Ovulation induction and assisted reproductive techniques

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Female Factor Infertility

- Uterine
- Cervical
- Tubal
- Unexplained infertility
- Ovarian

Ovarian causes

- • The World Health Organization (WHO) classifies ovulatory disorders into three groups

- • Class 1 (hypogonadotropic hypogonadal anovulation): 5-10%

Low or low to normal serum FSH and low serum estradiol due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH

- In Group where there is a deficiency in gonadotropin-releasing hormone (GnRH) leading to low levels of FSH and LH, the following drugs are commonly used:

1. **Gonadotropin-Releasing Hormone (GnRH) Therapy**: GnRH agonists or pulsatile GnRH can be administered to stimulate the pituitary gland to produce FSH and LH.
2. **Clomiphene Citrate**: Occasionally used to stimulate the hypothalamus, although it may not be as effective if GnRH is severely deficient.
3. **Lifestyle Modifications**: While not a drug, addressing underlying issues such as stress, weight, and exercise can be crucial.

- • Class 2 (normogonadotropic normoestrogenic anovulation): 70-85%
- May secrete normal amounts of gonadotropins and estrogen and may ovulate occasionally. However, FSH secretion during follicular phase is subnormal. Common cause: PCOS
- the following drugs are commonly used:

1. **Clomiphene Citrate**: An oral medication that stimulates the hypothalamus to release GnRH, leading to increased secretion of FSH and LH.
2. **Aromatase Inhibitors**: Such as letrozole, used off-label to promote ovulation by lowering estrogen levels, which can stimulate FSH production.
3. **Gonadotropins**: If Clomiphene or aromatase inhibitors are ineffective, injectable FSH and LH (or hMG) may be used to directly stimulate the ovaries.

- • Class 3 (hypergonadotropic hypoestrogenic anovulation): 1 0-30%
- Elevated FSH levels Primary causes: POF, ovarian resistance
- In Group III (Hypergonadotropic Hypogonadism), where there are high gonadotropin levels but poor ovarian response, the following drugs are commonly used:

1. **Estrogen Replacement Therapy**: To manage symptoms and support the uterine lining.
2. **Gonadotropins**: Such as Human Menopausal Gonadotropin (hMG) and recombinant FSH, which can help stimulate the ovaries for assisted reproductive technologies.

symptomatic treatment

extracted from Urine of menopausal women ⇒ due to high FSH levels in it

Clomiphene citrate

Depend on tissue type

- • Mechanism of action: Estrogen antagonist and agonist, results in increased FSH and LH release due to its anti-estrogen effects at level of the hypothalamus
- • Side effects: Hot flushes, visual symptoms (blurry vision, scotomata), headaches, mood swings
- • Risks: Approximately 10% risk of multiple gestation
- • Administration

• Begin on cycle days 2-5 at a dose of 50 mg every day for 5 days

• if ovulation doesn't occur in first cycle, increase to 100 mg

cont..

- • Advise intercourse every other day for 1 week beginning 5 days after last day of medications, or time intercourse based on ovulation predictor kit OR intrauterine insemination (IUI) just before ovulation
- • Can also check 2 1 -day serum progesterone level to confirm ovulation (ovulation if progesterone >3 ng/mL)
- • After six unsuccessful cycles, consider new treatment

Aromatase inhibitor

- Letrozole ("Femara)
- • Mechanism of action: Aromatase inhibitor: decreases estrogen negative feedback at level of hypothalamus, results in increased FSH. As follicle develops, negative feedback usually results in monofollicular development
- • Administration: Begin 2.5-7.5 mg on days 2-5 for 5 days
- • Side effects: Edema, hot flashes, headaches
- • Higher live-birth and ovulation rates with letrozole compared with clomiphene. May be a lower twin pregnancy rate.

gonadotropin

gonadotropin drugs commonly used for ovulation induction include:

- Human Menopausal Gonadotropin (hMG)mixed FSH and LH:

Menotropin

1-Menopur(urinary gonadotropins) : Contains both FSH and LH, stimulating ovarian follicle development

- Human Menopausal Gonadotropin (hMG) works by supplying both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to stimulate ovarian function.
- FSH Action: It promotes the growth and maturation of ovarian follicles, facilitating the development of eggs.
- LH Action: It triggers the final maturation of follicles and stimulates ovulation by inducing the release of the mature egg.
- SE : Ovarian Hyperstimulation Syndrome / Multiple Pregnancies/Headaches/Mood Changes/Gastrointestinal Symptoms/Injection Site Reactions

2-

- Recombinant Follicle-Stimulating Hormone (FSH only):

↳ Follitropin alfa

1-Gonal-F(Recombinant): A recombinant FSH used to promote follicle growth.

↳ Follitropin beta

2-Follistim(Recombinant) : Another form of recombinant FSH for ovarian stimulation.

- **Mechanism of Action of Recombinant Follicle-Stimulating Hormone (FSH) in Ovulation Induction:**

1. **Binding to FSH Receptors**: Recombinant FSH binds to FSH receptors located on the granulosa cells of the ovarian follicles.
2. **Follicular Development**: This binding stimulates the growth and maturation of ovarian follicles, promoting the development of multiple follicles in the ovaries.
3. **Increased Estradiol Production**: FSH also stimulates the granulosa cells to produce estradiol, an essential hormone that supports follicular growth and prepares the endometrium for potential implantation.

- SE : Ovarian Hyperstimulation Syndrome / Multiple Pregnancies/Headaches/Mood Changes/Gastrointestinal Symptoms/Injection Site Reactions

- Human Chorionic Gonadotropin (hCG):

1-Ovidrel (Recombinant): A recombinant hCG used to trigger ovulation.

2-Pregnyl (urinary): An injectable hCG derived from urine, also used to induce ovulation.

