OVULATION INDUCTION

or

Introduction

- Ovulatory disorders can be identified in 18 to 25 percent of couples presenting with infertility .
- The clinical approach to ovulation induction requires an understanding of the causes of anovulation.

- The four most common ovulatory disorders include p**olycystic ovary syndrome (pcos)**, **hypogonadotropic hypogonadism (ha)**, **primary ovarian insufficiency (POI)**, and **hyperprolactinemia**.

- The world health organization (WHO) which assign women to three categories of anovulation:

Who class 1 – hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea [ha]).

Who class 2 – normogonadotropic normoestrogenic anovulation (almost all women in this category have polycystic ovary syndrome [PCOS]). This is the most common cause of anovulation.

Who class 3 – hypergonadotropic hypoestrogenic anovulation (primary ovarian insufficiency [POI; premature ovarian failure]).

Goals

the overarching goals of ovulation induction in women with anovulatory infertility are:

- Induce monofollicular rather than multifollicular development and subsequent mono-ovulation and, ultimately, a singleton pregnancy and birth of a healthy newborn.

- Start with the least invasive, simplest, and cheapest treatment option; subsequent options should depend upon ovarian response (ovulation and number of follicles).

- Maximize the rate of singleton pregnancies, minimize multiple gestation rates.

- Minimize the risk of ovarian hyperstimulation syndrome (ohss) in women undergoing gonadotropin therapy, particularly those with polycystic ovary syndrome (pcos), who are at higher risk.

HYPOTHALAMIC AMENORRHEA

Hypothalamic dysfunction results in abnormal release of LH and FSH hormones from the pituitary. The end result is a lack of proper follicle development and ovulation.

Possible Causes of Hypothalamic Amenorrhea

Some medications (e.g. phenothiazines) as well as extremes of weight loss, stress or exercise can cause this type of secondary amenorrhea.

A pituitary or hypothalamic tumor would be a rare finding in these patients who were all screened with prolactin levels at the beginning of the diagnostic evaluation. However, if there is no cause apparent from the history, it is sometimes suggested to get a baseline CT or MRI scan of the sellar region to rule out a (very rare) tumor.

TREATMENT

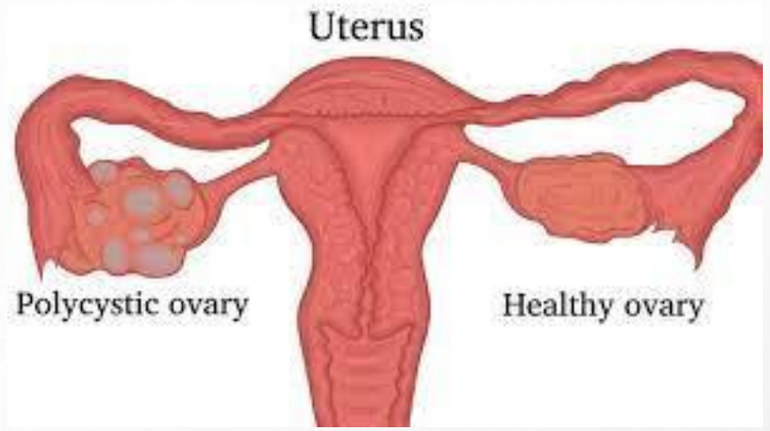
hypothalamic amenorrhea situations, the patients can be significantly hypoestrogenic (a low estrogen situation similar to menopause).

Treatments

If the state is persistent, hormone replacement therapy should be considered for protection against osteoporosis.

