patients of untreated Cushing's syndrome; on testicular biopsy can have following findings\(^{21}\).

   ii) Hypospermatogenesis (ii) Tubular thickening
   iii) Disorganisation of the tubular epithelium,
   
   These patients also have -
   - loss of libido
   - Impotence
Explained on the basis of reduced testosterone levels. Reversal of the impotence and imporved testicular biopsies have been documented with appropriate treatment of hypercorticoid state.

**TESTICULAR CAUSES OF INFERTILITY**

A. Chromosomal disorders
   1. Klinefelter's syndrome
   2. XYY syndrome
B. Vanishing testes syndrome
C. Noonan's Syndrome
D. Varicocele
E. Myotonic dystrophy
F. Orchitis : Mumps and Leprosy
G. Cryptorchidism
H. Chemicals
I. Irradation
J. Ageing
K. Miscellaneous - Paraplegia, Polyglandular failure, Obesity, Sickle cell Anemia, Chronic liver disease.
L. Idiopathic oligospermia
M. Germinal aplasia (Sertoli cell only syndrome)
N. Idiopathic testicular failure.

**CHROMOSOMAL DISORDERS LEADING TO INFERTILITY**

**Klinefelter’s syndrome -**

Most common known cause of primary testicular failure associated with impairment of both spermatogenesis and Leydig cell function.

Clinical presentation as small testes, azoospermia, gynecomastia, androgen deficiency and elevated urinary FSH. Not all patients share same findings.

These patients have an extra "X" chromosome in all their cell lines due to non-dysjunction of "X" chromosome during meiosis. Advanced maternal but not paternal age is associated with an increased incidence of these syndrome. Testicular biopsy in these patient shows -

- Seminiferous tubular rarely contain germ cells.
- Sertoli cells mophologically abnormal.
- Leydig cells are prominet and Hyperplastic.

**Hormonal studies** - FSH and LH

- Testosterone - low normal or low
- S. estradiol - Normal or increased.

**XYY SYNDROME**

- Usually have increased aggressiveness and criminal behavior.
- Usually tall stature.
- Rarely present with infertility due to impaired spermatogenesis.

**Vanishing Testes syndrome (Prepubertal castrate syndrome; Aorchia)**

Presentation as sexually innature males with no palpable testes due to testicular androgens.

Hormonal studies - FSH and LH with prepubetal level of testosterone.

Etiology :- Exactly unclear but studies suggest -

Testicular torsion, trauma or infection after fetal gonadal differentiation.

**NOONANS SYNDROME**

Clinical features : Short Stature, webbed neck, hypertelorism increased incidence of congenital heart disease, mild mental retardation, various skeletal abnomalities and undescended testes karotype : 46 + XY.

**SCROTAL VARICOCELE**

Amongst infertile males the incidence has been reported to be between 34.39%. Actually, the scrotal varicocele is the most common indentifiable and surgically correctable factor contributing to impaired testicular function and decreased semen quality.

Precise mechanism whereby a varicocele may lead to gonadal dysfunction remains unclear, although several theories have been proposed.

(A) Heat :- an elevation of only 2°C adversely affects quality of sperm production.

In human male, this heat effect has been cited as a contributing pathophysologic process in such entities as cryptochidism, febrile illnesses, prolonged and excessive use of hot tubs.
(B) Refluxing venous toxins: Macleod in 1965 proposed that an abnormal "chemical environment of the testes" may be a causative factor in depressed spermatogenesis associated with a varicocele. Chemical environment may include-

"Adrenal metabolite or catecholamine metabolite through renal vein into internal spermatic vein"

(C) Pressure ischemia

(D) Blood stagnation with germinal epithelial hypoxia.

(E) Alternation in hypothalamic gonadal axis.

Size of varicocele does not appear to determine the magnitude of its effect.

**ORCHITIS**

MUMPS virus and acid fast bacilli of lepromatous leprosy may lead to testicular failure. Rarely unilateral suppurative infections of epididymis may extend to include the testis inadequately or untreated genital infections with *N.* gonococcus may also occasionally cause orchitis.

