Infertility (Sub-fertility)

Infertility (Sub-fertility) **–** the inability to conceive; despite unprotected, regular sexual intercourse for at least 12 months.

Female sterility, is the intrinsic **inability** of the female to conceive, due to inadequacy in the structure or function of the genital organs

Male sterility - the inability of the male to fertilize the ovum; it may or may not be associated with impotence.

Primary infertility - applies to those who have never conceived

Secondary infertility - designates those who have conceived at some time in the past

Fecundity is the capacity to participate in the production of a child.

Fecundability - likelihood of pregnancy per month of exposure - used to express the chances of pregnancy occurring in any interval of time

Causes of infertility

Male Infertility

1. **Endocrine disorders**
    1. Hypothalamic – Pituitary dysfunction
        1. Kallmann's Syndrome
        2. Pituitary failure eg tumour, radiation, surgery
        3. Hyperprolactinaemia
    2. Gonadal hormone disorders
    3. Thyroid dysfunctions
    4. Adrenal hyperplasia/insufficiency
    5. Drug-induced
2. **Anatomical disorders**
    1. Congenital absence of vas deferens
    2. Obstruction of vas deferens
    3. Congenital abnormalities of the ejaculatory system eg absence of vas deferens or stenosis of ejaculatory ducts
3. **Abnormal spermatogenesis**
    1. Chromosomal abnormalities
    2. Mumps orchitis
    3. Cryptorchidism
    4. Chemical or radiation exposure
    5. Varicocele
4. **Abnormal motility**
    1. Absent cilia (Kartagener's syndrome)

2. Varicocele
3. Antibody formation

5. **Sexual dysfunction**
    1. Retrograde ejaculation
    2. Impotence
    3. Decreased libido

Female Infertility

1. **Ovulatory Factor**
    1. **Central defects**
        1. Chronic hyperandrogenic anovulation
        2. Hyperprolactinemia (drug, tumour, empty sella)
        3. Hypothalamic insufficiency
        4. Pituitary insufficiency (trauma, tumour, congenital)
    2. **Peripheral defects**
        1. Gonadal dysgenesis
        2. Premature ovarian failure
        3. Ovarian tumour
        4. Ovarian resistance
    3. **Metabolic disease**
        1. Thyroid disease
        2. Liver disease
        3. Renal disease
        4. Obesity
        5. Androgen excess, adrenal or neoplastic
2. **Pelvic Factor**
    1. **Infection**
        1. Appendicitis
        2. Pelvic inflammatory disease
        3. Uterine adhesions (Asherman’s syndrome)
    2. **Endometriosis**
    3. **Structural abnormalities**
        1. DES exposure
        2. Failure of normal fusion of the reproductive tract
        3. Myoma
3. **Cervical factor**
    1. **Congenital**
        1. DES exposure
        2. Mullerian duct abnormality
    2. **Acquired**
        1. Surgical treatment
        2. Infection

Other Causes/Related Factors

- Age-related decline in fertility
- Choice of prior contraception e.g. Use of some intrauterine devices (IUDs)
- Having an increased number of sexual partners leads to a greater potential for exposure to

sexually transmitted diseases

Diagnosis

The goals of the infertility evaluation are;

- to determine the probable cause of infertility
- to provide accurate information regarding the prognosis
- to provide counselling support and education throughout the process of evaluation
- to provide guidance regarding options for treatment

Management

Medical History for Female Factor Infertility.

- In utero DES exposure
- History of pubertal development
- Present menstrual cycle characteristics (length, duration, molimina)
- Contraceptive history
- Prior pregnancies, outcomes
- Previous surgeries, especially pelvic
- Prior infection
- History of abnormal Pap smear, treatment
- Drugs and medications
- General health (diet, weight stability, exercise patterns, review of systems)

Medical History for Male Factor Infertility.

- In utero DES exposure
- Congenital abnormalities
- Prior paternity
- Frequency of intercourse
- Exposure to toxins
- Previous surgery
- Previous infections, treatment
- Drugs and medications
- General health (diet, exercise, review of systems)

Physical examination

Relevant investigations

Treatment

Evaluation of Male Factors

Semen Analysis

A semen specimen is collected after **2-3 days of abstinence** (not more than 7 days), and the

specimen should be received in the laboratory within **30-60 minutes of production**.