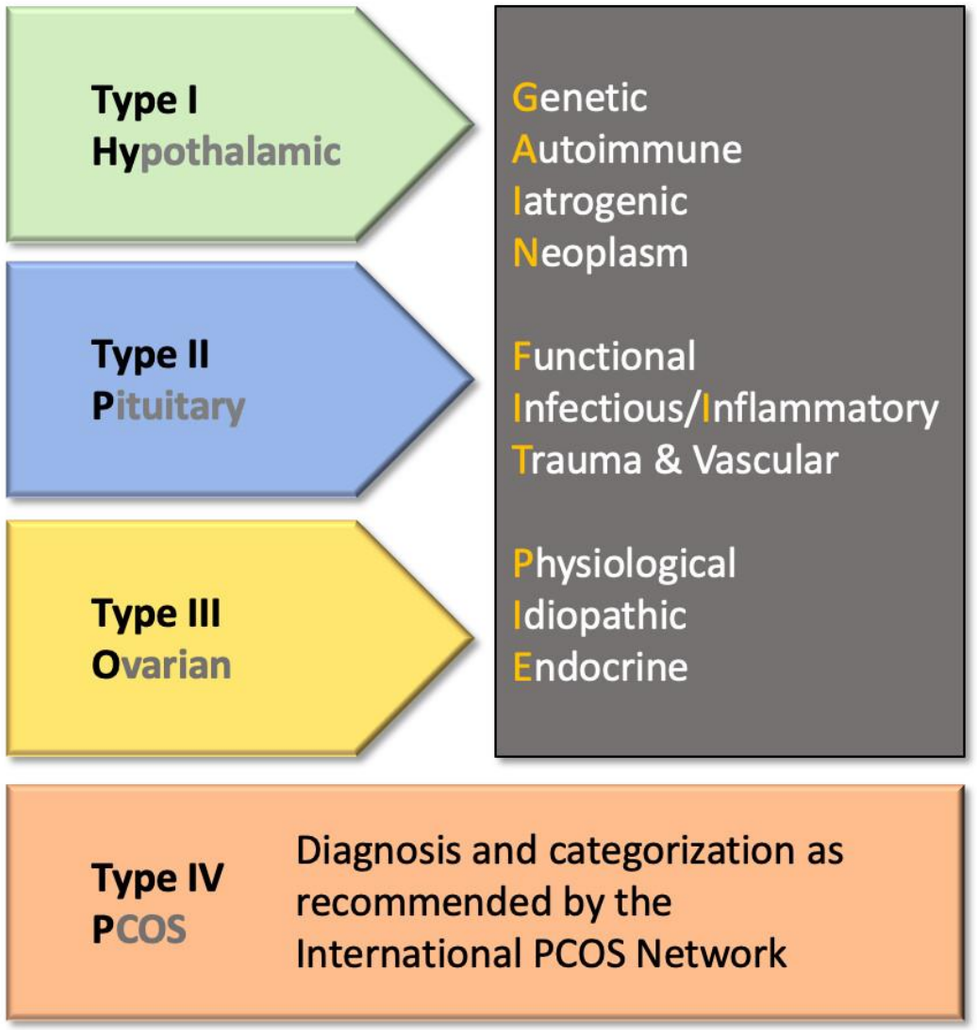
One approach is to get an estradiol level and if it is less than 30 pg/ml, counsel the patient that hormonal replacement therapy is indicated.

Ovulation induction in PCOS



- PCOS is the most common cause of anovulatory infertility 70-85% of the cases.
- According to who-classification of anovulation it goes under the who group ii norm-gonadotrophic normogonadic.(Most experts have moved away from this classification).
- And according to figo ovulatory disorders classification system it is considered type iv.

FIGO Ovulatory Disorders Classification (HyPO-P)

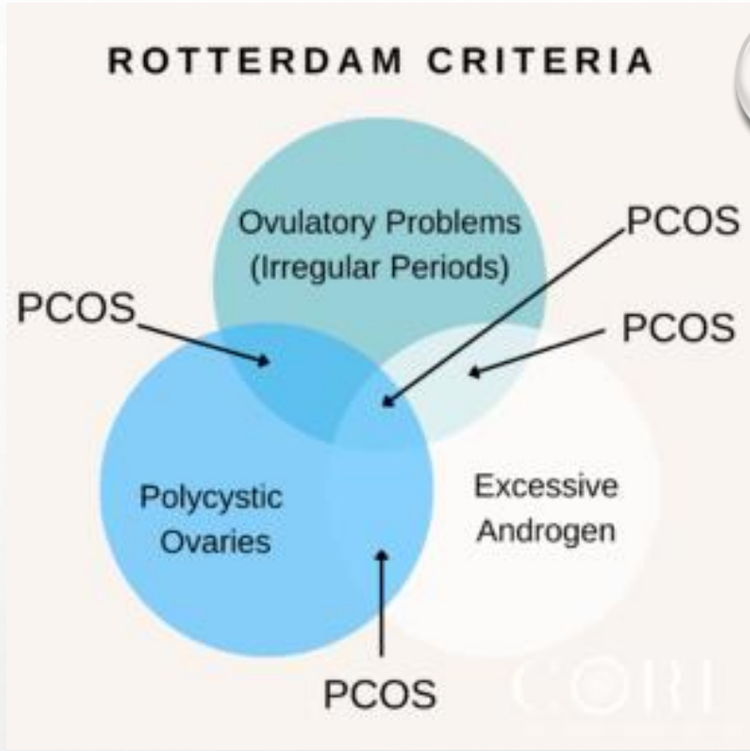


WHO group I	**Hypogonadotrophic hypogonadism**
	Idiopathic hypogonadotrophic hypogonadism
	Kallmann's syndrome (isolated gonadotrophin deficiency and anosmia)
	Functional hypothalamic dysfunction (e. g. excessive weight loss such as in anorexia nervosa, exercise, stress, drugs, iatrogenic)
	Pituitary tumour, pituitary infarct (e. g. Sheehan's syndrome)
WHO group II	Normogonadotrophic normogonadic ovarian dysfunction
	Polycystic ovary syndrome
WHO group III	Hypergonadotrophic hypogonadism (ovarian failure)
	Genetic (e. g. Turner's syndrome)
	Autoimmune causes
	Infection (e. g. mumps oophoritis)
	Iatrogenic (e. g. surgical menopause, post-radiotherapy or chemotherapy)
	Idiopathic
	Other endocrinopathies, such as hyperprolactinaemia, thyroid dysfunction, other conditions of androgen excess such as congenital adrenal hyperplasia and androgen-secreting adrenal and ovarian tumours.

