Review of Literature
REVIEW OF LITERATURE

Infertility implies apparent failure of couple to conceive. If a couple fails to achieve pregnancy of her one year of unprotected and regular intercourse it is an indication to investigate the couple. Due to increasing awareness in the medical community of the fact that sub infertility in the male contributes significantly to the society.

"Mathews and Duncan" originally defined infertility "If a married couple did not get any issue within 1 yr. of 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.

It 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 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 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
quantitative 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, as 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.

Mack et al found an incidence of 45 per cent subfertile cases out of a total of 2433 males.

Keettel et al reported an incidence of 41.4 per cent amongst his 152 studied cases and 17.7 per cent cases in his series were azoospermic.

Ferguson – Smith et al. in a series of 758 cases found 332 with counts below 40 million/c.c., 76 with counts below 1 million/c.c., and 50 with azoospermia.

Kreutzman and Keettel et al reported presence of azoospermia in 12-15 per cent and 17.7 per cent of their subfertile cases respectively.

Nelson et al reported obstructive azoospermia in 25 per cent cases; Raboch and Zahor et al in 40.4 per cent cases.
Vaidya et al reported azoospermia in 7 per cent cases.

Dor et al reported azoospermia 11.9 per cent cases and Oligospermia in 10.3 per cent cases. He found male factor to be responsible in 28 per cent cases.

Hernandez Urive et al reported azoospermia in the range of 10-20 per cent.

Acacio BD et al reported that 51 per cent of cases had at least one semen abnormality.

Mbizoo MT et al reported that 24 per cent cases had complete absence of spermatozoa from their semen (azoospermia) of 1518 consecutive cases.

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 steroid hormones. The epididymes contributes to maturation of sperm. The sex accessory glands provide the bulk of the ejaculate.

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

Thus the entire male sexual development depends 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. Yq arm of the Y chromosomes 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 specialised procedures (testicular biopsy) towards end of evaluation.

**CAUSES OF MALE INFERTILITY**

**Causes may be:**

1. Pretesticular (mainly endocrinial).
2. Testicular or defective sperm production.
3. Post testicular or defective sperm delivery.

**1. Pretesticular causes:**

Mainly constitutes endocrinial, other causes are stress. The various endocrinial defect leading to infertility are -
A. **Hypothalamic diseases:**
   - Isolated gonadotropin deficiency (Kallmans' syndrome)
   - Isolated LH deficiency ("Fertile eunuch")
   - Isolated FSH deficiency
   - Congenital hypogonadotropic syndromes.

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

**Hypogonadotrophic state of male infertility**

Depressed levels of gonadotrophins, in concert with subnormal level of testosterone and absent spermatogenesis, characterize the clinical state of hypogonadotrophic hypogonadism. Causes of hypogonadotrophic state :-

1. Idiopathic 
2. Acquired

**Acquired:**

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

1. Primary and metastatic tumors
2. Infiltrative processes
3. Trauma
4. Infection.

In Idiopathic

1. Isolated gonadotrophin deficiency (Kallman's syndrome)

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 initially to depressed gonadotrophin levels, followed by decreased testosterone levels and spermatogenesis.

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 & Drugs - Spironolactone, Cimetidine, Cyproterone Acetate, Ketoconazole, Alcohol, Nitrofurantoin.
I. Irradiation - > 20 rads
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.

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. **Congenital**: Can be due to -

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

   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.

2. **Acquired**: Can be due to -
   
a. **Infection**: accounts for upto 40 to 50% cases of obstructive azoospermia. Gonorrhea is by far the most important bacterial agent, other agent can be E.coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus fecalis. 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.

**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.
2. DISORDERS OF SPERM FUNCTION

Once the spermatozoa leave the male genital tract, surprisingly little is known about their subsequent behavior and physiologic function. The abnormal 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

<table>
<thead>
<tr>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kartagener’s Syndrome</td>
</tr>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>Intrinsic-varicocele</td>
</tr>
<tr>
<td>Prolonged abstinence</td>
</tr>
<tr>
<td>Androgen deficiency</td>
</tr>
<tr>
<td>Epididymal dysfunction</td>
</tr>
<tr>
<td>Infection and occult disorders of accessory sex glands</td>
</tr>
<tr>
<td>Agglutinating and immobilizing antibodies</td>
</tr>
<tr>
<td>Extrinsic-drugs-Dilantin</td>
</tr>
<tr>
<td>Marijuana</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
</tbody>
</table>

SMOKING - Various detrimental effects of smoking on sperm concentration, sperm motility and percentage of morphologically normal spermatozoa. The effect of smoking on human leydig cell function is controversial. Inhalation of smoke, whether 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 are found in men who smoke. Fluctuations in male hormones (androgens) and other hormones responsible for the regulation of spermtogenesis and sex drive have been documented in male smokers. Seminal
plasma obtained from smokers have 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.

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 ultra structure of the flagellum and the axonemal structures of the sperm tail. 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 low 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 gynaecomastia.
<table>
<thead>
<tr>
<th>Anti androgens</th>
<th>Antineoplastic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiironolactone</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Melphalan, Chlorambucil</td>
</tr>
<tr>
<td>Cimeticidine</td>
<td>Nitrosoureas, Carmustine,</td>
</tr>
<tr>
<td><strong>Estrogens and Hormones</strong></td>
<td><strong>Busulfan, Cisplatin, Cytarabine</strong></td>
</tr>
<tr>
<td>Estrogen agonists</td>
<td>Procarbazine, Vinblastine</td>
</tr>
<tr>
<td>HCG hormone</td>
<td><strong>Psychoactive agent</strong></td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Amphetamines Narcotics,</td>
</tr>
<tr>
<td></td>
<td>Tranquilizers</td>
</tr>
<tr>
<td></td>
<td><strong>Others</strong>: Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
</tr>
</tbody>
</table>

**Anti hypertensive / CVS agents**

- Digoxin
- Calcium channel blockers
- Amiodarone

**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 men 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 counseling HIV-infected males willing to have a child.

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 genital 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 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 reproductive 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. Both male and female
can be rendered infertile by immunization with sperm. 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 to normal. 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. In this group antisperm antibodies does 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 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 on infertility is not adequately known but it is certainly reasonable to assume that these factors would play an important part in infertility.