- **Mechanism of Action of Human Chorionic Gonadotropin (hCG) in Ovulation Induction:**

1. **Mimics Luteinizing Hormone (LH)**: hCG closely resembles LH in structure and function. It binds to LH receptors on the ovarian follicles.
2. **Triggers Final Follicular Maturation**: When administered, hCG stimulates the ovaries to complete the maturation of follicles that have been developing under the influence of FSH. This process prepares the follicles for ovulation.
3. **Induces Ovulation**: Approximately 36-40 hours after administration, hCG triggers the release of the mature egg from the dominant follicle, resulting in ovulation.
4. **Supports Luteal Phase**: After ovulation, hCG helps maintain the corpus luteum, which secretes progesterone to support the uterine lining for potential implantation.

more GnRH ⇒ More Response ⇒ More follicles

In-vitro fertilization

→ Aim: Producing more # of oocytes ⇒ improve succes Rates later

لكن الزيادة بجرعة الدوا بتكون لحد معين ما بيتجاوزه

عشان ما انتج عدد مبالغ فيه من البويضات تا…

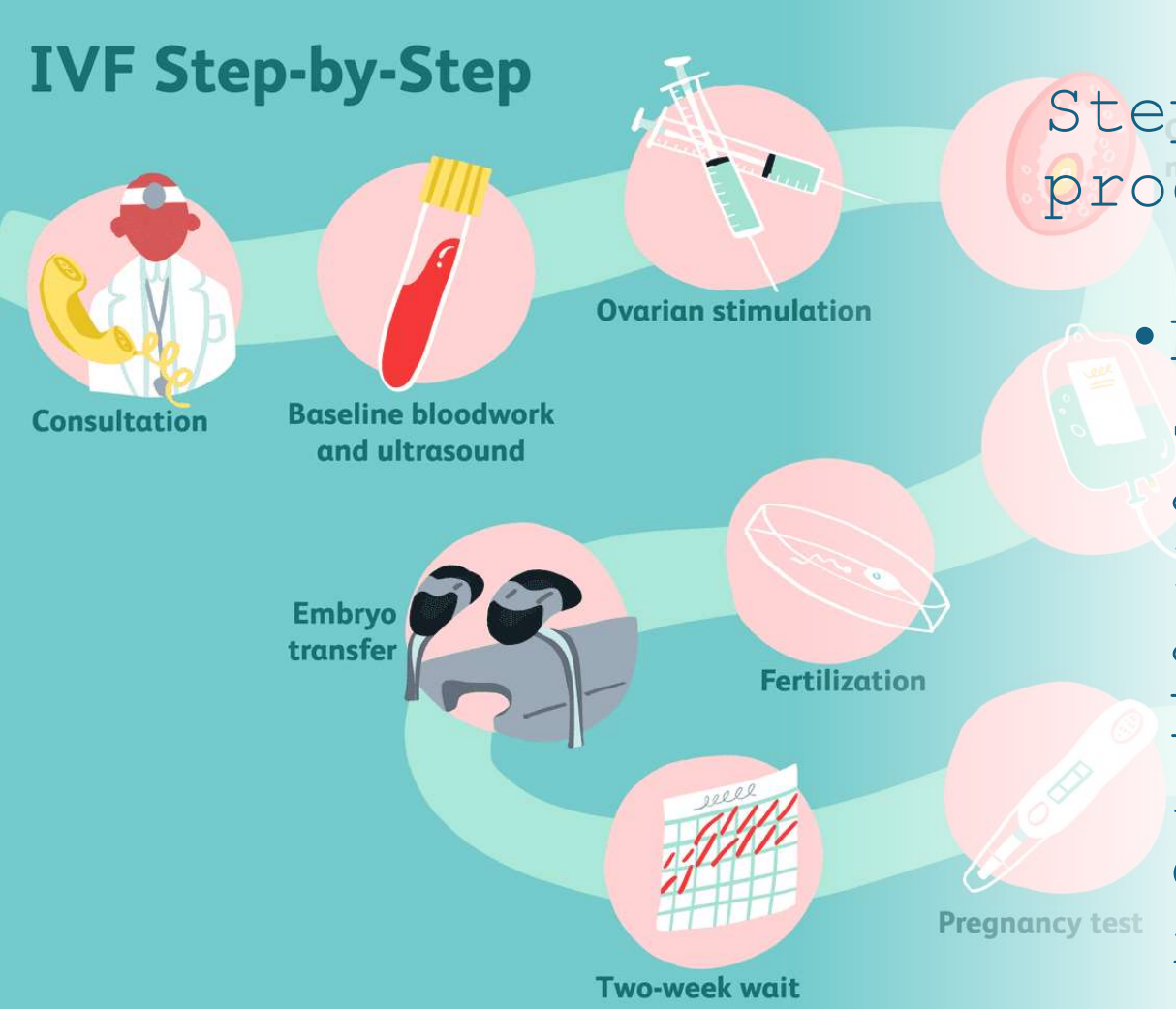
اللي بدورها رح ترفع الاستروجين فبالتالي ما اعرف اتوقع متى رح يصير LH surge ورح يصير avolution بشكل سريع ما أتحكم فيه فيروح كل شغلي

طيب استعجلهم بعد ال LH surge مباشرة؟! لأ هيك ما بستفيد اشي لأنه لسا ما صار عملهم maturation ← which occur within 36h after LH surge

Introduction

- In Vito fertilization(IVF) is a type of assisted reproductive technology.
- It involves retrieving eggs from a woman’s ovaries and fertilizing them with sperm.
- The embryo can then be frozen for storage or transferred to a woman’s uterus.

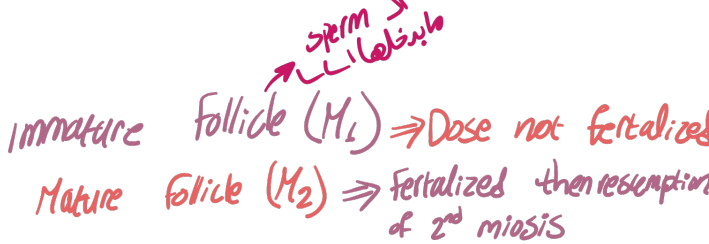
- IVF was originally designed for couples with tubal factor sub fertility. Steptoe and Edwards performed the first successful case in 1978. There are now over 5 million babies worldwide as a result of IVF. IVF is now used for almost all cases of sub fertility including tubal disease,



Steps involved in IV process

- Ever since that successful attempt in 1978, numerous advancements have been made in IVF but the core procedure remains the same.