Polycystic ovarian syndrome (PCOS) is characterized clinically by oligomenorrhea and hyperandrogenism, as well as the frequent presence of associated risk factors for cardiovascular disease, including obesity, glucose intolerance, etc…

diagnosis of PCOS should be suspected in any women of reproductive age who presents with irregular menses and symptoms of hyperandrogenism (such as acne, hirsutism, female pattern hair loss). The presence of overweight or obesity should further raise suspicion.

The diagnosis of PCOS is currently made using the Rotterdam criteria.



Rotterdam Criteria for Diagnosis of PCOS

Diagnosis confirmed by 2 of 3 criteria after exclusion of other etiologies:

1. Oligo and/or anovulation

2. Biomchemical and/or clinical signs of hyperandrogenism
   - Biochemical: Total T > 70 ng/dL, Androstenedione > 245ng/dL, DHEA-S >248 ug/dL)
   - Clinical: Acne, Hirsutism, acanthosis nigrans

3. Polycystic Ovaries:
   - ≥ 12 follicles (2-9mm diameter) in each ovary or ovarian volume > 10cc

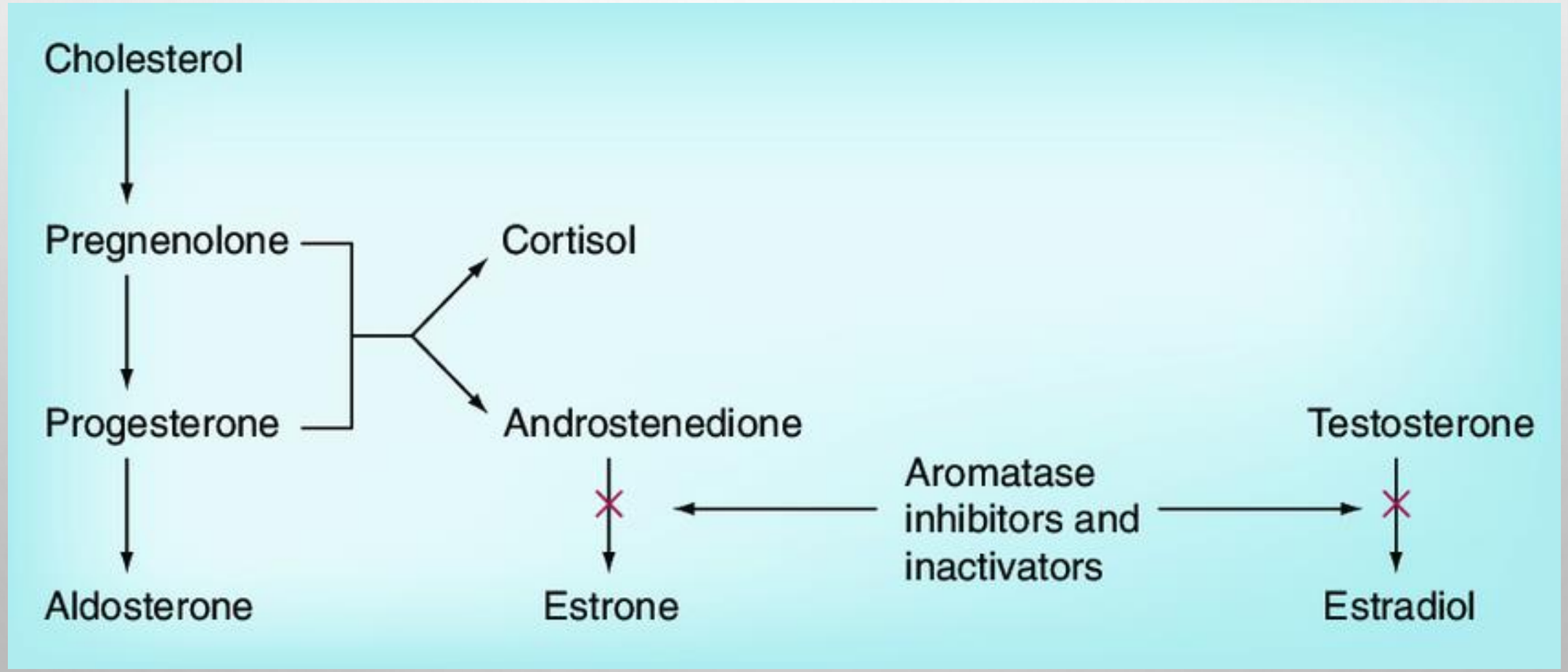
TREATMENT OF ANOVULATION IN PCOS WOMEN :

- Before starting ovulation induction ,women with obesity and PCOS :
    - **Lifestyle modification** (diet and exercise) aimed towards weight loss may restore spontaneous ovulation in many women and improved pregnancy rates.(**Weight reduction results in improvement in all symptoms of PCOS ,10% weight loss will restore normal hormones level and spontaneous ovulation in 40% of women.)**
    - **Bariatric surgery** is another strategy for weight loss which as mentioned will restore the ovulatory cycles and improve the insulin resistance.