Orchitis was observed in 30% of males who were 10 years of age or older when mumps parotitis occurred. Fortunately, most males develop parotitis before age of 10 years and orchitis is rarely observed in that age group. Bilateral orchitis develops in up to one third of the affected individuals resulting in subsequent presentation with severe oligospermia or azoospermia.

**HISTOLOGY**  :-  testicular atrophic changes

**HORMONAL STUDIES**  :-  Serum FSH and occasionally, LH may be elevated whereas testosterone levels are usually normal.

**LEPROSY**  :-  Testicular involvement occurs in up to 90% cases of lepromatous leprosy clinically, testicular atrophy 10-20% of infected patients.

**HORMONAL STUDIES**  :-  FSH and LH and reduced testosterone level
MYOTONIC DYSTROPHY

- Autosomal dominant trait with variable penetrance.
- Upto 80% of affected males will eventually develop testicular atrophy.
- Besides involvement of muscles of distal extremities and cranium; other clinical features include prematre baldness, posterior subcapsular cataracts, cardiac conduction defects, impotence, rarely gynecomastia and, at later stages, variable degree of dementia.

CRYPTORCHISM

Review of fertility in operated and nonoperated unilaterally cryptorchid patients has demonstrated a 62% fertility rate in patients operated on before puberty versus 46% in a nontreated group\textsuperscript{31}. Eldrup and Steven have demonstrated extremely low sperm densities in ejaculates from testes that had been subjected to orchidopexy during childhood.

Hormonal studies :- Various conclusions have been documented, however as geminal epithelium becomes progressively damaged, the LH response and total plasma testosterone levels, however, were not significantly abnormal. This exaggerated FSH response may reflect abnormal feedback inhibition due to damaged sertoli cells.

CHEMICALS

Exogenous chemicals may affect the testis directly of indirectly

Directly acting compounds : Flutamide, Cyproterone acetate, spironolactone and cimetidine.

- Various alkylating gents and antimetabolites.
- Nitrofurantion impairs testicular function in high doses interfering with carbohydrate metabolism in germinal epithelium to produce a arrest at primary spermatocyte stage.
Exposure to 1,2 dibromo 3 chloropropane in the pesticide industries has been observed to impair testicular function in man and melerfertelty. No chemical have been associated with effects as strong as DBCP.

Recent reports show that larger amounts of ethanol or its metabolites, actaldehyde, can directly impair synthesis of testosterone in man by increasing testosterone metabolic clearance rates and by suppressing gonadotropins.

Indirect acting compounds such as natural or synthetic androgeus, progestins and estrogens can supress the hypothalamic-pituitary axis to inhibit spermatogeneses. Estrogens may have a direct suppressant effect on the testis.

An increased frequency of reduced speem count among workers expend to glycol ethers has be reported. Risk of spontaneous abortion was increased among wives of men occupationally involved in organic solvents handling in general or to have in particular.

**IRRADIATION**

Germs cells are particularly sensitive to radiation while the leydig cells are relatively resistant. The effect is dose dependent with no significant change in sperm density following exposure of the testis to either 8 or 20 rads but a 3 oospermia was observed in man who recieved more than 70 rads to the testis prepubertal testes seems to be more suscetible to radiation injury. Longer periods are required before spermatogenesis reappears if the dose is increased to 100 rads. Spermatogonia are most radiosensitive, spermatids and spermatocytes are relatively resistant, whereas leydng cells and sertoli cells are most resistant to irradiation.
PARAPLEGIA

Development of paraplegia after puberty has been associated with development of gynecomastia, impotence and testicular dysfunction with normal gonadotropin and subnormal testosterone. The exact mechanism implicated are unknown but probable are autonomic dysfunction and high scrotal temperature.

POLYGLANDULAR FAILURE:

The association of hypothyroidism and adrenal insufficiency with diabetes mellitus, hypoparathyroidism, pernicious anemia, vitiligo, alopecia and hypogonadism has been well established, probable (mechanisms) are autoantibodies to various endocrine tissues.