- Step 1: Controlled ovarian stimulation:
- Prevention of premature LH surge and ovulation
- Monitoring(growth of follicle) with transvaginal ultrasound
- Oocyte maturing with HCG
- Step 2: Oocyte retrieval
- Step 3: Luteal phase support
- Step 4: Fertilization by IVF/ICSI
- Step 5: Invitro embryo culture
- Step 6: Transfer of fresh embryo/ cryopreserve of excess
- Step 7: First trimester pregnancy monitoring (doing pregnancy test after 2 weeks of embryo transfer)



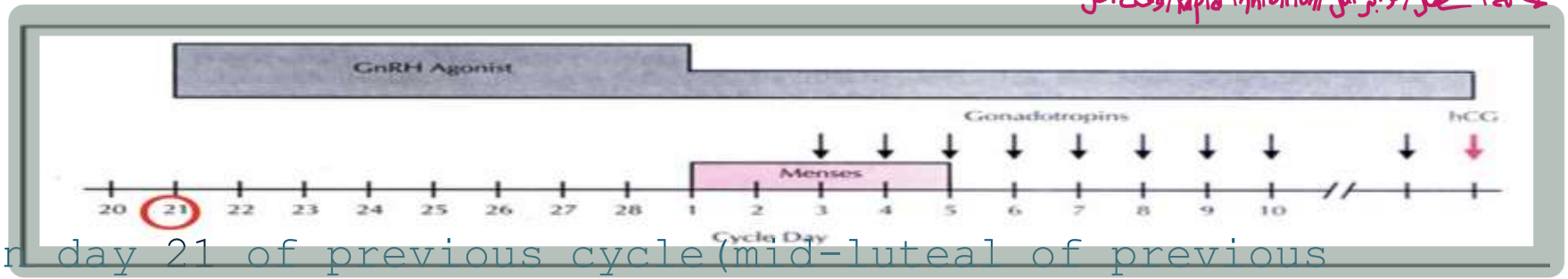
- We have 3 protocols for ovarian stimulation:
- 1. Long protocol(most common)
- 2. Short protocol → started in luteal phase with gonadotropin → DOR معالج المريضات اللي عندهن
- 3. The antagonist protocol

Protocol

GnRH agonist
Down Regulate
Pituitary gland

GnRH antagonist
Prevent LH Surge

The Long Protocol



On day 21 of previous cycle(mid-luteal of previous cycle give long acting GnRH agonist (Deycapeptyl (3.75 mg i.m) OR Deycapeptyl 0.1mg/d sc OR Nafarlen intranasal spray 400mcg till menses then 200mcg)

Ovulation Stimulation

*AIM:-+for down regulation of pituitary gland to prevent spontaneous "endogenous"LH surge that will cause ovulation

Risk of LH surge في ← لاكنه مش موجود

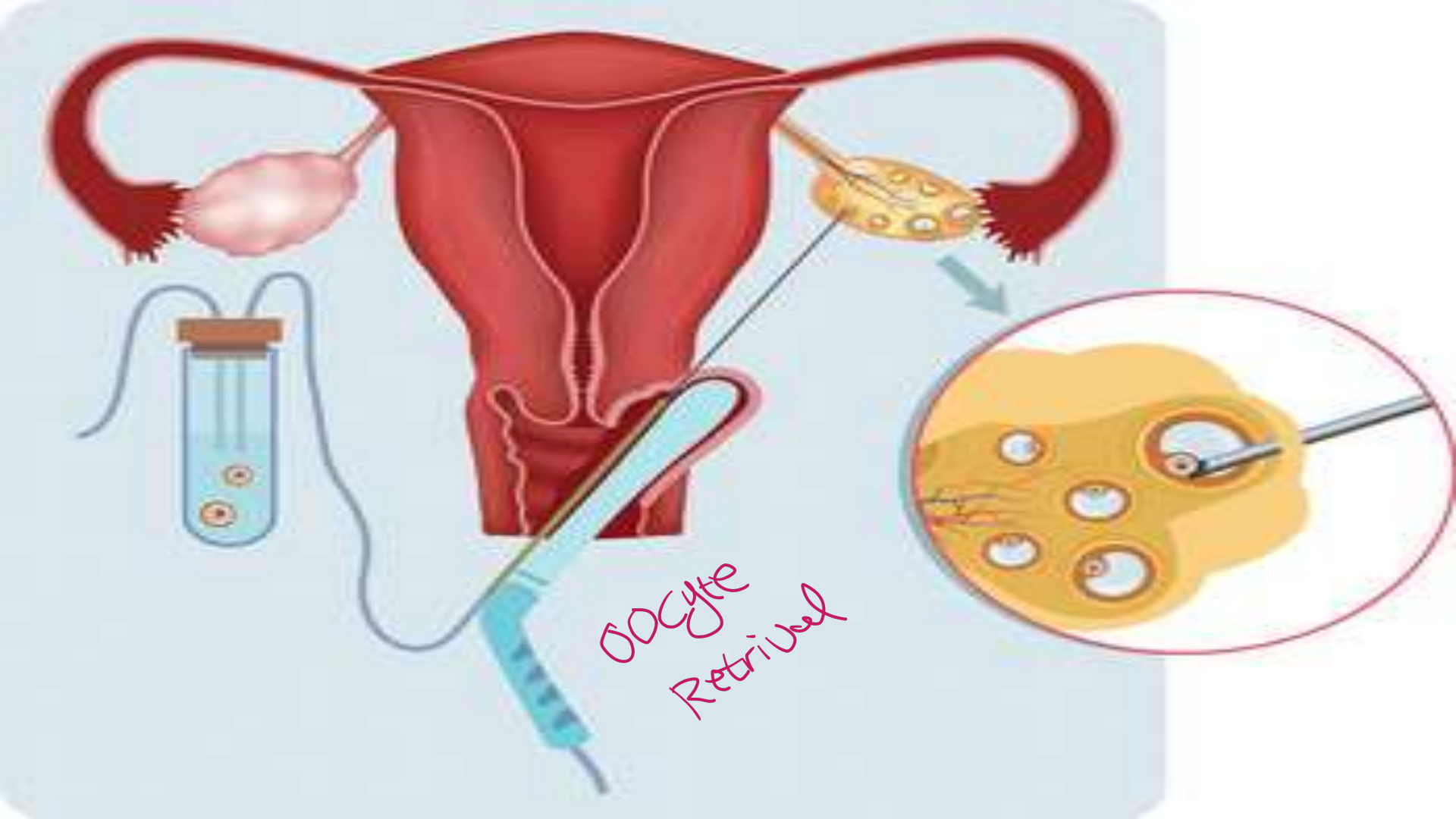
- On day 3 of period give injectable gonadotropin for ovulation induction. Two types can be administered:
- 1. rFSH: These medications contain only FSH and are administered by subcutaneous injection. These are the most commonly prescribed medications for ovulation induction
- 2. Human menopausal gonadotropins: These medications contain equal amounts of FSH and LH, and are administered on a daily basis by subcutaneous injections.