- In addition, women with pcos should be screened for impaired glucose tolerance
    - As it was found that correction of hyperinsulinemia with **metformin** have a beneficial effect in anovulatory women with pcos will lead to restoration of ovulatory cycles, and improvements in insulin resistance.

AROMATASE INHIBITOR

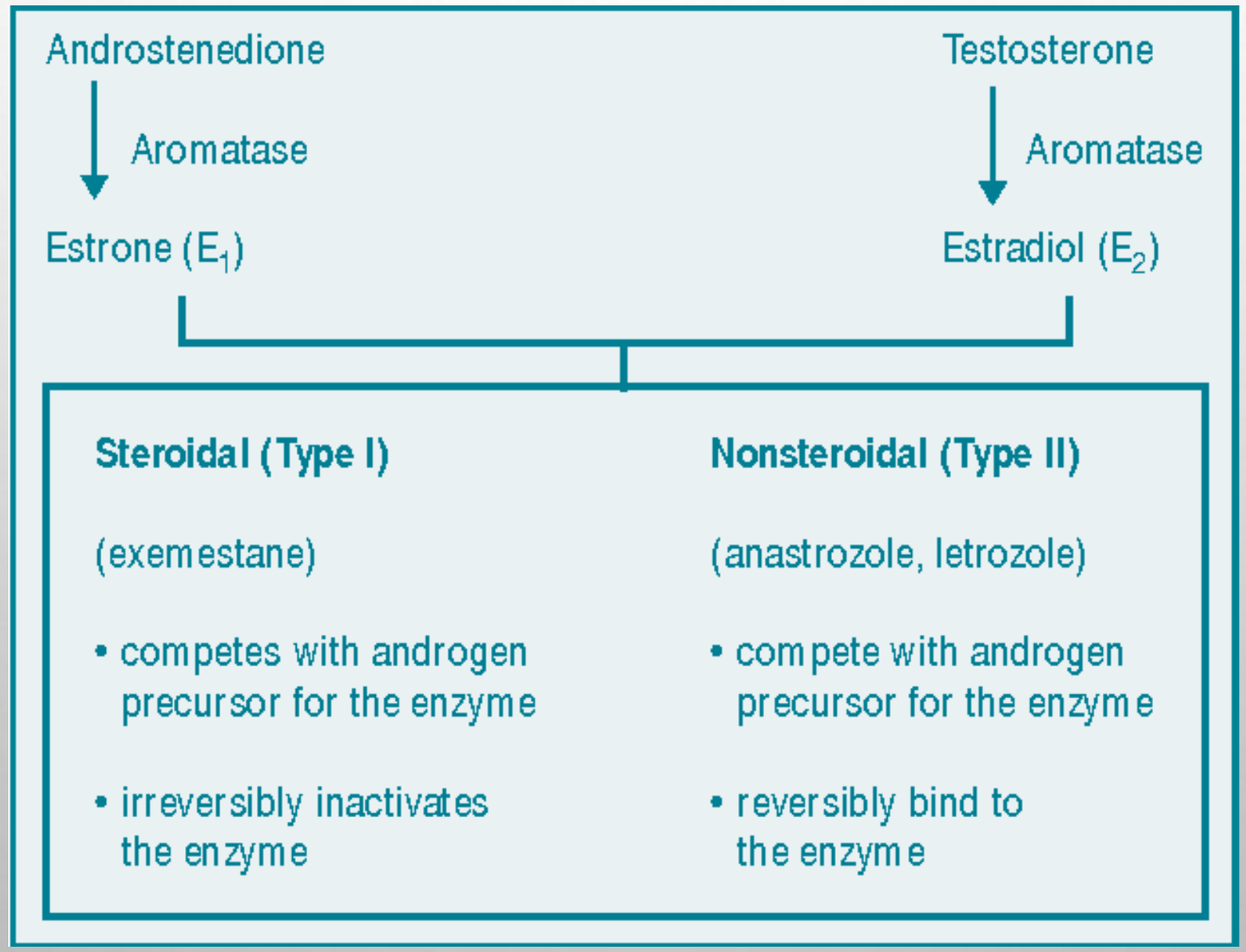
- Mechanism of action : work by inhibiting the action of the enzyme aromatase , which converts androgens into estrogens by a process called aromatization



Types of aromatase inhibitors :

1) steroidal (type1):irreversibly inactivates the enzyme , exemestane .

