

# Medical induction of ovulation

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## \*\*Ovulation...

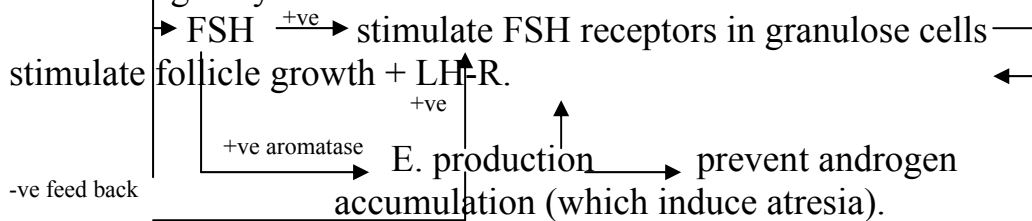
\* Ovulation... is the result of a maturation process that occurs in the hypothalamic-pituitary-ovarian (HPO) axis.

\* Ovarian cycle has three phases...

### 1) Follicular Phase:

1-Primordial Follicle: Oocyte arrested at pro-phase of meiosis + single layer of granulosa cells...under an unknown control... (not Gn.H).

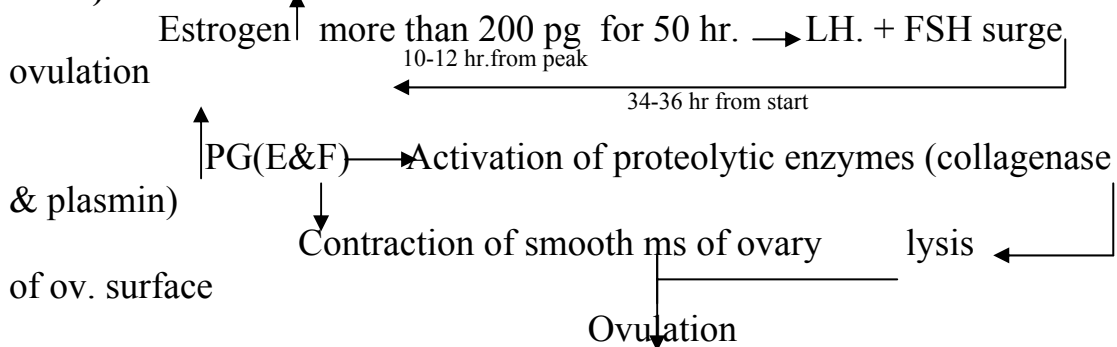
2-Pre-antral Follicle: Several layers of granulosa cells surrounding oocyte.



3-Antral Follicle: E & FSH stimulate formation of follicular fluid Antrum formation... rich in E & contain also PG, PRL.

4- Pre-ovulatory Follicle: only 1-2 follicle reach to pre-ovulatory stage

### 2) Ovulation:



### 3) Luteal Phase...Corpus Luteum:

Granulosa cells become vascularised with carotene deposition yellow lutein cells

## \*\* An-ovulation...

\* An alteration results in a failure to release a mature ovum, leading to an-ovulatory cycles.

\* Chronic anovulation affects 6-15% of women during the reproductive years. It accounts about 30 % of infertility and often present with irregular periods (oligomenorrhoea) or an absence of periods (amenorrhoea).