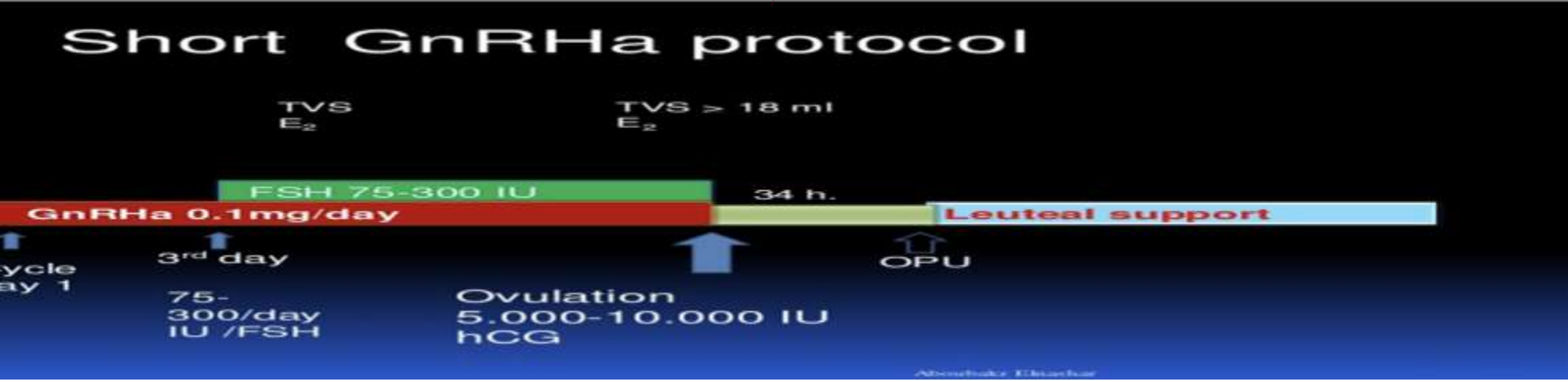
- ** we must assess follicular growth by vaginal ultrasound to see the number and the size of follicles.

- Continue dose and repeat ultrasound day after day, until we have at least 3 follicles measuring at least 18 mm in size. then stop the agonist + gonadotropins and start

- Give HCG (5000-10,000iu OR rhCG 250 micro gram) to stimulate the final maturation of the egg (release of egg should occur 38 hours after HCG is given) .

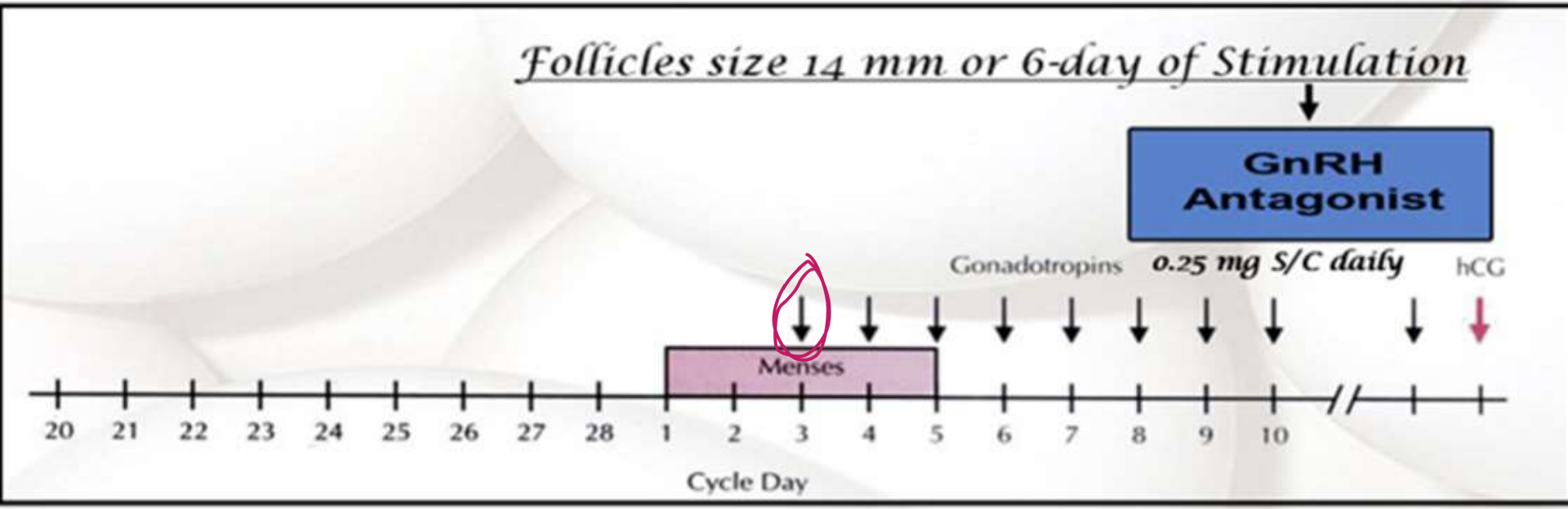
- Oocyte retrieval should be done 36 hours after HCG (not beyond to avoid rupture and release of egg) by TVUS , under I.V sedation


OOcyte
Retrival



1. On day 2 of period start giving daily injections of low dose GnRH agonist (Decapeptyl0.1 mg s.c on D2 OR Gn D3 150-450iu.)
2. On day 3 of period start giving injectable ovulation induction agent.
3. At day 13 of period give HCG .