OBESITY:

Gross obesity may be an important factor causing male SUBFERTILITY. These patients have significantly reduced size and secondary sexual characteristics, conversion of T to E$_2^{37}$ in the adipose tissue has been suggested the responsible mechanism. Semen analysis - oligospermia or impairment of viability and motility.

SICKLE CELL ANEMIA:

Males with sickle cell anemia frequently manifest impairment of statural and sexual maturation. Abbasi et. al.$^{38}$ have reported abnormal secondary sexual characteristics in 29 and enunchoide proportions in 31 of 32 patients. Testicular failure is usually associated with elevated basal levels of gonadotropins and exaggerated responses with administration of LH-RH. Spermatogenesis has also been found to be impaired. Because zinc levels are frequently reduced in these patients and because zinc deficiency and cause testicular atrophy in animals.
UREMIA:

Imotence dysfunction in the hypothalamic-pituitary testicular axis and impairment of spermatogenesis are common findings in uremic males\textsuperscript{30}. In Men with CRF including those receiving chronic dialysis, impotence, oligospermia and germinal cell dysplasia are common, as reduced plasma testosterone levels. Like growth, sexual maturation is often impaired in adolescent children, even among those receiving chronic dialysis\textsuperscript{47}.

CHRONIC LIVER DISEASE:

In a review of 108 patients with chronic liver disease it was noted that importance was present in 79% gynecomastia in 52% and testicular atrophy in 47%.

POST - TESTICULAR CAUSES OF INFERTILITY

Account for upto 15\% of male infertility. Causes can be:

1. Disorders of sperm transport
   
   (a) Mechanical obstruction: Account for upto 6 to 7\% cases of infertility

   1. Congential: Can be due to -

      'Atresia of the cauda epididymis or the proximal part of the vas deferens. It is amenable to surgical repair by epididymovasotomy.

      Absence of the vas deferens may occur unilaterally or bilaterally. It may be accompanied by absence of the seminal vesicles or part of the epididymis. It is always associated with azoospermia, semen that does not coagulate at ejaculation, in absence of fructose.

      Definitive diagnosis will require scrotal exploration.

      Patients with cystic fibrosis also have a high Incidence of congential absence or hypoplasia of the efferent ducts and seminal vesicles.
Intrauterine drug exposure eg. diethylstilbestrol (DES) may result in obstructive epididymal lesions\textsuperscript{40}.

2. **Acquired**: Can be due to -
   
   a. **INFECTION**: accounts for up to 40 to 50% cases of obstructive azoospermia. Gonorrhea was by far the most important bacterial agent, other agent can be E.coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus fecails. Tuberculosis involving the epididymis and vas is usually diffuse and is secondary to prostatic or seminal vesicular infection. Bilateral infection is observed in 10 to 15% of all cases of genital tuberculosis. Treatment with chemotherapeutic agents may result in spontaneous recanalization.

   b. **TRAUMA**: Apart from vasectomy for voluntary sterilization, vas may accidentally be ligated during hernia repair, orchiopexy, and even during varicocelectomy, hydrocelectomy and vasography.

   Functional obstruction of sperm transport results from neuropathic insults like injuries to the sympathetic nerves during retroperitoneal lymph node dissection or pelvic surgery. This may cause lack of peristalsis of the vas deference with the resultant lack of emission and or failure of the bladder neck of close at the time of ejaculation leading to retrograde ejaculation.

**DIABETIC** males with autonomic neuropathy frequently present with both erectile dysfunction and or retrograde ejaculation.

**SPINAL CORD INJURY** can result in paraplegia or quadriplegia with resultant erectile dysfunction and lack of emission and ejaculation.

**DISORDERS OF SPERM FUNCTION**: Once the spermatozoa leave the male genital tract, surprisingly little is known about their subsequent behavior and physiologic function. The normal sperm
function can result in impaired ability to penetrate the ova. Isolated sperm motility/viability problems may be congenital or acquired.

