Infertility

429 OB/GYN Team

Sources:

- Infertility lecture
- Infertility tutorial
- Obstetrics and Gynecology by Elmar P. Sakala 2nd edition

By: Zeinah AlHalees

Infertility:

***Terminology**:*

Fecundability: the probability that conception will occur in a given population of couples during a specific time period. It is inversely related to the advancing age of the female partner.

Fertility: the ability to conceive after 12 months of regular unprotected sexual intercourse without contraception. In normal fertile couples, 50% will conceive within 3 months, 75% will conceive within 6 months, and 90% will conceive within 12 months.

Infertility: reduced capacity to conceive compared with the general population after 12 months of regular unprotected sexual intercourse without contraception. After 18 months of unprotected sexual intercourse, couples have low monthly conception rate without treatment.

Female fertility declines after the age of 35 and declines more rapidly after the age of 40 so investigations should not be delayed.

In the US, infertility is prevalent in 10% of couples (1/3 in females, 1/3 in males, and 1/3 in the couples combined).

Remember: always deal with the couples together

The couple may be:

Hypofertile (substerile): couples who ultimately conceive but require more time or assistance.

Sterile: couples with absolute and irreversible ability to conceive.

Classification of infertility:

1- ***Primary infertility:*** couples in whom pregnancy has never been established.
2- ***Secondary infertility***: couples who previously conceived but are currently unable to do so.

Requirements for normal fertility:

1- Spermatozoa are present and functional: testes must produce mature functional gametes
2- Occurrence of ovulation: hypothalamic pituitary ovarian axis must be intact
3- Fallopian tubes are patent and functional: fimbria must be able to sweep eggs into the patent and functional oviducts
4- Cervical mucus is favorable: mucus quality must facilitate sperm entry and storage
5- Endometrium is receptive: uterine lining must be hormonally ready for implantation
6- Coitus is timely and suitable: intercourse must take place at midcylce, placing sperm in the vagina

Abnormalities in any of the previous components can result in infertility and should be considered by the clinician evaluating the couple.

Causes of infertility:

1. Male: Spermatozoa either not present or not functional (30-40%) –Oligospermia (low sperm count), Azospermia (absence of sperm in semen, may be obstructive or non-obstructive), Asthenospermia (reduced sperm motility), or Poor sperm morphology

- ***Possible causes include:***
  - Lifestyle – smoking, high alcohol intake
  - Environmental- constantly increased scrotal temperature, exposure to toxins, radiation
  - Drugs-salfasalyasin
  - Coital Abnormalities- Impotence
  - Ejaculation disorders – Retrograde, Premature Ejaculation
  - Congenital abnormalities- crypotoorchidism
  - Chromosomal anomalies
  - Traumatic, Vascular, Hormonal, Inflammatory (epididymitis/orchitis), Infection (mumps) or Immunological causes
- ***Examination:***
  General Health
  Presence of secondary sexual characteristics
  Genital Examination: Epididymis and Testes
- ***Investigations:***
  The aim of the investigations is to give an explanation of the cause, to form basis for treatment, as well as for prognosis
  Investigations include:
  - Hormonal: Testosterone and FSH
  - Chromosome Karyotype
  - Semen Analysis (diagnosis is by semen analysis)

  Semen specimen must be obtained 2-7 days after coitus and should be examined within 30-60 minutes.
  Semen volume and sperm concentration, motility and morphology must be assessed.
  At least 75% of fertile men have at least 1 abnormal characteristic, and 25% have 2 abnormalities. It is more important to consider the number of abnormal parameters than the extent of abnormality in a single parameter.
  If the semen analysis is abnormal, semen analysis should be repeated on 2 or 3 different occasions at least 1 month apart. Semen quality may vary over time and the spermiogenensis cycle is 74 days.