Normal Semen Parameters

- Liquification – 30 minutes
- Count – 20-250million/mL
- Motility - >50% with forward progression
- Volume - 2-5mL
- Morphology - >50% normal
- Strict criteria - >14% normal
- Viability - >50% live
- pH – 7.2-7.8
- WBC - <1*106/mL

*Spermiogenesis takes about **74 days**

Oligospermia - < 5 million sperm per mL

Mucus Studies

The initial interaction of sperm and female genital tract can be determined by postcoital examination of the cervical mucus (**Sims-Huhner test**).

When mucus is obtained from the cervical canal in the **preovulatory phase**, it normally exhibits a response to the **high estrogen** environment. The mucus is **thin, watery,** and **acellular**; it **dries in a crystalline pattern (ferning),** and acts as a facilitative reservoir for the sperm.

When mucus is collected **2 hours** after intercourse at the appropriate time in the cycle and examined; a satisfactory test results in **large numbers of forwardly progressive sperm** seen in **thin, acellular mucus** and indicates a healthy sperm-mucus interaction.

When the mucus and timing appear favourable, but the sperm appear immobile, tests for **autoantibodies**, in the **male** (Autoimmunity is more likely in men with a history of **trauma, infection**, or **previous surgery**)

or **serum antibodies** in the **female** are appropriate.

Evaluation of Female Factors

- **Ovulatory Factors**

- Follicular phase- The follicular phase can be examined with the assistance of vaginal ultrasound monitoring, so that the development of a normal dominant follicle can be detected by ultrasound around or before the **10th day** of the cycle, with subsequent linear growth of about **1-2 mm per day**, ultimately achieving a preovulatory size of **18-26 mm** prior to rupture.

- Luteal phase The luteal phase is characterized by the production of progesterone and the clinical assessment of the luteal phase relies on the determination of the adequacy of progesterone effects. Indirect evidence of progesterone production can be determined by assessing the following

biological effects of progesterone.

- **Basal body temperature-** Progesterone has a central thermogenic effect; when it is produced in sufficient concentrations, it causes the basal body temperature to become elevated.
- **Secretory endometrium-**The true adequacy of ovulation and of progesterone production is determined only by the establishment of a successful pregnancy, but the use of an endometrial biopsy near the end of the luteal phase can provide reassurance of an adequate maturational effect on the endometrial lining.
- **Premenstrual molimina-**Premenstrual molimina are largely due to the cyclic hormonal influences of estrogen followed by progesterone with estrogen. The particular constellation of symptoms that affect each woman is usually fairly constant, so headaches, bloating, cramping, and emotional lability may be experienced differently, but often repetitively, by different women.
- **Mucus changes-** Within 48 hours of ovulation, the cervical mucus changes under the influence of progesterone to become thick, tacky, and cellular, with loss of the crystalline fern pattern on drying.
- **The Pelvic Factor**

The pelvic factor includes abnormalities of the uterus, fallopian tubes, ovaries, and adjacent pelvic structures. Factors in the history that are suggestive of a pelvic factor include any history of pelvic infection, such as salpingitis, appendicitis, use of intrauterine devices, endometritis, and septic abortion. Endometriosis is in- included as a pelvic factor in infertility and may be suggested by worsening dysmenorrhea, dyspareunia, or previous surgical reports.

- Hysterosalpingogram - Used to determine and demonstrate the uterine contour, the patency of the tubes, and the ability of the dye to freely spill into the pelvis. The test is usually scheduled for the interval after menstrual bleeding and before ovulation

- Laparoscopy - Tubal abnormalities such as agglutinated fimbria or filmy adhesions, which restrict motion of the tubes, or peritubal cysts, may suggest tubal disease that would not necessarily be detected on a hysterosalpingogram. The diagnosis of endometriosis is usually based on laparoscopic findings.

- **The Cervical Factor -** A cervical factor may be indicated by a history of abnormal Pap smears, postcoital bleeding, cryotherapy, conization, or DES exposure in utero.