Factors associated with impairment of sperm Motility/viability

**Congenital**

Kartagener's Syndrome

**Acquired**

Intrinsic-varicocele

Prolonged abstinence

Androgen deficiency

Epididymal dysfunction

Infection and occult disorders of accessory sex glands

Agglutinating and immobilizing antibodies

Extrinsic-drugs-Dilantin

Marijuana

Alcohol

Cigarette smoking

**SMOKING** - Various detrimental effects of smoking on sperm concentration, sperm motility and percentage of morphologically normal spermatozoa. The effect of smoking on human leyding cell function is controversial. Despite the reported adverse effects of smoking metabolites mcell. Inhalation of smoke, whether through active or passive smoking, leads to absorption of these substances through the pulmonary vasculature and blood-borne circulation.

It is also that these substances could end up in the seminal plasma of smokers via Various modes of diffusion and active transport. Higher incidence of abnormally shaped sperm cells as well as decreased motility and sperm concentration in men who smoke. Fluctuations in male hormones (androgens) and other hormones responsible for the regulation of spermatogenesis.
and sex drive have been documented in male smokers\textsuperscript{49}. Seminal plasma obtained from smokers and detrimental effects on the sperm quality. SP from nonsmokers may contain a protective substance or factor involved in protection of spermatozoa against cigarette smoke metabolites and that this substance or factors may be decreased or inactivated in the SP of smokers\textsuperscript{55}.

Spermatozoa from smokers showed decreased sperm qualitative and quantitative characteristics. Although semen volume was not reduced in smokers, the spermatozoa count decreased by 26\%. Spermatozoa from smokers exhibited lower motility and progressive motility characteristics. Lower motility and progressive motility problems have been associated with abnormalities noted within the ultrastructure of the flagellum and the axonemal structures of the sperm tail\textsuperscript{56,57}. The most severe abnormality noted in the axoneme of spermatozoa from smokers was the complete disappearance of one or more of the nine fiber doublets and one or more of the central fibers. Axonemal deficiencies are often the cause of lowed motility, progressive motility, and fertility in spermatozoa with a high incidence of defects such as those observed in asthenozoospermic specimens.

**DRUGS**-Drugs may impair androgen action through numerous distinct and sometimes multiple mechanisms-Medications associated with testicular dysfunction and/or gynecomastia.

<table>
<thead>
<tr>
<th>Anti androgens</th>
<th>Antineoplastic drugs</th>
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<tbody>
<tr>
<td>Spironolactone</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Melphalan, Chlorambucil</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Nitrosoureas, Carmustine,</td>
</tr>
<tr>
<td>Estrogens and Hormones</td>
<td>Busulfan, Cisplatin, Cytarabine</td>
</tr>
<tr>
<td>Estrogen agonists</td>
<td>Procarbazine, Vinblastine</td>
</tr>
<tr>
<td>HCG hormone</td>
<td></td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Psychoactive agent</td>
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<td>-------------------</td>
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<tr>
<td>Growth hormone</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Anti hypertensive / CVS agents</td>
<td>Narcotics</td>
</tr>
<tr>
<td>Digoxin(^{58})</td>
<td>Tranquilizers</td>
</tr>
<tr>
<td>Calcium channal blockers</td>
<td>Others: Phenytoin</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Ketoconazole(^{59})</td>
</tr>
</tbody>
</table>

**Testicular Function in HIV-Infected Males:** Testicular function is affected by the progression of patient's disease as males classified as in class IV of disease have a reduced seminal output volume. These man have more frequently a reduced total sperm count, a reduced total motile sperm count, and a higher concentration of round cells. A reduction of seminal quality in males staged as in class IV of disease is supported by higher serum gonadotrophins levels recorded in these males. The concentration of FSH is increased two-folds, the LH values are nearly tripled, and also Prolactin titres are higher in males with severe immunodeficiency. These data could be of help for counselling HIV-infected males willing to have a child\(^{60}\).

Not all bacteria are considered pathogens however many Gram negative bacteria are more often thought to be pathogenic (Meares 1973). However, chronic nonsymptomatic prostatitis caused by gram negative bacteria have not been documented as a cause of male infertility (Amelar and Dubin, 1973). Whether Myoplasma and ureaplasma although frequently isolated, cause of infertility is not clear but Friberg and Gnarpe (1974) reported a conception rate of 24% following antibiotic therapy in such patients. Viral agents including cytomegalovirus and Herpes virus homins are found in semen of normal men (Lang and Kummar 1972). There have been no reports associating infertility with the presence of
these viral agents.