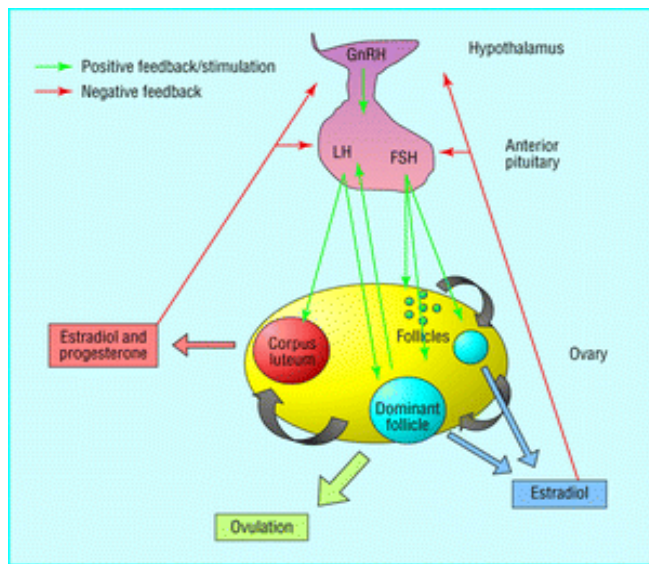
\* In one study, the frequency of anovulation was greater among white women (9 [14.3%] of 63) than black women (4 [7.1%] of 56)<sup>1</sup>.

\* Anovulation is physiologic at the extremes of reproductive age. during menarche..... immaturity of the HPO axis,

during peri-menopause..... dys-regulation of feedback mechanisms are responsible.

### \*Causes of anovulation...

Simply....any defect in the HPO axis —————>anovulation



Hypothalamic-pituitary-ovarian axis (FSH=follicle stimulating hormone; GnRH=gonadotrophin releasing hormone; LH=luteinising hormone)

### 1) Hypothalamic-pituitary causes...

# **Hypo-pituitarism** ..... characterized by a selective failure of the pituitary gland to produce LH & FSH.

1- The commonest cause is excessive exercise, underweight (anorexia), or both. Women who have a low BMI (< 20) or who exercise excessively (gymnasts, marathon runners, ballerinas) may develop amenorrhoea due to physiological reduction in the hypothalamic production of GRH... (leptin, "a serum hormone secreted by adipose tissues in proportion to total body lipid stores", levels similar to those of prepubertal girls and consequently lose the diurnal release pattern).

2- Sheehan's syndrome..... infarction of the anterior pituitary venous complex (usually after massive postpartum hemorrhage or trauma). It is considered the most common cause of pan-hypopituitarism in women of childbearing age<sup>2</sup>.

3- Kallman's syndrome.....(amenorrhoea with anosmia caused by congenital lack of hypothalamic production of GRH)... are rare.

4- Hyperprolactinaemia... usually caused by a pituitary microadenoma, (Approximately 10% of all intracranial tumors are pituitary adenomas). This leads to inhibition of pituitary LH & FSH via suppression of Gn-RH pulsatility).

- Mild hyperprolactinemia may cause infertility, even in the presence of a regular menstrual cycle, while elevated levels of prolactin may cause galactorrhea.

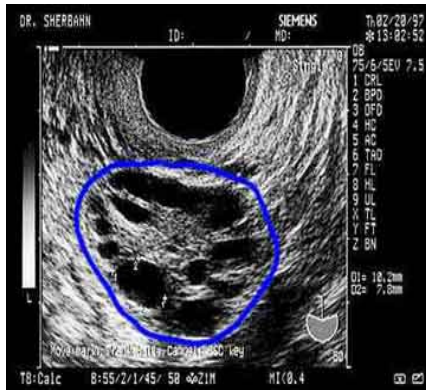
- Empty sella syndrome is a benign cause of hyperprolactinemia in 4-16% of women who present with amenorrhea and galactorrhea<sup>3</sup>. It is characterized by an abnormal relationship between the sella turcica and the sellar diaphragm that results in the herniation of the subarachnoid space into the pituitary fossa..

**N.B.** The hypothalamus is a radiosensitive structure; therefore, external irradiation can cause damage to the hypothalamus and impair its function...(70% of women undergoing cranial irradiation experience menstrual irregularities)<sup>4</sup>.

## 2) Ovarian causes...

# **Polycystic ovarian syndrome** is the commonest cause (70%) of anovulatory subfertility.

- Women with PCO commonly present in their late teens or early 20s with hirsutism, acne... (hyperandrogenism), or irregular periods. Even if they ovulate, the chance of conception for these women is reduced because fewer ovulatory events occur in a given time frame.



