**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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