The Antagonist Protocol



Oocyte retrieval: should be done 36 hours after HCG (not beyond to avoid rupture and release of egg) by TVUS , under I.V sedation

- Prophylactic antibiotic doxycycline 100mg/cefoxitin 2g
- Complications:hemorrhage
- pelvic infection
- rupture of a cyst
- laceration of sacral vein
- lumbosacral osteomyelitis

- Luteal phase support:-
  Starting at the same day of oocyte retrieval

  ***Progesterone (best)
  orally 300-800mg/d
  vaginally 100-600mg/d
  injection 25-50 mg/d

  For 5 weeks

Insem ods :

A. Conventional IVF : → conventional

*** If husband has good number of sperms , Semen is collected by masturbation

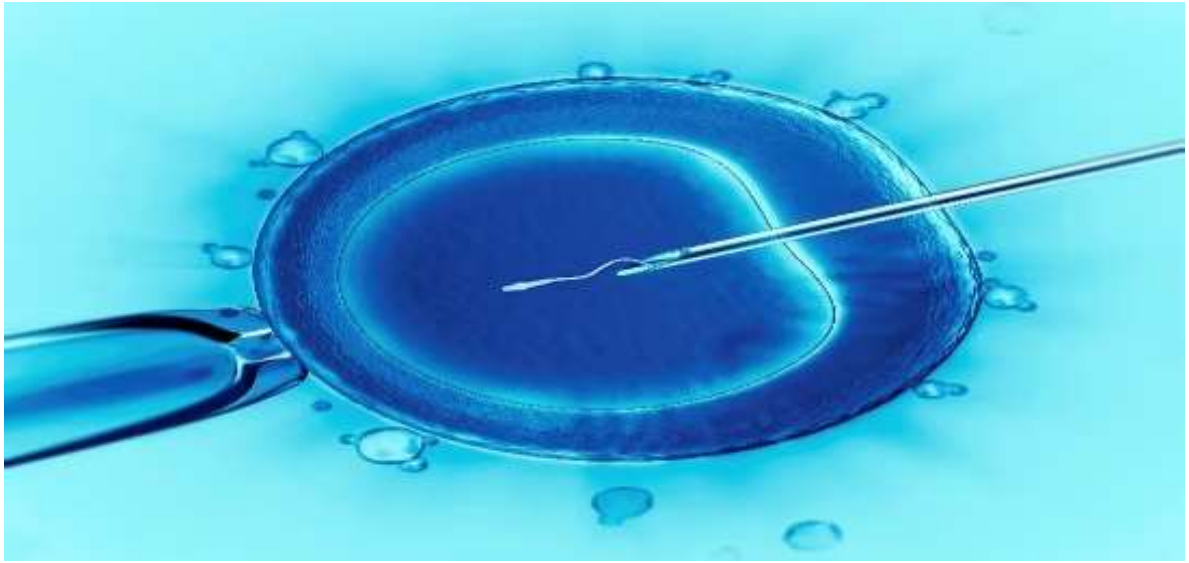
***then put 50,000-100,000 motile sperms in each test tube , and put one egg(after removing cumulus oophorus) in each , then wait for spontaneous fertilization to occur

***50-60% fertilization occur

***Achieves second meiotic division

***Extrude second polar body

ICSI



What is the ICSI

- Intracytoplasmic sperm injection is a micromanipulation technique used in the process of fertilization(IVF). It involves injecting a single sperm in to the centre of a mature oocyte under a microscope.

(ICSI) differs from conventional(IVF)

- ICSI is a type of IVF. Intracytoplasmic sperm injection differs from conventionl in vitro fertilization in that the embryologist selects a single sperm to be injected directly into an oocyte instead of fertilization taking place in a dish where many sperm are placed near an egg.

Indications of ICSI:

- Male factor
- Oligospermia
- Asthenospermia
- Teratospermia
- Poor IVF/failed IVF
- in azospermic patients sperms are retrieved either from the testis or epididymis:
- Epididemal sperm aspiration (MESA, open, percutaneous).
- Testicular sperm extraction (TESA)

Percutaneous Epididymal Sperm Aspiration

Percutaneous epididymal sperm aspiration is often the first choice in men with obstructive azoospermia because it is the least invasive option and does not require any special surgical equipment..

.A small 30-Ga needle is inserted percutaneously into the epididymis and its contents are aspirated. If no sperm are identified, the surgeon may elect to proceed to a microsurgical epididymal sperm aspiration procedure or, more commonly, testicular sperm extraction.

Microsurgical Epididymal Sperm Aspiration

- Microsurgical epididymal sperm aspiration is performed in a similar manner to percutaneous epididymal sperm aspiration, except that it uses an open incision and surgical microscope.
- a Both procedures may provide enough sperm for IVF-ICSI or cryopreservation, but the microsurgical approach is more precise as the epididymis is directly visualized under magnification.

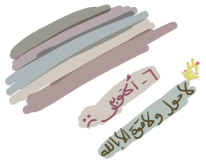
Testicular Sperm Extraction

- A testicular biopsy (or testicular sperm extraction) is executed through an open scrotal incision. [23] It can be performed with or without the use of a surgical microscope.

- Risks from the surgery such as hematoma, scarring, or testicular atrophy are similar with or without the use of the microscope

Fertilization and pregnancy success rates with ICSI

- Success is 35% in women aged 30 to 35, 20% at 35 to 40 and less than 10% after 40. It is better to avail IVF before it is too late.
- Blastocyst embryo transfer at the 5-6 day stage, generally has higher success rates than embryo transfer at the 2-3 day stage.
- Depending on the age of the couple, hormone levels, disease and lifestyle



Disadvantages of ICSI

- The risk of multiple births and ectopic pregnancy.
- The risk of congenital abnormalities.
- There is an increased risk of genetic problem carried by the sperm.
- ICSI is more expensive than IVF.

Preimplantation genetic testing (PGT)

- What is it ?

its a technique used to identify chromosomal genetic abnormalities in embryos created through in vitro fertilization (IVF) *before* pregnancy. Preimplantation genetic testing is an umbrella term that refers to the assessment of embryos prior to implantation or pregnancy.

Primary candidates for PGT

- These include the following:
- Carriers of autosomal recessive diseases (for carriers of autosomal recessive diseases, the risk an embryo may be affected is 25%)
- Carriers of autosomal dominant diseases (for carriers of autosomal dominant disease, the risk an embryo may be affected is 50%)
- Couples with a family history of X-linked disorders (couples with a family history of X-linked disease have a 25% risk of having an affected embryo [half of the male embryos])
- Couples with chromosomal translocation, which can cause implantation failure, recurrent pregnancy loss, or mental or physical problems in offspring

Types of PGT

- There are three different types of tests performed on embryos during IVF: preimplantation genetic testing for monogenic/single-gene diseases (PGT-M), preimplantation genetic testing for structural chromosome rearrangements (PGT-SR), and preimplantation genetic testing for aneuploidy (PGT-A).

PGT-A

Most early pregnancy losses can be attributed to aneuploidy. Because only chromosomally normal embryos are transferred into the uterus, the risk of first and second-trimester loss is markedly reduced.