2) nonsteroidal (type2) : reversibly inactivates the enzyme Anastrozole , letrozole.



- Letrozole is now considered to be the drug of choice for ovulation induction in women with PCOS.
- When prescribing letrozole, the starting dose is 2.5 mg/day, cycle days 3 to 7, following a spontaneous menses or progestin-induced bleed.

- Potential advantages of letrozole over clomiphene citrate include :

1. A high rate of monofollicular development, which should theoretically reduce the risk of multiple pregnancies.
2. A shorter half-life (48 hours versus two weeks for clomiphene citrate), which would predict a lower risk of teratogenicity.
3. No direct antiestrogenic adverse effects on the endometrium, due to an absence of peripheral estrogen receptor blockade and the shorter half-life.
4. Lower serum estradiol levels – this is a particular advantage for women with breast cancer undergoing ovarian stimulation prior to gonadotoxic therapy and possibly for women with endometriosis undergoing in vitro fertilization (ivf), but this is speculative.

Parameters	Clomiphene citrate	Letrozole
MOA	SERM	Aromatase inhibitor
Half-life	Long, 5-7 days	Short, 48 h
Anti-estrogenic effects	Thin endometrium & altered cervical mucus	Thick endometrium & favourable cervical mucus
Uterine blood flow	Decreased	Increased
OHSS risk	High	Low
Multiple pregnancy	High	Low

ADVERSE EFFECTS

- Nausea , dizziness
- Hot flushes
- Osteoporosis / fractures
- Arthritis
- Ischemic cardiovascular events
- Hair loss
- Kidney failure

CLOMIPHENE CITRATE

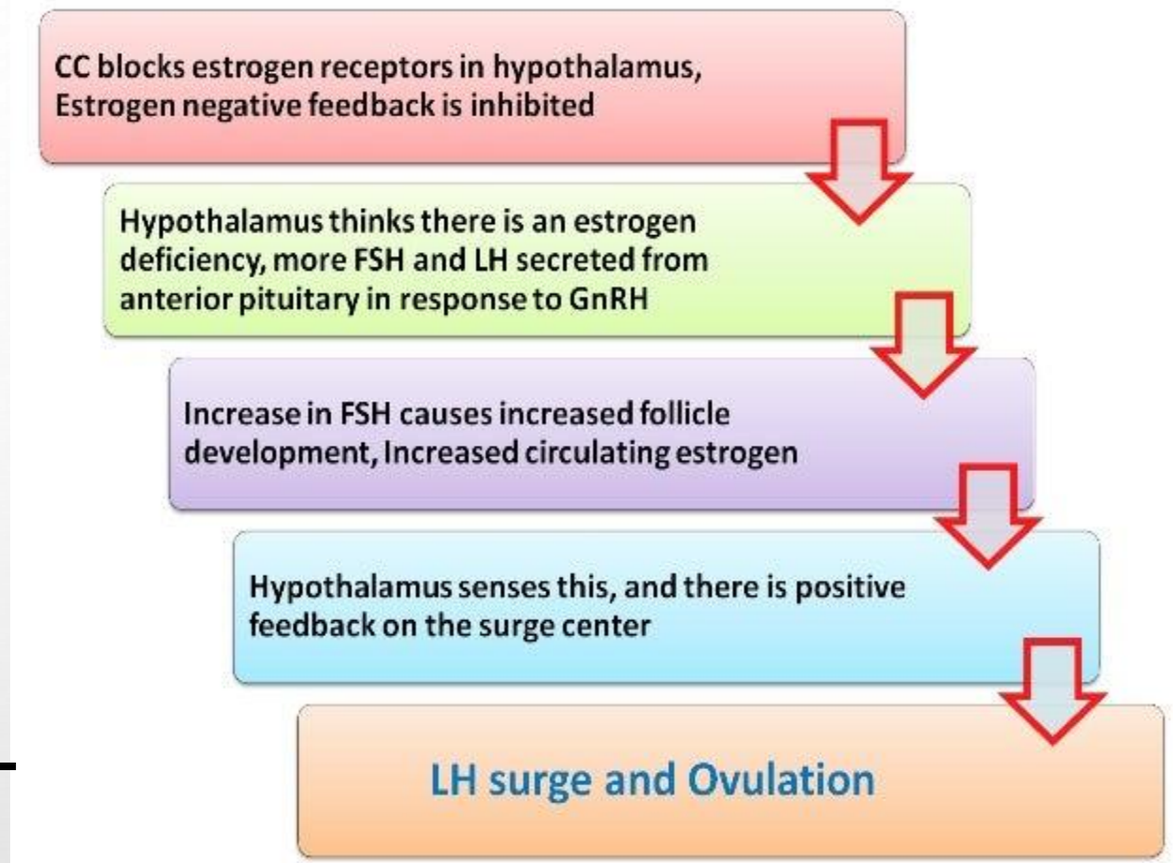
- Nonsteroidal, triphenylethylene derivative.
- known as selective estrogen receptor modulators.
- are competitive inhibitors of estrogen binding to estrogen receptors.
- have mixed agonist and antagonist activity, depending upon the target tissue