## # **Premature ovarian failure (premature menopause)**

- This is an irreversible condition. The only treatment option that can result in conception is the use of donated eggs within IVF. Patients will need HRT to alleviate menopause symptoms and to reduce loss of bone density.

## 3) Genetic abnormalities..

# The commonest genetic abnormality is Turner's syndrome (45,0X), in which the streak ovaries result in primary ovarian failure.

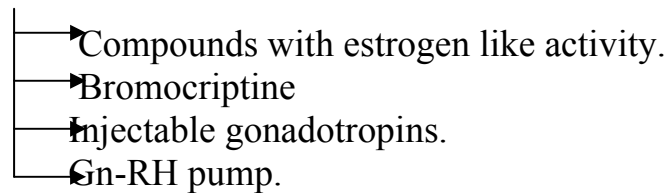
- With adequate oestrogen replacement the uterus can grow large enough for the woman to conceive using donated eggs.

# 10% of primary amenorrhoea is caused by androgen insensitivity syndrome (testicular feminization...46,XY karyotype, intra-abdominal gonads "testes", phenotypically female....due to absence of or non-functionally androgen receptors).

The gonads should be removed because of an increased risk of malignant change.

## Medical induction of ovulation

- \* Use of medication to stimulate development of one or more mature follicles.
- \* **Success** rates for induction of ovulation vary considerably and depend on many factors as: **age** of the woman, **type** of medication used, **other** infertility factors present in the couple, etc..
- \* **There** are four basic types of medication that are used to induce ovulation....

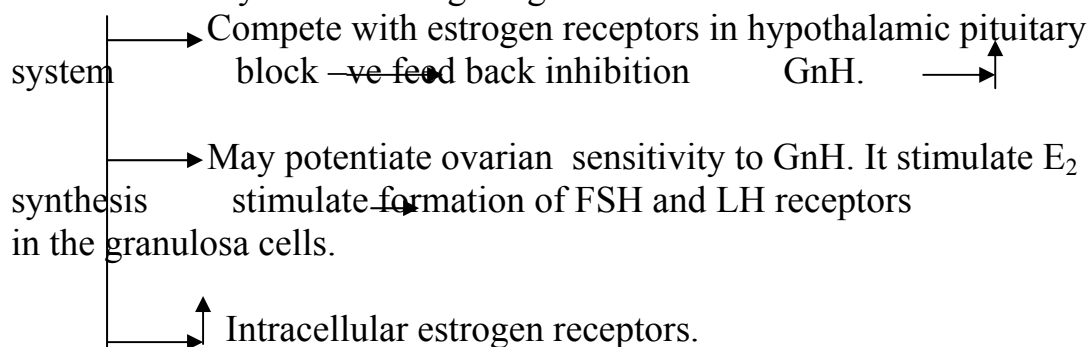


### 1) Compounds with estrogen like activity...include:

#### A- Clomiphene citrate..

\* Clomiphene citrate is a non-steroidal compound has a remarkable structure similarity to Estradiol ( $E_2$ ) which bind to  $E_2$  receptors in various tissues such as the hypothalamus, hypophysis, ovaries uterus and cervix.

\* CC act mainly as anti-estrogen agents..



\* **Dose** ...CC is administered at daily doses from 50 to 250 mg/day for 5 days during the follicular phase starting on day 2, 3, or 5 of the cycle depending on the length of the menstrual cycle of that particular individual.

\* Ovulation is known to occur in about 70% of cases , while pregnancy occurs in about 25-30% ....

### **# Failure of ovulation is due to:**

1- Weak effect of the drug ( **dose** "up to 250mg/day", or **duration** " 50 mg/day for 5 days & every 5days by 50mg till maximum dose)... if failed use adjuvant.

2- Another cause of anovulation.

### **# Failure of pregnancy is due to:**

1- Anti-estrogenic effects of CC on the cervix ( make it hostile to sperm penetration) & on the endometrial growth (aninical to embryo implantation).