Primary candidates for PGT-A can include the following:

- **Women of advanced maternal age**
- **Couples with a history of recurrent pregnancy loss**
- **Couples with repeated IVF failure**
- **Male partner with severe male factor infertility**

Advanced Maternal Age

- **The risk of aneuploidy in children increases as women age. The chromosomes in the egg are less likely to divide properly, leading to an extra or missing chromosome in the embryo (see Table 1). The rate of aneuploidy in embryos is greater than 20% in mothers aged 35-39 years and is nearly 40% in mothers aged 40 years or older.**

Recurrent Prergnancy Loss

- **Recurrent pregnancy loss (RPL) is usually defined as 2 or more consecutive pregnancy losses before 20 weeks of gestation. The cause is frequently unknown but may be secondary to fetal anomalies or uterine abnormalities. Chromosomal abnormalities are noted in 50-80% of abortuses, [11] and couples with RPL have a higher percentage of aneuploid embryos than patients without RPL.**

Recurrent IVF Failure

- **Recurrent IVF failure (RIF) is usually defined as 3 or more failed IVF attempts involving high-quality embryos. Evidence suggests that this patient population has more chromosomally abnormal embryos. [14] However, no study has shown an improvement in pregnancy rate with PGT in patients who have a history of RIF**

Male factor infertility

- **Gonadal failure in men has been linked to the generation of embryos with an increased incidence of inherited and de novo chromosomal abnormalities. Normal fertile men have approximately 3-8% of sperm that are chromosomally abnormal. This risk increases significantly in men with severe infertility (ie, low sperm count, poor morphology, and poor motility) to approximately 27-74% abnormal spermatozoa**

PGT-M

- **Preimplantation genetic testing for monogenic/single-gene diseases is used to identify single-gene defects such as cystic fibrosis, neurofibromatosis type 1, Tay-Sachs disease, sickle cell anemia, and Huntington's disease. In such diseases, the abnormality is detectable with molecular techniques using polymerase chain reaction (PCR) amplification of the DNA from a single embryonic cell.**

PGT-SR

- **Preimplantation genetic testing for structural chromosome rearrangements is used to identify potential chromosomal disorders. Chromosomal disorders involve various chromosomal rearrangements, including translocations, inversions, and deletions**

Process

- **In order to have embryos to biopsy for PGT, patients must undergo in vitro fertilization (IVF). After fertilization of the egg with sperm, embryos are allowed to develop into day 5 blastomeres. On day 5 after egg retrieval, between three and five trophectoderm cells are removed from the developing embryo for genetic evaluation of the embryo. In most instances, the embryos are frozen after the biopsy is performed and transferred at a later date, given the time frame of completing PGT. Genetic evaluation is performed using PCR, FISH, comparative genomic hybridization (CGH), or most commonly, next generation sequencing (NGS).**

Methods of assessing chromosomal constitution

- ***Polymerase chain reaction***
- ***Fluorescence in situ hybridization (FISH)***
- ***Comparative genomic hybridization (cGH)***
- ***Next generation sequencing (NGS)***

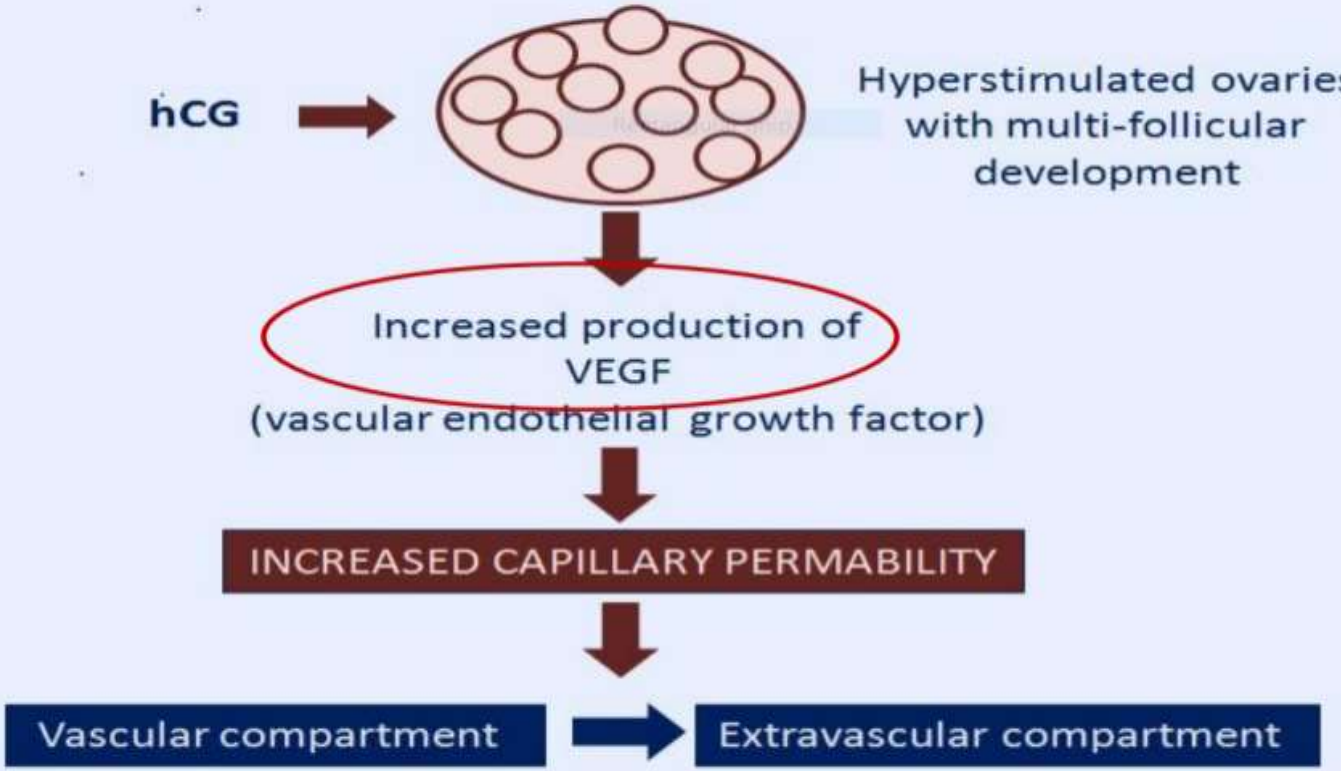
Ovarian Hyperstimulation syndrome - OHSS

- **Definition**
- iatrogenic complication for ovarian stimulation by assisted reproduction technology and other infertility treatments
- mainly when injectable ovulation induction drugs are used as HMG, FSH, rFSH.
-

Incidence: -Mild OHSS; 20-30%.