ESTROGENS
Conjugated estrogens PREMARIN
Esterified estrogens MENEST
Estradiol (oral) ESTRACE
Estradiol (topical) DIVIGEL, ESTROGEL
Estradiol (transdermal) ALORA, CLIMARA, VIVELLE
Estradiol (vaginal) ESTRACE, ESTRING, FEMRING, VAGIFEM
Estropipate GENERIC ONLY
*Ethinyl estradiol**
SELECTIVE ESTROGEN-RECEPTOR MODULATORS (SERMs)
Clomiphene CLOMID
Ospemifene OSPHENA
Raloxifene EVISTA
Tamoxifen GENERIC ONLY
PROGESTOGENS
*Desogestrel*** DESOGEN
*Dienogest*** NATAZIA
*Drospirenone*** YASMIN, YAZ
Etonogestrel (subdermal) NEXPLANON
*Etonogestrel** (vaginal ring)* NUVARING
Levonorgestrel PLAN B ONE-STEP
Levonorgestrel (IUD) KYLEENA, LILETTA, MIRENA, SKYLA
Medroxyprogesterone DEPO-PROVERA, PROVERA
*Norelgestromin** (transdermal)* XULANE
Norethindrone MICRONOR
*Norethindrone** ORTHO-NOVUM, TRI-NORINYL
Norethindrone acetate AYGESTIN
*Norethindrone acetate** FEMHRT, LOESTRIN
*Norgestimate** ORTHO TRI-CYCLEN, SPRINTEC
*Norgestrel** LO/OVRAL
Progesterone PROMETRIUM
PROGESTERONE AGONIST/ANTAGONIST
Ulipristal acetate ELLA

Clomiphene citrate

Mechanism of action:

- primary site of clomiphene action is the hypothalamus.
- bind to and deplete hypothalamic ERs,
- blocking the negative feedback effect of circulating endogenous estradiol.
- results in an increase in hypothalamic gonadotropin-releasing hormone
- Which will lead to increase serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).



Clomiphene citrate has no apparent progestational, corticotropic, androgenic, or antiandrogenic effects, nor does it interfere with adrenal or thyroid function.

CLOMIPHENE CITRATE

- considered as second ulternative after letrozole for PCOS
  - **Pretreatment evaluation:**
  - Before initiating therapy: presence of ovulatory dysfunction must be established.
  - Disorders of pituitary, adrenal, and thyroid origin that can cause anovulation should be excluded prior to the initiation of therapy as targeted treatment of these endocrinopathies can result in normal ovulation.
  - Lab test include: hcg, tsh, prl, ogtt, lft

Diagnostic tests suggesting ovulatory dysfunction

Absence of a 0.5°F rise on measurement of basal body temperature
Low value (<2 ng/mL) of midluteal phase serum progesterone concentration
Lack of an LH surge on monitoring urinary LH excretion
Out of phase timed endometrial biopsy
Lack of a periovulatory follicle on serial transvaginal sonography

PCOS	Treatment	Cost	Multiple pregnancy risk
First line	Weight loss for high body mass index	Low	Not increased
First line	Letrozole (alternative: clomiphene citrate)	Low	Low
Second line	Follicle-stimulating hormone injections	High	High, includes high-order multiples
Second line	Ovarian drilling	High	Not increased
Third line	In vitro fertilization	Very high	High but reducible with single embryo transfer

CLOMIPHENE CITRATE

- **Treatment protocol:**
- Empirically start with 50mg/daily,
- Start on the fifth day of a cycle, for five day duration.
- Starting with a higher dose does not result in higher pregnancy rates.
- If ovulation failed, increase dose to 100mg/daily in the 2nd cycle
- ---
- If ovulation succeed, the same dose should be continued for four to six cycles
- The lh surge occurs from 5 to 12 days after the last day of clomiphene administration
- The couple is advised to have intercourse every other day for one week beginning five days after the last day of medication (time of ovulation)

Start with 50mg/daily for 5 day

Ovulation failed

Increase dose to 100mg/daily in 2nd cycle

Ovulation failed

Reevaluate after the 6th cycle

Other ART (2nd , 3rd line therapy)

Ovulation succeed

Repeat for 4-6 cycle

Ovulation succeed

Repeat for 4-6 cycle

CLOMIPHENE CITRATE

- **Ovulatory and pregnancy rates: in women with PCOS**
- Ovulatory rate of 80 percent.