2- Other reasons as LPD . CC can impair development of the granulosa cells and thus cause Luteal phase defect.

3- Other cause of infertility.

**N.B.**...Pregnancy rates with CC are about 10-15% per ovulatory cycle for the first 3 cycles. After 3 cycles without a pregnancy, pregnancy rates are lower & after 6-9 failed cycles, the chances are very lowe with further clomiphene therapy.

**\* CC + Adjuvant**.... **1)** CC + HCG.....HCG act like LH , given (10,000 I.U. once or 5000 I.U. /day for 2days) after 7 days after stoppage of CC or when GF reach 16-18 mm in diameter.

**2)** CC + Dexa.....decrease androgens which makes patient resistant to clomiphene therapy.

**3)** CC + Bromocryptine.....used if PRL is high, some use it even with normal PRL level. It intensified release of the FSH & LH.

**4)** CC + HMG +HCG...either Clomiphene started from 5<sup>th</sup> to 9<sup>th</sup> days then continue with HMG with monitoring by USS or serum E<sub>2</sub> till mature GF & give HCG.....**OR** ....both used from 5<sup>th</sup> day till 9<sup>th</sup> then stop Clomiphene & continue HMG till mature GF & give HCG.

**5)** CC + Levothyroxine....used if luteal phase dysfunction is caused by hypothyroidism.

6) CC + Metformin.... It is an oral hypoglycaemic medication approved for use in the U.S.A. for treatment of Type 2 diabetes in December,1994 .It reduces hepatic glucose output, decreases intestinal absorption of glucose, and increases glucose uptake in the peripheral tissues .

- It has been used in the last few years by some infertility physicians to assist in inducing ovulation in some women with anovulation and PCO. Studies report that Metformin at doses of 1500 mg a day may improve menstrual regularity by reducing insulin and free testosterone concentrations in both lean and obese women with PCO who are not ovulating.

7) CC + Estrogens.....May be used for restoration of regular menstrual cycles, which may prevent endometrial hyperplasia associated with anovulation.

**\* Side effect of CC:**

1) OHSS...rare with CC 1% & only happened when HCG is given, So strict evaluation must be done before given.

2) Hot flushes 10% & drug vaginitis due to poor cervical mucous(anti-estrogenic effect).

3) Nausea, vomiting, abdominal distension & constipation.

4) Headache, visual disturbances (stop drug at once).

5) Breast discomfort & alopecia(rare).

6) Rarely allergic reaction (urticaria & dermatitis).

7) Multiple pregnancies 5-10% , So increase incidence of abortion. It have teratogenic effect on animals studies.

**B- Cyclofenil (Ondogyne)..**

\* Chemically related to Clomiphene & have similar mechanisms of action. It have low % of side effects & low incidence of multiple pregnancy. It given in dose 100-200 mg as Clomiphene with maximum dose 400mg.

## **C – Tamoxifen..**

\* Triphenylethylene compound, have anti-estrogenic effect, compete with estrogen at its receptors. It given in dose 20mg/day ( maximum 40 mg /day).... Its side effect includes:

1- risk of endometrial carcinoma as it stimulate growth of endometrial cells.

2- Thrombotic stroke (less than 1%).

3- Hair & nail thinning.

## **2) Dopamine Agonists..**

\* Prolactin excess manifests clinically as sub-fertility, oligomenorrhea, and amenorrhea...( inhibit pituitary gonadotropins via suppression of GnRH pulsatility, So, serum gonadotropins levels are significantly decreased & may cause secondary hypogonadism).

\* Mild hyperprolactinemia may cause infertility, even in the presence of a regular menstrual cycle, while elevated levels of prolactin may cause galactorrhea.

\* Patients with hyperprolactinemia must always have a complete history and physical examination to rule out easily correctable causes of hyperprolactinemia ( as drug induced eg: neuroleptics , antidepressants, some antipsychotics). All women with unexplained elevations of prolactin over about 50-100 ng , MRI must be done to exclude prolactinoma.