Treatment

- **Artificial insemination** - When semen parameters are normal but results from postcoital examinations are repeatedly poor, treatment with intrauterine insemination of washed concentrated sperm has been effective in overcoming an apparent barrier to fertility.
- **Induction of ovulation** - patients with chronic anovulation but normal FSH and prolactin
- **Clomiphene citrate,**
- **Pergonal**, or
- **Bromocriptine**

until a normal follicle with apparent ovulation has been consistently achieved - **3-6 cycles** with timed intercourse/inseminations should be attempted.

- **Endometriosis** and the **effects of salpingitis** are 2 of the most common problems confronting infertile couples - Corrected by;

- Salpingoneostomy is the surgical creation of a new ostium in a tube whose fimbrial end is occluded, forming a hydrosalpinx or sactosalpinx. Depending on its location on the tube, **salpingostomy** may be terminal, ampullary, or isthmic.

- Tubocornual anastomosis for pathologic cornual occlusion of the tubes due to disease process and obstructions due to cornual spasm, mucus plug, or intratubal synechiae

- Tubotubal anastomosis

- Fimbrioplasty involves reconstruction of existing fimbriae in a partially or totally occluded oviduct.

The absence of adequate nurturing mucus at midcycle can be treated either by

Attempts to improve the mucus (To improve the amount of mucus, **estrogen** can be administered during the mid- to late follicular phase of the cycle.) or by

Bypassing the mucus with **intrauterine insemination**.

The ultimate therapy for male factor infertility as shown by unfavorable sperm parameters, a negative sperm penetration assay, or both, is **IVF-ET or gamete or zygote intrafallopian transfer (GIFT or ZIFT)**

a) In vitro fertilization and embryo transfer (IVF-ET)

Involves removing eggs from the ovary, fertilizing them in the laboratory, and replacing them into the patient's uterus

Indications

- Severe tubal disease/damage compromising function
- Bilateral salpingectomy
- Antisperm antibodies
- Endometriosis
- Oligospermia
- Unexplained infertility
- When the probability of conception by IVF-ET exceeds that of conception by conventional therapy

Technique

- **Superovulation -** to stimulate several eggs and to better time egg aspiration; At least 2 or 3 follicles should be developing before proceeding with egg aspiration. Drugs used - Clomiphene citrate, Human menopausal gonadotropins (hMG), human follicle-stimulating hormone (hFSH), Gonadotropin-releasing hormone agonist (GnRH-a)
- Evaluating the maturation and growth of the developing follicles by **ultrasound scanning**

or **serum estradiol levels**

- **hCG** is given to mature the oocytes when ultrasonography has determined the presence of an adequate number of preovulatory follicles (17-20 mm). **Ovulation** ordinarily begins **36 hours after hCG injection**.
- **transvaginal aspiration of preovulatory follicles** using a needle is passed through the posterior vaginal fornix using a vaginal ultrasound probe and directed into the ovary. Aspiration of the is performed approximately **34 hours after the hCG injection** or **24 hours after the beginning of the natural LH surge**.
- **Fertilization With Capacitated Sperm -** Freshly ejaculated sperm cannot fertilize an egg; the sperm must be capacitated by a short incubation period in a culture medium. Between **10,000** and **50,000 motile sperm** are placed with each **mature egg**.
- **Culture** of Fertilized Eggs in the Laboratory for **48-72 hours**
- **Replacement of Fertilized Egg into the Uterus -** usually at the **2-cell to 8-cell stage**. The embryos are aspirated into a small catheter, the catheter is passed **transcervically** into the uterus, and the eggs are injected into the **uterine cavity.**

b) Gamete Intra-Fallopian Tube Transfer (GIFT)

Superovulation is induced as in IVF-ET; an hCG injection is given; and the follicles are aspirated via laparoscopy. Prior to laparoscopy, semen is collected and capacitated. The eggs are identified in the laboratory. Sperm are then mixed with the eggs and drawn up into a catheter. The sperm and eggs can also be separated by an air bubble in the catheter. The eggs and sperm are then transferred to the uterine tubes, permitting natural fertilization and cleavage.

GIFT is applicable only in patients who have normal tube function.