Approximately 50 percent do so at a dose of 50 mg, another 20 to 25 percent at 100 mg,

- Cumulative pregnancy rate of 30 to 40 percent.
- No difference in the miscarriages or congenital anomalies rate similar to that in spontaneous pregnancies.
- Risk of ovarian hyperstimulation syndrome is less than 1 percent.

Clomiphene citrate: side reaction

- Not dose related
- Hot flash(10%-20%)
- Abdominal distention and pain (5.5%)
- Nausea and vomiting (2.2%)
- Breast discomfort (2%)
- Mood swings, depression, headache(rarely to be considered serious)
- Uncomplicated ovarian enlargement (14%)

Clomiphene citrate: CONTRAINDICATIONS

- Liver disease
- Undetermined uterine bleeding
- Ovarian cysts or enlargement not due to polycystic ovarian syndrome
- Uncontrolled thyroid or adrenal dysfunction
- pituitary tumor
- premature ovarian failure

LAPAROSCOPIC OVARIAN DRILLING

Advantages :

- Spontaneous monovulation
- Effective as gonadotropins
- Less intensive monitoring
- No risk of OHSS or risk of multiple pregnancy comparing of gonadotropins
- Cheaper overall

Disadvantage :

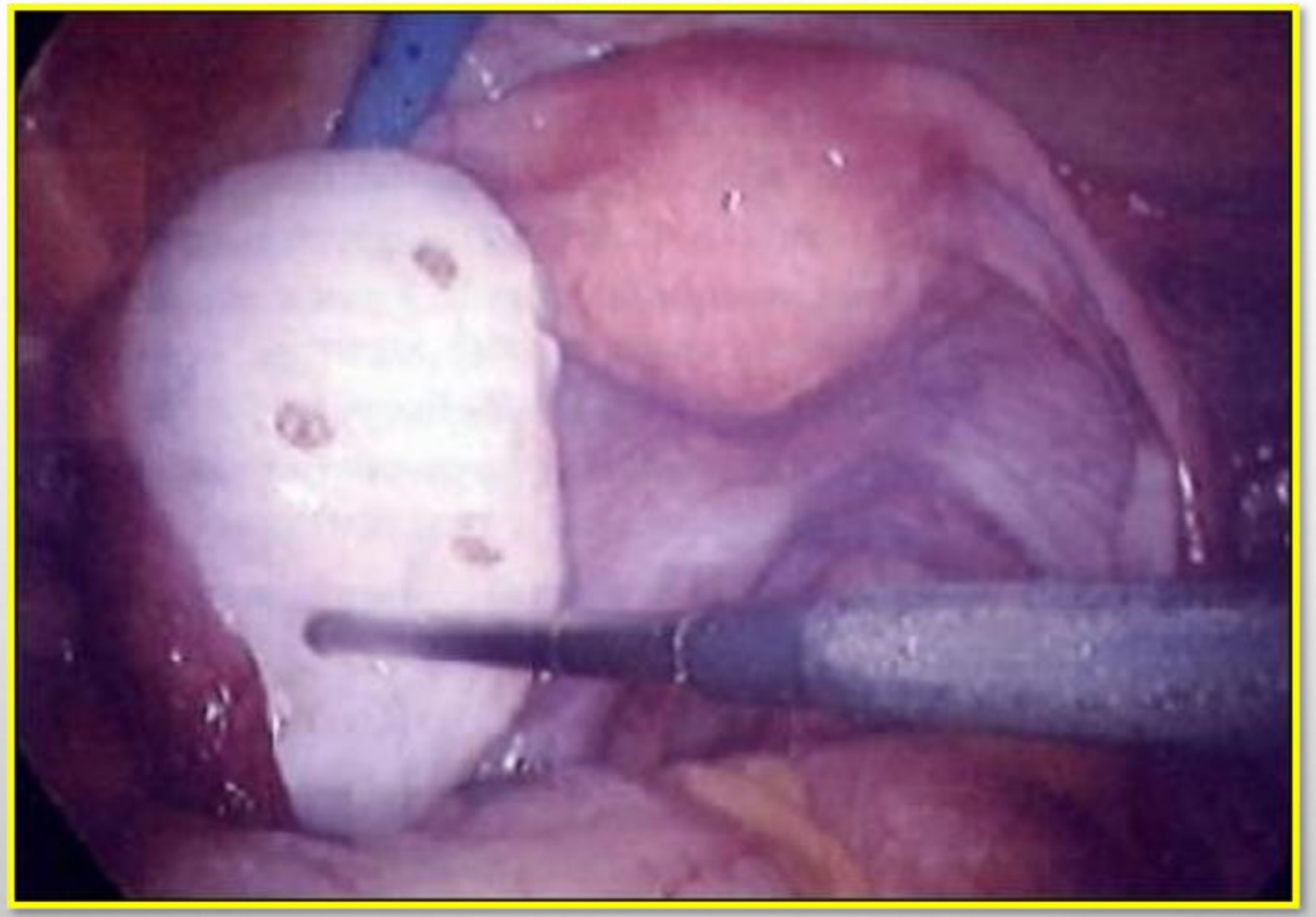
- Iatrogenic adhesions
- Decreased ovarian reserve
- Complication of anesthesia