Mononucleosis and hepatitis can cause temporary but often marked depression in sperm production, whether these agents have specific effect on spermatogenesis is not known. Concern has also been raised on effect of severe febrile reactions that accompany viral infections. Most of these effects however, are self-limiting and normal sperm viability will be recovered within 12 months.

GENITAL TRACT TUBERCULOSIS: deserves special mention as tuberculosis is quite prevalent in our country. Tuberculosis of epididymis is generally a part of systemic tuberculosis. When genit al tract tuberculosis alone is present either the prostate or seminal vesicle or both are involved in 100% of cases while epididymis in 62% of cases. Most cases develop gradually with little pain. Tuberculous orchitis as a primary infection is rare but tubercular epididymitis will eventually involve the testes and cause cessation of spermatogenesis at later stage of disease.

Lastly among the causes of infertility is factor which has of all factors received attention very lately and these are immunological factors.

IMMUNOLOGICAL FACTORS IN MALE INFERTILITY:

It is well established that antisperm antibodies (ASA) are etiologically implicated in female infertility. In general, the presence of ASA will reduce the likely occurrence of a pregnancy. The presence of ASA in the female reproductive tract may impair sperm-egg interaction by interfering with the dispersion by interfering with the dispersion of cumulus mass and sperm binding, penetration of the sperm into the zona pellucida, and sperm egg fusion.

The presence of ASA in the male reported ductive tract
affects sperm function by possibly causing premature acrosome reaction and sperm immobilization (agglutination) as well as by decreasing membrane integrity and opsonizing sperm for phagocytosis. Antisperm antibodies may bind to the sperm surface within the testis or epididymis (before ejaculation) or during the mixing of the sperm and seminal plasma at ejaculation\textsuperscript{63}. Both male and female can be rendered infertile by immunization with sperm\textsuperscript{61}. Sperms are very antigenic and normally isolated from body, disruption in this anatomic and functional barrier in seminiferous tubules can lead to antibody formation. Sperm autoimmunity is the most common medically treatable condition seen in men with infertility. It is characterised by immunoglobulins coating the sperm, immunoglobulins localized in the intestinal spaces/tubular wall/both, the presence of sperm antibodies in semen and blood of both the male and female partners and a variable semen quality ranging from azoospermic top normal\textsuperscript{62}. Sperm antibodies can be present in fertile and infertile men at low levels insufficient to further impair fertility. There are two groups of patients with anti sperm antibodies. One is in whom antisperm antibodies are associated with andrological problem causing disruption in blood-testis barrier as mentioned above i.e. (prostato-vesicular inflammation, orchiepididymitis, testicular injury, torsion of spermatic cord, ligation of spermatic cord\textsuperscript{63}. In this group antisperm antibodies not necessarily cause infertility.

Antisperm antibodies have been found to be present in 17 to 30\% of men in various reports.

In the worldwide survey W.H.O found immunological factor be suspected as cause of infertility in 2.8\% of males consulting for infertility. In another report fertile men with history of vasovasotomy, 1 to 2\% may be expected to have sperm bound antibodies, but the percentage is 7-14\%. In men attending a
fertility clinic and in 70% of them, there appears to be no known cause.

PSYCHOSOCIAL STRESS AS A CAUSE OF INFERTILITY:

Psychosocial stress plays an important part in etiology of some forms of infertility. Emotional factors contribute to about 25% of all infertility. One marriage in 10 is involuntarily infertile. The sexual and psychological problems of the infertile couple, however, have been frequently overlooked or knowingly neglected. Anxiety must be reduced to the point that the patient can talk about sexual performance and dysfunction. Stress may significantly alter both spermatogenesis and ovulation to affect fertility in men. The stress must be extreme in nature, however; the effects of daily stress or environmental contamination and nurtainly on infertility is not adequately known but it is certainly reasonable to assume that these factors would play an important part in infertility.