- Severe OHSS: 3-8%

Pathophysiology



Early onset	Late onset
3 to 7 days after HCG	12-17 days after HCG
Excessive response to stimulation	Due to pregnancy

CLASSIFICATION OF OHSS

Grade	Ovary	Clinical	Lab. Blood
1)Mild	5-I0cm	-Abdominal Distension -GIT upset	-PCV < 45 - WBC < 15.000/cc -Normal renal function
2) Moderate	10-12 cm	-Moderate ascites	-PCV < 45 - WBC < 15.000/cc -Normal renal function
3)Sever	> 12cm	-Marked ascites -Dyspnea -Hypovolemia -Mild Thromboembolism	-PCV > 45 - WLC > 15.999/cc -Impaired renal function -
4) Critical	MARKED	-Tense ascites, -Hydrothorax. -Sever Thrombocmbolism. -Adult respiratory distress syndrome - Life threatening	-PCV(55%), -WLC > 25000/mm3, -serum creatinine> 1.6 mg%^, -creatinine clearance < 50ml/min.

COMPLICATIONS OF OHSS:

1-Thromboembolic complications.

2-Liver dysfunction: liver enzymes are elevated in 15% and persist for 2 months after.

3-Respiratory complications: (adult respiratory distress syndrome

4-Renal complications: renal failure due to hypoperfusion.

5-Adnexal torsion: due to enlargement, however laparoscopic unwinding is successful.

6-Internal hemorrhage.

7-Abortion rate: Increased form 30% to 50% in OHSS stimulated cycles. .

RISK FACTORS

- **Primary risk factors (patient-related):**
- 1. Young age
- 2. polycystic ovary syndrome (PCOS)
- 3. Low body weight
- 4. Previous OHSS

Pure FSH: OHSS is reported to be lower in using HMG (FSH+LH)

Clomid: usually mild degree occur in 13.5%.

Luteal phase support:

risk increased with HCG and decreased with progesterone.

Conception cycles:

3-4 times more risk for OHSS

PREDICTION OF OHSS:

US folliculometry >18 (11-14mm in size)

E2 plasma levels highly rapidly rising 3000-5000 pg/ml

PREVENTION OF OHSS:

1- **coasting :** Withhold HCG administration until E2 levels plateau decreases

2. **Luteal phase support:** use of progesterone, no HCG.

3.**Follicular aspiration**: it was suggested that aspiration of the follicles is protective against OHSS.

4- **Cryopreservation** of embryo with subsequent replacement in non stimulated or natural cycle.

5 - Intravenous albumin administration

6-Hydroxyethyl-starch: Large molecule, long 1/2 life.

7- Immunoglobulin:

IgG, IgA gammglobuins have low level in patient with severe OHSS. When given IV reduce the severity.

8-metformin

9. **Cabergolin**

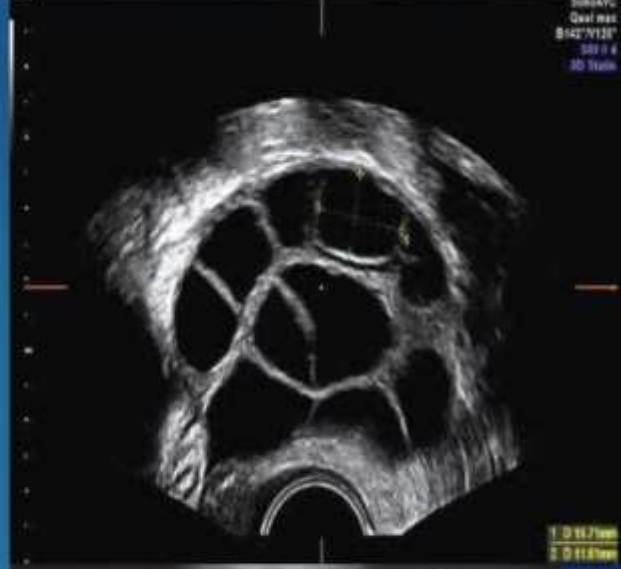
DIADNOSIS

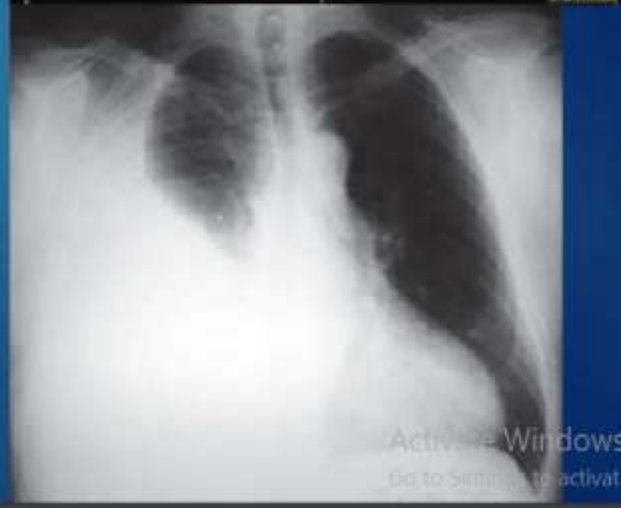
- ☐**Examination**
- ☐General: dehydration oedema (pedal, vulval and sacral); heart rate, respiratory rate, blood pressure body weight
- ☐Abdominal: Ascites palpable mass Peritonism measure girth
- ☐Respiratory: pleural effusion Pneumonia pulmonary oedema

- ☐**Investigations**
- 1. Full blood count Haematocrit (haemoconcentration)
- 2. CRP (severity)
- 3. Urea and electrolytes (hyponatraemia and hyperkalaemia)
- 4. Serum osmolality (hyper-osmolality)
- 5. Liver function tests (elevated enzymes and reduced albumin)
- 6. Coagulation profile (elevated fibrinogen and reduced antithrombin)
- 7. hCG (to determine outcome of treatment cycle)