Normal values of semen analysis:

Liquefa - within 30 min
Volume - 2 – 5ml
Motility - > 50% progressive movement
Morphology - > 30% normal forms
PH - 7.2 – 7.8
Density (concentration) - 20-250 million/ml

Remember: Normally under GnRH

Steroidogenesis: Leydig cells between seminiferous tubule → Testosterone – (LH)

Spermatogenesis: Sertoli cells (inhibin) – (FSH)

Both lead to production of healthy spermatozoa

2. Female:

1- **Ovulatory: ovulation does not occur (10-15%)**

- ***In general, assessment of ovulation includes:***
  - History of unpredictable, irregular cycles
  - BBT (basal body temperature chart) showing absence of midcylce elevation. This elevation results from the thermogenic effect of progesterone.
  - ↑ Level of progesterone in serum approximately 8 days after LH surge (Mid luteal phase)
  - Endometrial histology (biopsy) in what should be the luteal phase showing proliferative changes without evidence of progesterone effect.
  - Cervical mucus
  - LH detection kits
- ***Possible causes of anovulation include:***
  - **HYPOGONADOTROPIC HYPOGONADISM:**
    - Hypogonadotropic hypogonadism is caused by a lack of secretion of the gonadal stimulating pituitary hormones: follicle stimulating hormone (FSH) and luteinizing hormone (LH).
    - Normally, the hypothalamus in the brain releases gonadotropin-releasing hormone (GnRH). This hormone stimulates the pituitary gland to release other hormones, including FSH and LH. These hormones tell the female ovaries to release hormones that lead to normal sexual development in puberty. Any change in this hormone release chain causes a lack of sex hormones and prevents normal sexual maturity.
    - Note that Resistant ovary syndrome is: elevated gonadotrophin in the presence of good reserve follicle due to abnormalities of FSH receptors.
    - **Hypogonadotrophic hypogonadism may be due to:**

A- Pituitary dysfunction: failure of pituitary gland to produce gonadotrophin, which will lead to lack of ovarian stimulation. Possible causes include: Pituitary tumor – adenoma/Pituitary inflammation - TB/Ischemia as in Sheehan's Syndrome/ Pituitary damage by radiation or surgery

B- Hypothalamic dysfunction: if pulsatile secretion of GnRH is slowed or stops secondary to: Excessive exercise/ Physiological distress/Anorexia nervosa/ Failure of the hypothalamus as a result of Kallmann syndrome. Kallmann syndrome is an inherited form of hypogonadotropic hypogonadism that can occur with a loss of smell.

- **Treatment**: Induction of ovulation: clomiphene citrate- leads to enhanced GnRH release. Patients resistant to clomiphene citrate, use human menopausal gonadotropin combined with midcylce hCG instead. Another alternative is GnRH which has the advantage of lower rates of hyperstimulation (pulsatile GnRH or by gonadotrophin)

- **PCO (POLYCYSTIC OVARIAN DISEASE):** Usually in obese woman, Reversed FSH: LH ratio in the proliferative phase of the cycle, ↑ Estrogen, Hirsutism, Raised level of circulating insulin and Raised blood sugar.

  Diagnosis:

  History: irregular cycle/oligomenorrhea/Infertility/? Galactorrhea/recurrent abortions

  Examination: Usually obese but it can happen in thin patients/Hirsutism

  Investigations:

  a- ↑ LH

  b- FSH may be normal

  c- ↑ Estrogen

  d- Free testosterone may be ↑ or normal

  e- Ultrasound - multiple small cysts at the periphery of the ovary looks like necklace.

  f- Laparoscopy – thick, enlarged non-active ovaries

  Treatment:

  a- Weight reduction

  b- Induction of ovulation: clomiphene citrate- leads to enhanced GnRH release. Patients resistant to clomiphene citrate, use human menopausal gonadotropin combined with midcylce hCG instead. Another alternative is GnRH which has the advantage of lower rates of hyperstimulation

  c- Metformin

  d- Laparoscopic ovarian diathermy

  e- IVF (in vitro fertilization)

- **HYPERPROLACTINEMIA**: Can lead to infertility by preventing ovulation or by causing luteal defects.

