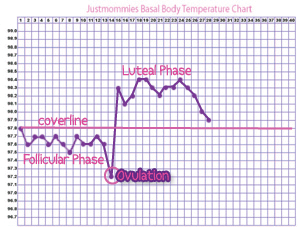
**Infertility**

* **Definitions :**
  + Infertility :

Inability to conceive after one year of unprotected intercourse at the fertile phase of the cycle, (day 11-17 in 28 day cycle, if her period is 30 days >> fertile phase increases 2 days to become from day 13-19, if period 26 days it becomes from day 9-15 and so ) , OR 6 months for women over 35 (because ovulation decreases with age , so don’t wait 1 year حتى نكسب وقت)?

* + PRIMARY Infertility : Couple without a prior pregnancy
  + SECONDARY Infertility : Couple with previous pregnancy including miscarriage/ectopic/molar .
  + Fertility : Ability to conceive
  + Fecundity : Ability to carry to delivery
* Infertility rate after 2 years 14-20 % , 80% of couples will conceive within 1 year of unprotected intercourse , ~86% will conceive within 2 years .
* Origin : (male and female are both equally responsible for infertility to a certain degree )
  + Female factor ~40%
  + Male factor ~30%
  + Combined ~30%
* **Etiologies :**
  + Sperm disorders 30.6%
  + Anovulation/oligoovulation 30%
  + Tubal disease 16%
  + Unexplained 13.4% ( all investigations are normal )
  + Cx factors 5.2% (thick cervical mucus which prevents sperms from getting through cervical canal , or sometimes there are antibodies that attack sperms )
  + Peritoneal factors 4.8% (adhesions mainly endometriosis )
* **Associated Factors :**
  + PELVIC INFLAMMATORY DISEASE (tubal factor )
  + Endometriosis
  + Ovarian aging (> 35 years )
  + Spermatic varicocoele
  + Toxins (who work in factories )
  + Previous abdominal surgery (adhesions that lead to tubal obstruction eg. appendectomy)
  + Cervical/uterine abnormalities (eg. septate uterus )
  + Cervical/uterine surgery (cervical cone biopsy because we remove mucus-producing part of cervix , or asherman syndrome which occurs due to aggressive curettage of uterus )
  + Fibroids (submucous )
* What do we assess in infertility ?
  + Female
    - Ovary
    - Tube
    - Corpus (UTERINE)
    - Cervix
    - Peritoneum
  + Male
    - Sperm count and function
    - Ejaculate characteristics, immunology
    - Anatomic anomalies as HYPOSPADIUS
* The Most Important Factor in the Evaluation of the Infertile Couple Is: HISTORY
* History :
  + General :
    - Both couples should be present at first visit
    - Age fertility is reduced after 35 years of age
    - Previous pregnancies by each partner
    - Length of time without pregnancy
    - Sexual history (do they have intercourse during fertile phase ?)
    - Frequency and timing of intercourse
    - Use of lubricants (most of them are spermicidal )
    - Impotence, dyspareunia (if deep dyspareunia think of >> chronic PID , adenomyosis , endometriosis or fibroid)
    - Contraceptive history (implantation), IUCD (mainly copper IUCD) may cause pelvic infection and block the tubes
  + Male :
    - History of pelvic infection (gonococcal )
    - Radiation, toxic exposures (include drugs)
    - Mumps after puberty causes orchitis
    - Testicular surgery/injury
    - Excessive heat exposure (spermicidal)(tight jeans may kill sperms due to over heat )
  + Female :
    - Previous female pelvic surgery
    - PID
    - Appendicitis
    - IUCD use
    - Ectopic pregnancy history (because we remove tubes , if we remove 1 tube fertility will reduce by one third = 66% of her original fertility )
    - Endometriosis
    - Irregular menses (may be anovulatory cycle), amenorrhea, detailed menstrual history. Regular painful cycles are usually ovulatory cycles
    - Vasomotor symptoms (may be having menopause >> feel warm , sweating )
    - Stress
    - Weight changes (increase or decrease weight cause amenorrhea and thus infertility )
    - Exercise
    - Cervical and uterine surgery
* Physical exam :
  + Male :
    - Size of testicles
    - Testicular descent
    - Varicocoele
    - Outflow abnormalities (hypospadias, etc)
  + Female :
    - Pelvic masses
    - Uterosacral nodularity (endometriosis)
    - Abdomino-pelvic tenderness (PID)
    - Uterine enlargement (fibroid or adenomyosis)
    - Thyroid exam (hyper or hypothyroidism )
    - Uterine mobilitys, post operatibe as ovaran cystectomy or appendectomy: fixed uterus incase of pelvic adhesions due to PID, endometriosi
    - Cervical abnormalities