***Dopamine agonists***.....Directly activates postsynaptic dopamine receptors. The dopaminergic neurons in the tuberoinfundibular process modulate the secretion of prolactin from the anterior pituitary by secreting a prolactin inhibitory factor.

**1) Bromocriptine**.... a dopaminergic agonist. It activates the postsynaptic dopamine receptors, which results in a diminishing of the increased prolactin secretion and intensify the release of FSH & LH.

\* Dose... start with a small dose "1.25 mg taken with food " at night, then↑ gradually to effective dose. Prolactin level checked, and if it is below 1000 IU/l, the dose should be maintained.

\* About 28% of the dose is absorbed in the GIT. About 90 – 96% of bromocriptine are bound to the plasma proteins. Before excretion the drug is completely metabolized. The main route of excretion is through the bile and only 2.5 – 5% is eliminated in the urine

\* Bromocriptine decreases also the level of somatotrophic hormone in Acromegaly & in Parkinson's disease its therapeutic effect is exerted by direct stimulation of the dopamine receptors in the striate body.

\* The side effects of bromocriptine ( postural hypotension, nausea, vomiting, dizziness, fatigue, constipation, abdominal cramps ) can make it unacceptable to the patient.

**2) Cabergoline** (Dopergine, Dostinex) and Quinagolide (Permax) are newer long acting dopamine agonists with fewer side effects.

### **3)Injectable gonadotropins...**

-The first successful induction of ovulation and pregnancy in the human was described by Gemzell et al. in 1958.

#### **\*Indication...**

- Women with hypothalamic-pituitary causes of anovulation.
- Ovarian causes as PCO failed to respond to clomiphene.
- Induce multiple ovulation in patient undergoing IVF.

#### **\*Preparation..**

1- Human menopausal gonadotropins HMG... is a purified preparation of gonadotropins extracted from the urine of post menopausal and pregnant women. It contains 75IU of FSH + 75IU of LH as Humigone, Pergonal.

2- Highly purified FSH as Metrodin, Puergon...less side effects & used in some cases especially those with very high level of LH....

#### **\*Dose&Administration..**

- There are many protocols to use HMG according to the indication & response of the ovaries..( gynecologic & endocrinologic evaluation must be performed prior to treatment with HMG. The evaluation may include HSG, serial vaginal smears & cervical mucus, & in some cases endometrial biopsy).

- The usual initial dosage of HMG to produce follicular maturation is 75 IU of FSH / LH daily, administered i.m. every other day, eg. days 1,3,5,7 or 3,5,7,...up to 12 days in a single course therapy with continuous monitoring of follicular maturation. Follicles of 17 mm or more in diameter, as revealed by ultrasound, can be considered mature.

**\*When HCG given?**

1- Serum  $E_2$  = 1000-1500 pg/ml..( measurement starting 1 week after the beginning of each course of HMG and continuing through the day of hCG administration).

2- Urinary E = 100-150 ug/24H .

3- Uss folliculometry... 16-18mm in diameter.

**\* Aim of monitoring...**

- To give HCG at the proper time to avoid premature lutenization of GF.

- To avoid hyperstimulation (likely to occur when serum  $E_2$  more than 2000 pg/ml or urinary E more than 200ug/24h or if daily response of E is doubled).

**N.B.**...Urinary pregnanediol levels higher than 2 mg/24 hours, indicate that ovulation has occurred. A serum progesterone level over 10 ng/mL also provides adequate proof of a functional corpus luteum.

**\*Results...**

- Ovulatory rate up to 90% & pregnancy rate vary from 50-90% in properly selected patient in 2-6 cycles.

**\*Causes of failure:**

1-Ovaerian dysgenesis or agenesis...

2- Resistant ovarian syndrome..

3- Premature menopause...

4- Poor cervical condition

5- Other causes of infertility ...