May be due to:
Stress – one reading is not enough to diagnose hyperprolactinemia.
Secondary to ↑ TRH as in cases of hypothyroidism.
Drugs – antihypertensive or antidependents dyes.
Macro or micropituitary adenoma.
Diagnosis:
History: note any drug usage
Examination: galactorrhea and visual equity
Investigation: prolactin level, lateral skull X-ray, and CT Scan
Treatment: Bromocriptin- induces ovulation /Surgery

- **THYROID DYSFUNTION (hypothyroidism)**
- **OBESITY, AGE, AND STRESS**

Note: A method for treating anovulation is the surgical approach. Surgical methods are either ovarian drilling or wedge resection. The theory was that the thick tunica albugenia prevented the release of the ovum.
Disadvantage: tubal damage and adhesion form Destruction of the ovarian stroma and reduction of ovarian reserve
Advantage: No risk of multiple pregnancy & OHSS

Remember:
HIRSUITISM: can be either
Pathological - PCO, adrenal cortex trauma, Cushion syndrome or Constitutional
SITE:
Face, Chest, or Anterior abdominal wall
INVESTIGATION: Free testosterone level, ATCH, FSH, and LH
TREATMENT:
Difficult, needs reassurance, and will take a long time
Hair removal by different methods (ex laser therapy)
Cypretone acetate (Diane) – anti-androgen

2- Tubal (30-40%): fallopian tube is neither functional nor patent

- ***Possible causes include:***
  Adhesions from previous pelvic inflammatory disease/ ruptured appendix/ peritonitis from any cause/ endometriosis/ ectopic pregnancy
  Diagnosis*:*
  May be radiological (hysterosalpingogram, Falloscopy – assessment of tubal patency and mucosa, or Ultrasound scan and hydrotubation) / or operative (laparoscopy)
  Management:
  Can be treated with tubal surgery, IVF and embryo transfer (IVF-ET) or selection salpingography. Although tubal surgery is no longer recommended for severe tubal disease since the introduction of IVF-ET, it still has a place in less severe forms of the disorder.

3- **Cervical (10%)**
   - ***Possible causes include:***
     Lack of estrogen stimulation around the time f ovulation. This low estrogen effect results in thick mucus through which the sperm cannot pass.

4- **Unreceptive endometrium (aka luteal phase defect)**
   - ***Possible causes include:***
     Decreased FSH/ abnormal patterns of LH secretion/ decreased response of endometrium to progesterone
     Other uterine causes: Submucus fibroid – occlude tubes/ congenital uterine abnormalities/ intrauterine adhesion due to excessive curettage/ Asherman's syndrome
     Diagnosis:
     - HSG
     - Hysteroscopy
     - TVU with injection of N/S (Hsyterosonography)
     - Postcoital test: provides information concerning the ability of the sperm to penetrate and survive in the cervical mucus

     Management*:*
     - Myomectomy either laparoscopically or by laparotomy
     - (Entry into the uterine cavity should be avoided if possible, and adhesion barriers and microsurgical technique to reduce the risk of adhesions)
     - Hysteroscopy: Resection of submucous fibroids depending on the size of the fibroid and its degree of protrusion into the uterine cavity
     - (Risk of hemorrhage, uterine perforation and endometrial scarring leading to intrauterine adhesions)

3. Other causes of infertility: coitus is not timely or not performed properly (uncommon cause)

4. Unexplained causes of infertility: 30% of couples will fall into this category

Complete of routine investigation fail to reveal cause in 15-30% of cases does not indicate absence of a cause but rather inability to identify it. The result of IVF shown there may be undiagnosed problems of oocytes or embryo quality or of implantation failure neither of which can easily be tested unless IVF is undertaken.

Management:

Conservative management, ovulation induction with or without intrauterine insemination, and IVE-ET are the main approaches to managing unexplained infertility. It provides information about fertilization and egg and embryo quality. Due to its high cost, IVF-ET is usually seen as a last resort in unexplained infertility.

Note: Multiple causes of infertility will be in 40% of the cases

***Endometriosis**:*

Endometriosis is seen in 40% of infertile women. A proposed mechanism for infertility causation involved increased intraperitoneal macrophages that enter the oviducts and phagocytose sperm. A cause and effect relationship has not yet been established. Endometriosis may be as a result of infertility rather than a cause.

No medical therapy increases fertility rates with endometriosis. In absence of tubal diseases, surgical resection or ablation of peritoneal endometriosis is controversial.

Pregnancy rates with surgical management of tubal diseases are 60% if the damage is moderate and 35% if the damage is severe.

Severe endometriosis cases may undergo IVF-ET