1. **Ovarian function :**
   * Document ovulation: (how can we know if she is ovulating ?)
     + BBT (basal body temperature )
     + Luteal phase progesterone
     + LH surge
     + Endometrial Biopsy
   * FSH, LH,Prolactin.
     + FSH ,LH are done at 2nd day of cycle (when they are at lower level ), but prolactin can be done anytime .
     + Low FSH &LH means >> hypothalamic pituitary disorder e.g Kallman syndrome,
     + normal FSH & high LH indicates >> PCOS,
     + high FSH & LH indicates >> menopause.
   * Hperprolactinemia suppresses ovulation
   * TSH and adrenal functions if indicated
   * The only convincing proof of ovulation is **pregnancy**
2. BBT (basal body temperature) :
   * Tell her to measure her temperature from the beginning of cycle to beginning of next cycle , in early morning before eating or drinking anything )
   * At time of ovulation there is reduction of temp by 0.3 C then rise by 0.5 degree due to progesterone (biphasic temperature chart )



* + Cheap and easy, but…
    - Inconsistent results
    - 98% of women will ovulate within 3 days of the nadir
    - Biphasic profiles can also be seen with ovulation (30%)

2- Luteal Phase Progesterone : (easiest and cheapest )

* + Progesterone is produced by corpus luteum .
  + Pulsatile release, thus single level may not be useful unless elevated
  + Performed 7 days after presumptive ovulation or day 21 of 28 day cycle (midluteal phase)
  + Done properly, if Progesterone >15 ng/ml consistent with ovulation (or > 30 mmol/ml)

3- Urinary LH Kits :

* + LH usually surges 24-36 hours before ovulation
  + Very sensitive and accurate
  + Do this test by morning urine (concentrated ) , from day 11-17 of 28days cycle
  + Positive test precedes ovulation by ~24 hours, so advice her to have intercourse 24-36 hours after test is positive (or do IUI at this time ).
  + Downside: price, obsession with timing of intercourse

4- Endometrial Biopsy : (not done nowadays )

* + Done in the luteal phase of the 2nd half of cycle.
    - During ovulation the endometrium will change from proliferative to secretory .
    - if histology shows proilferative endometrium this means >> patient is NOT ovulating,
    - if shows secretory endometrium this means >> OVULATION
  + Invasive, but the only reliable way to diagnose Luteal Phase Defect (LPD)
  + Perform around 2 days before expected menstruation (= day 28 by definition)
  + Lag of >2 days is consistent with LPD
  + Must be done in two different cycles to confirm diagnosis of LPD

5- Tubal Function :

* + There are 2 ways to assess tubal function : laproscope and salpingogram .
  + Evaluate tubal patency whenever there is a history of PID, endometriosis or other adhesiogenic condition
  + Kartagener’s syndrome can be associated with decreased tubal motility
  + Tests: done during proliferative phase (after bleeding stops and before getting pregnant ) of the cycle because of fear of pregnancy (day 11) , not done during period (because we might push endometrial cells to circulation because endometrial blood vessels are opened >> risk for endometriosis )
  + HSG note (done during period, we put dye in uterus and take Xray to see if it reaches tubes this means patent tubes) , can diagnose uterine abnormalities , submucous fibroid and asherman syndrome
  + Laparoscopy (we inject methylene blue dye through cervix and use telescope to see if it reaches peritoneum this means patent tubes) , what is advantage of laproscope over hysteroscope ? we see inside the peritoneal cavity eg. Adhesions , endometriosis . but we cannot diagnose uterine abnormalities or asherman .
  + Falloposcopy (not widely available)