**\*Side effect....**

1- Expensive.....may leading to psychological impotence.

2- pain & swelling at injection sites.

3- Multiple pregnancy... **So** abortion rate increased. Generally about 81% are single, 15% twins, 3% triplets and 1% quadruplets or more.

- In very rare cases, 9 or more fetuses have implanted and shown heartbeat activity on ultrasound studies. Rarely can a pregnancy of more than 5 fetuses result in viable live birth unless a fetal reduction procedure (selective abortion) is performed at about 9-11 weeks of gestation.

4- Hyper-stimulation syndrome OHSS most serious & may be fatal, **So** it is essential that this treatment is monitored by reproductive specialists with access to ultrasonography and tertiary care facilities.

### **\*OHSS...**

- **It** occur in approximately 1% of cycles with Clomiphene & nearly 10% with HMG. With Clomiphene & purified FSH occurs only when hCG is given but with HMG contain FSH & LH can happen even without hCG.

**\* Pathology** ...ovarian enlargement , ascitis , hydrothorax , DIC , ...etc

□ Hyper-stimulated ovaries — secretion of high amount of estrogen which \_\_\_increase capillary permeability....SO.. leak of fluids extravascullary —>ascitis , hydrothorax , sever electrolytes imbalance & haemo-concentration up to DIC ( HV is the most important follow up test)....So the larger the ovaries ..increase severity & if pregnancy occurs improvements delay.

**\* Clinical presentation.....1) Mild cases....** ov. enlargement more than 8cm, transient lower abd. discomfort + distention + wt. gain (any discomfort with or without fainting occurring 2-4days after hCG is given must be taken seriously).

**2) Moderate cases ...wt. gain more than 2 kg/day + sever ov. enlargement (above umbilicus) + ascitis + pleural effusion ( hypo-proteinaemia + electrolyte imbalance & heamo-concentration ) + dyspnea ...marked nausea & vomiting, hypovolaemia with orthostatic hypotension + decrease renal blood flow.**

**3) Sever cases....** sever haemo-concentration with increasing of HCV more 50% + sever hypovolaemia & hypotension. Life-threatening complications of OHSS include renal failure, adult respiratory distress syndrome (ARDS), hemorrhage from ovarian rupture, and thromboembolism

## \* **Treatment....**

↳ **Prevention....** The keys to preventing OHSS are experience with ovulation induction therapy & recognition of risk factors. Caution is indicated when any of the following indicators for increasing risk of OHSS are present:....Rapidly rising serum estradiol levels

An estradiol concentration in excess of 2,500 pg/mL.

**NB:** Prophylactic IV administration of 25% albumin (20–50 g) at time of oocyte retrieval (in IVF) has been suggested as a means to reduce risk of OHSS when E<sub>2</sub> levels are markedly elevated or there is history of a previous episode of OHSS.

↳ **Curative.. # Outpatient treatment....** Patients with mild manifestations of OHSS can be managed on an outpatient basis. Treatment usually requires only oral analgesics & counseling regarding the signs and symptoms of progressing illness. Intercourse is avoided as it may be painful and may increase the risk of ovarian rupture.

**# Hospitalization...** Hospitalization should be considered when one or more of the following are present:

- Severe abdominal pain or peritoneal signs
- Intractable nausea and vomiting that prevents ingestion of food and adequate fluids.
- Severe oliguria or anuria
- Tense ascites
- Dyspnea or tachypnea.
- Severe electrolyte imbalance (hyponatremia, hyperkalemia)
- Hemoconcentration
- Abnormal liver function tests.