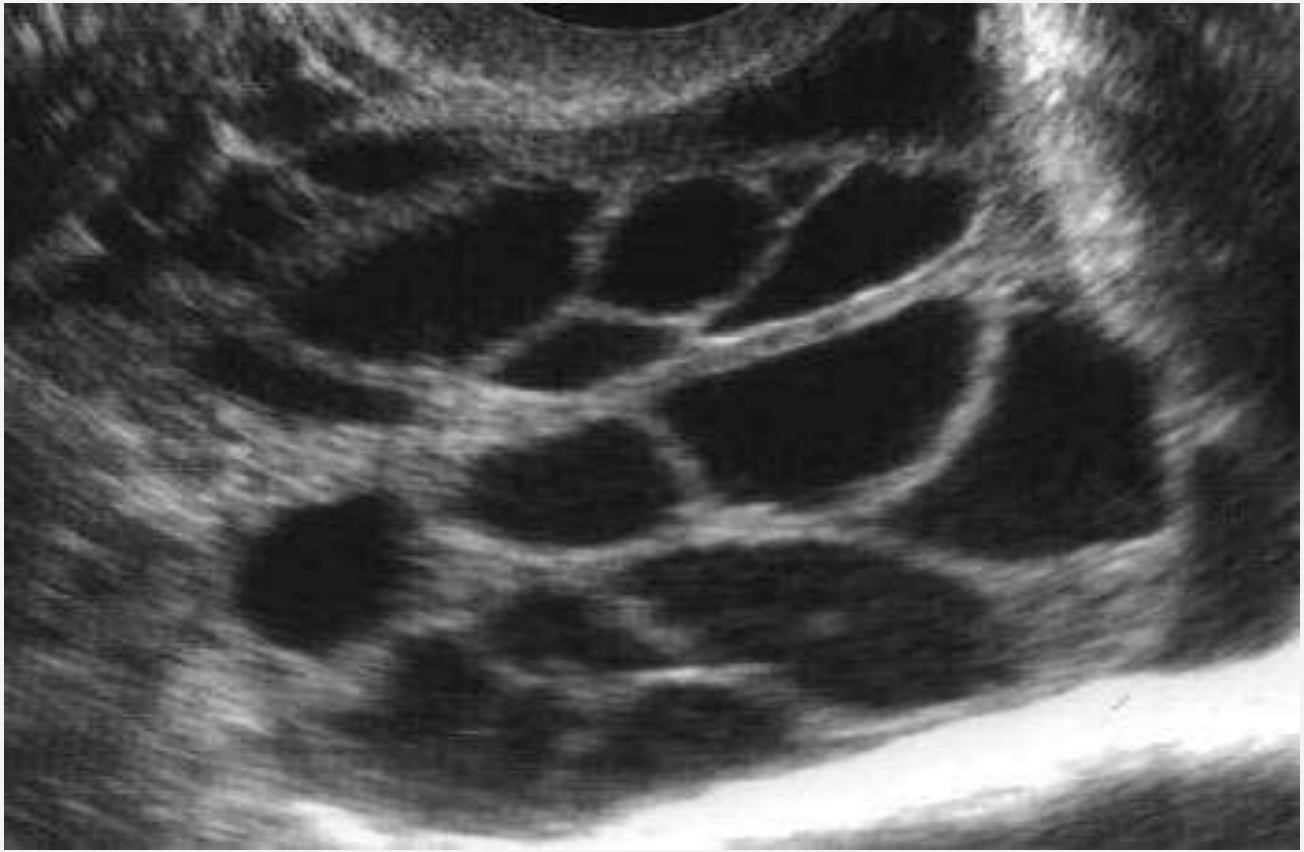
Imaging

- **Ultrasonography**
  - to assess the follicles
  - To measure the size of the ovaries
  - to evaluate ascites
- **Chest radiography**
  - may be indicated if dyspnea is present.





U/S FOR DIAGNOSIS OF OVARIAN HYPERSTIMULATION SYNDROME



TREATMENT

A- Mild cases: Spontaneous recovery within 2-3 Wk (conservative measures and follow up)

- **adequate hydration**
- **dopamine agonist**
- **daily weigh and follow up**

B- Moderate and severe cases:

1-General treatment:

a- Hospitalization and reassurance.

b- Observations; (ICU)

MEDICAL TREATMENT:

a- Circulation and electrolytes:

- Preserve the intravascular volume and renal perfusion.
- Done using colloid plasma expanders or human albumin, (effect is temporary)
- Sodium and water restriction (non effective).

b-Symptomatic treatment:

-*Analgesia*: paracetamol and opoids.

-*Antiemetics:* metoclopramid.

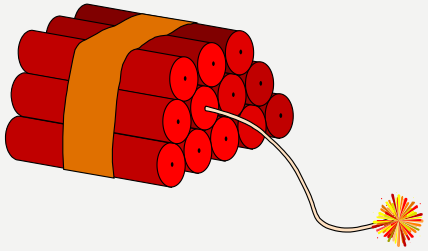
c-Prevent TE{Thromboembolism} through:

Anticoagulant therapy:

d- Antihistamines: was suggested to cause stabilization of capillary membrane.

e- Dopamine: in oliguric cases to improve perfusion and avoid renal failure.

AVOID:



1- **Anti-PG**: disturb renal function.

2- **Diuretics:** used only in pulmonary edema.

NEVER to use **Diuretics** before proper intravascular volume replacement to avoid further renal hypoperfusion

ASPIRATION OF ASCETIC FLUID OR PLEURAL EFFUSION:

***Method:**

-Paracentesis or transvaginal aspiration under U/S guidance.

-The amount of aspirate ranges from 200-1400 ml/session.

***Advantages:**

- Improvement of respiration .
- Decrease abdominal discomfort..
- Increase venous return and COP.
- Increase urine output and createnine clearance reflecting improving renal functions.

SURGICAL TREATMENT:

**Indications of surgery in severe OHSS:*

a- Signs of intraperitoneal Hemorrhage and/or rupture of ovarian cyst.

b- Adnexal torsion.

Laparotomy: should always be avoided and if deemed necessary, measures are done to preserve (Ovary)

quality of follicles ⇒ Mostly depend on maternal age

antral follicles Reflect primordial follicles (the pool)

ما بنشوفهم

AFC ⇒ Normally ⇒ Up to 10

Low ⇒ less than 7

PCOS ⇒ 20<

Ovarian Reserve ⇒ Quantity + Quality of ovarian follicles in both ovaries

THANK YOU

Ovarian hyperstimulation syndrome

↳ pathophysio ⇒

ovary produce EGF ⇒ ↑ capillary permiability ⇒ 3rd spacing

ascitis ↘ PE ↘ hypovolemia → thromboembolism

↓

affect kidney + liver