6- Hysterosalpingography (HSG) :

* + Radiologic procedure requiring contrast
  + Performed optimally in early proliferative phase (before chance of getting pregnant, day 7-10 in these days her period would have stopped and no pregnancy yet)
  + Low risk of PID except if previous history of PID (give prophylactic doxycycline or consider laparoscopy)
  + Oil-based contrast
    - Higher risk of anaphylaxis than H2O-based
    - May be associated with increased fertility rates
  + Can be uncomfortable
  + Pregnancy test is advisable
  + Can detect intrauterine and tubal disorders but not always definitive
  + Can detect Suterine malformation, Uterine adhesions (Asherman syndrome),submucous fibroid and congenital uterine malformation as septate and double uterus

7- Laparoscopy :

* + Invasive;
  + Can offer diagnosis and treatment in one sitting
  + Not necessary in all patients
  + Uses (examples):
    - Lysis of adhesions
    - Diagnosis and excision of endometriosis
    - Myomectomy

8- Hysteroscope : can diagnose uterine abnormalities , submucus fibroid and asherman

**B- Corpus (uterine body or UTERUS) :**

* + Asherman Syndrome
    - Diagnosis by HSG or hysteroscopy
    - Usually follows D+C, myomectomy, other intrauterine surgery
    - Associated with hypo/amenorrhea, recurrent miscarriage
  + Fibroids, Uterine Anomalies
    - Rarely associated with infertility
    - Work-up:
      * Ultrasound
      * Hysteroscopy
      * Laparoscopy

**C- Cervical Function :** (not done and doctor skipped it )

* + Infection
    - Chlamydia suspected
  + Stenosis
    - follows cervical surgery as LEEP , Cryosurgery, Cone biopsy (probably overstated)
  + Immunologic Factors
    - Sperm-mucus interaction

**D- Peritoneal Factors :**

* + Endometriosis
  + 2x relative risk of infertility
  + Diagnosis (and best treatment) by laparoscopy
  + Can be familial; can occur in adolescents
  + Etiology unknown but likely multiple ones
    - Retrograde menstruation
    - Immunologic factors

**E- Male factors :**

* + Serum T, FSH, PRL levels
  + Semen analysis
  + Testicular biopsy
  + Sperm penetration assay (SPA)
* **Semen Analysis :**
  + Collected after 480 of abstinence (by masturbation ) in sterile container .
  + Evaluated within one hour of ejaculation , during transporting it don’t expose it to excessive heat or cold , so best to be collected in lab .
  + If abnormal parameters, repeat twice, 2 weeks apart
  + **Normal Semen Analysis (spermogram) :**
    - Volume : >**1.5** cc
    - Concentration : >**15** million/ cc
    - Initial Forward Motility : >**32**%
    - Normal Morphology : >**4**%
    - Total sperms per ejaculate : >**39** million
    - If patient is azospermic (no sperm in semen) we take fine needle biopsy (multiple samples) from testis to check , there are 2 types of azospermia :
      * Obstructive :testis produce sperms but vas deferens or epididymis are blocked
      * Secretory : more serious , testis don’t produce sperms . (Tx : sperm donation)
* **Treatment Options : (according to the cause )**

A- Female factors :

* + Ovarian Disorders :
  + Anovulation :
    - Clomiphene Citrate ± hCG. (Side effects of clomiphene citrate include ) :
      * Vasomotor symptoms
      * H/A
      * Ovarian enlargement
      * Multiple gestation 5%
      * NO risk of abortion or malformations
    - hMG (side effects of hMG or FSH include : )
      * hMG or rFSH
      * Multiple gestation 15-20%
      * OHSS (~1%)
      * Can often be managed as outpatient
      * Diuresis
      * Severe cases fatal if untreated in ICU setting
    - Induction + IUI (often done but unjustified)
  + Central amenorrhea :
    - CC first, then hMG
    - Pulsatile GnRH
  + Luteal Phase Defect :
    - Progesterone suppositories during luteal phase
    - CC ± hCG
  + Ovulation Induction :
    - Given for 6 cycles + timed intercourse , if no pregnancy >> give for another 6 cycles + IUI ,