\* Laboratory findings in serious cases include: Hemoconcentration ( HC: >45%), Leukocytosis (WBC<sub>s</sub> count > 15,000) . Electrolyte imbalances ( hyponatremia:Na <135 mEq/L, hyperkalaemia:K: >5.0 mEq/L). Elevated liver enzymes, Decreased creatinine clearance (serum creatinine >1.2; creatinine clearance <50 mL/min)

\* Evaluation and monitoring of hospitalized cases include:

- Vital signs (every 2–8 hours, according to clinical status)
- Weight (recorded daily)
- Abdominal circumference (at the navel, recorded daily)
- Monitoring of fluid intake and output.
- Ultrasound examination (ascites, ovarian size).
- Chest x-ray and echocardiogram (when pleural or pericardial effusion is suspected), repeated as necessary
- Complete blood count.
- Electrolytes (daily)
- Serum creatinine or creatinine clearance, urine specific gravity, repeated as necessary
- Liver enzymes, repeated as necessary

**1) Fluid Management**...IV fluid is very important for volume expansion, but monitoring must be done to prevent overflow. SO Strict monitoring of fluid intake and urine output is essential until symptoms improve or diuresis begins & also Oral fluid intake should be carefully recorded and limited to those amounts necessary to maintain the patient's comfort.

- Fluid used include... mainly D/S to correct hypovolemia, hypotension, and oliguria. Albumin 25% in doses of 50–100 g, infused over 4 hours and repeated at 4- to 12-hour intervals as necessary, is an effective plasma expander (mannitol, fresh frozen plasma may be used). Dextran has been associated with development of ARDS & is best avoided.

- Use of diuretics as furosemide, may be used after hypovolaemia correction (hematocrit <38%).

- Hyperkalemia is associated with risk of cardiac dysrhythmias. Acute management involves treatments that move potassium into the intracellular space (insulin & glucose, sodium bicarbonate, albuterol) or protect the heart from the effects of elevated potassium levels (calcium gluconate).

- ECG manifestations of hyperkalemia (prolonged PR & QRS intervals, ST segment depression, tall peaked T waves) indicate the need for immediate treatment with calcium gluconate. ( Kayexalate is a cation exchange resin that removes potassium from the body but works more slowly (onset of action 1–2 hours); it may be administered orally or rectally as a retention enema).

**2) Paracentesis...** Ultrasound-guided (TV or TA) paracentesis may be indicated for patients with ascites that causes pain, compromised pulmonary function (e.g., tachypnea, hypoxia, hydrothorax), or oliguria/anuria that does not improve with appropriate fluid management.

- Serial paracentesis may be required to maintain adequate renal and pulmonary function. Severe ascites may be associated with hydrothorax, most commonly on the right, resulting from transfer of abdominal fluid to the chest via the thoracic duct.

- Paracentesis will generally be effective in resolving hydrothorax and thoracentesis may be reserved for those with bilateral or severe pleural effusions that persist.

- Thromboembolism is a life-threatening complication of severe OHSS, and prophylactic measures are warranted. Full-length venous support stockings are recommended, and prophylactic heparin therapy (5,000 U SC every 12 hours) should be considered.

- Renal failure will often respond to low-dose dopamine therapy (0.18 mg/kg/h) that will dilate renal vessels and increase renal blood flow.

**3) Surgical treatment..Only** indicated when internal hemorrhage is sure (sudden decrease of HV, peritoneal irritation signs, increase pulse, decrease BP. &UOP), & must be after correction of condition otherwise un necessary laparotomy could be danger.

#### **4) Gn-RH pump..**

\* Indicted...only in hypothalamic causes with intact pituitary gland.

- Advantages: no multiple ovulation & no hyperstimulation.

- Disadvantages: very expensive , need intact pituitary , must be given in apulsatile manner (2.5ng/kg/90minutes for 28days iv or sc by special automatic pump or recently as nasal spray). and this usually leads to unifollicular ovulation. Local reactions may occur at the injection site.

- Conception rates are similar to those in the normal population at around 20-30% per cycle and 80-90% after 12 months' use.



**Patient wearing a gonadotrophin releasing hormone pump**

- 1) (Haiman, 2002).
- 2) (Mestman, 2002).
- 3) (Speroff, 1999).
- 4) (Warren, 2001).