if no pregnancy >> IVF

* + - Oral >> Clomophine citrate: antiestrogen, increases FSH, stimulates follicular growth
      * One tab 50 mg at 2nd – 6th day of cycle , maximum doses = 3-4
      * 70% ovulation rate, ~40% pregnancy rate after 6 cycles
      * Patients should typically be normoestrogenic
      * Induce menses and start on day 2-day 6 of the cycle
      * With dosages, antiestrogen effects dominate
      * Side effects : Multifetal rates 5-10% (95% are twins), rarely ovarian hyperstimulation syndrome OHSS .
      * Other new oral drug is letrozole (Femara) it is aromatase inhibitor .
    - Injectable >> Human Menopausal Gonadotrophins: (if oral fails )
      * Consists of LH +FSH (also FSH alone = Metrodin)
      * For patients with hypogonadotrophic hypoestrogenism or normal FSH and E2 levels
      * Close monitoring essential, including estradiol levels and ultrasound to monitor number of follicles
      * Extracted from the urine of menopausal women .
      * 60-80% pregnancy rates overall after 6 cycles, lower for PCOS patients
      * Side effects : 15-20% multifetal pregnancy rate (66% are twins, and the rest are high order pregnancy ) and may cause OHSS which could be fatal.
      * Do serial U/S during treatment to see if she is ovulating (size of eggs)
      * Now recombinant FSH is commonly used for ovulation induction but very expensive
  + Hyperprolactinemea :
    - Hyperprolactinemea: mostly idiopathic , May be caused by drugs as major tranquilizers, stress, 1ry hypothyroidism, piuitary gland adenoma (Microadenoma < 10mm, Macroadenoma >10mm
    - Check TSH , MRI to exclude pituitary adenoma, and visual field studies (bitemporal hemianopia) due to pressure by the adenoma on optic chiasma
    - Hyperprolactimea with and without adenoma is treated firstly by
      * Bromocriptine given usually twice daily (is dopamine agonist, given during meals, cause severe nausea, GIT bleeding, and hpotension),OR
      * Cabergolin e: less side effect given usually once or twice weekly but expensive
      * Macroadenoma : If there is no response, Trans Sphenoidal Hypophesectomy is performed
  + Fallopian Tubes :
    - Tuboplasty (not done any more )
    - IVF (best method in tubal problem)
    - GIFT (gamete intrafallopian transfer) , ZIFT (zygote intrafallopian transfer) not options
  + Corpus :
    - Asherman syndrome
    - Hysteroscopic lysis of adhesions (scissor)
    - Postop antibiotics, Estrogen or combined pill and Insert IUCD or paediatric Follys catheter inside the uterus to keep the walls of the uterus away from each other
    - Fibroids (rarely need treatment)
    - Myomectomy(hysteroscopic, laparoscopic, open)
    - Uterine anomalies (rarely need treatment)
    - metroplasty also called Strassman  (reconstructive surgery used to repair congenital anomalies of the uterus, including septate uterus and bicornuate uterus)
  + Peritoneum (Endometriosis) :
    - From a fertility standpoint, excision is better than medical management
    - Lysis of adhesions
    - GnRH-a (not a cure and has side effects, expense)
    - Danazol (side effects, cost)
    - Continuous OCP’s (poor fertility rates)
    - Chances of pregnancy highest within 6 mos-1 year after treatment

B- Male factors :

* + If severe male factor , or azospermia >> IVF
  + Hypogonadotrophism
    - hMG
    - GnRH
    - CC, hCG results poor
  + Varicocoele (controversial )
    - Ligation (no definitive data yet)
  + Retrograde ejaculation
    - Ephedrine, imipramine
    - AIH Artificial Insemination with Husbands sperm with recovered sperm from the urinary bladder or with micturation
  + Idiopathic oligospermia
    - No effective treatment
    - IVF
    - donor insemination

C- Unexplained Infertility :

* + 10-15 % of couples
  + Is diagnosed by exclusion i.e all investigation are normal, this include normal semen analysis, normal ovulation tests, normal uterus, tubes and pelvis by laparascopy
  + Empiric treatment:
    - Ovulation induction
    - IUI
    - Consider IVF and its variants
* Check pictures in the lecture .

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