MECHANISM OF ACTION

- Mechanism unknown, destruction of luteinized follicles??
- Thermal damage leads to release of inflammatory intra-ovarian cytokines
- lod destroy ovarian androgen-producing tissue (effect on the ovarian steroidogenesis reductions in intraovarian androgens production) the local effect is followed by a fall in the serum levels of androgens and luteinising hormone (lh) and an increase in follicle-stimulating hormone (fsh) levels
- Increase blood flow provoked by surgery facilitate increase gonadotropins delivary

SURGICAL PROCEDURE

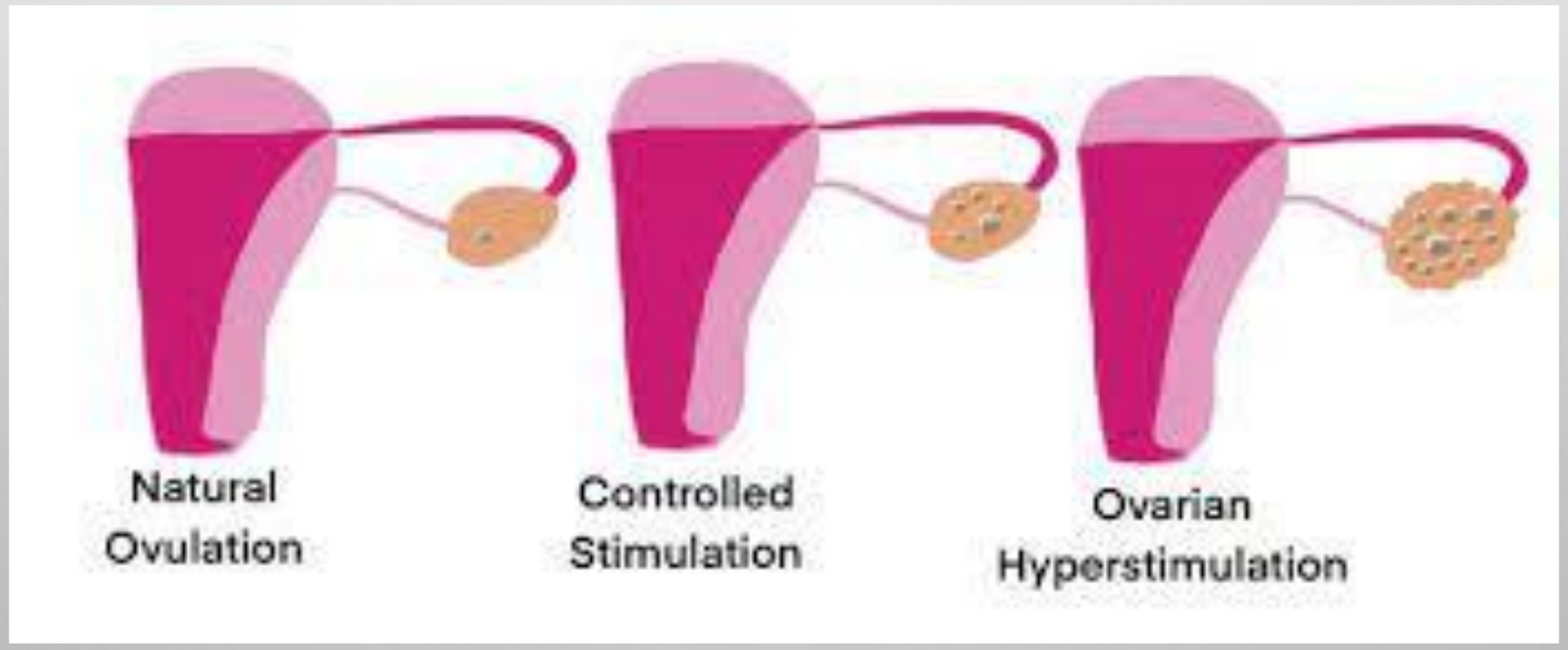
- When medical rx. Failed
- Rule of 4 , 4 punctures , 2–4 mm deep in the cortex of each ovary. 40 w
- for 4 seconds to avoid pof from unintentional ovarian damage
- ovulation rate of 80% & clinical pregnancy 60%



COMPLICATIONS OF OVULATION INDUCTION

1) Hyperstimulation ovarian syndrome

- Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of ovulation induction and controlled ovarian hyperstimulation (COH) for assisted reproduction technologies (it occurs when the ovaries are hyper-stimulated and enlarged due to fertility treatments, resulting in the shift of serum from the intravascular space to the third space, mainly to the abdominal cavity) .

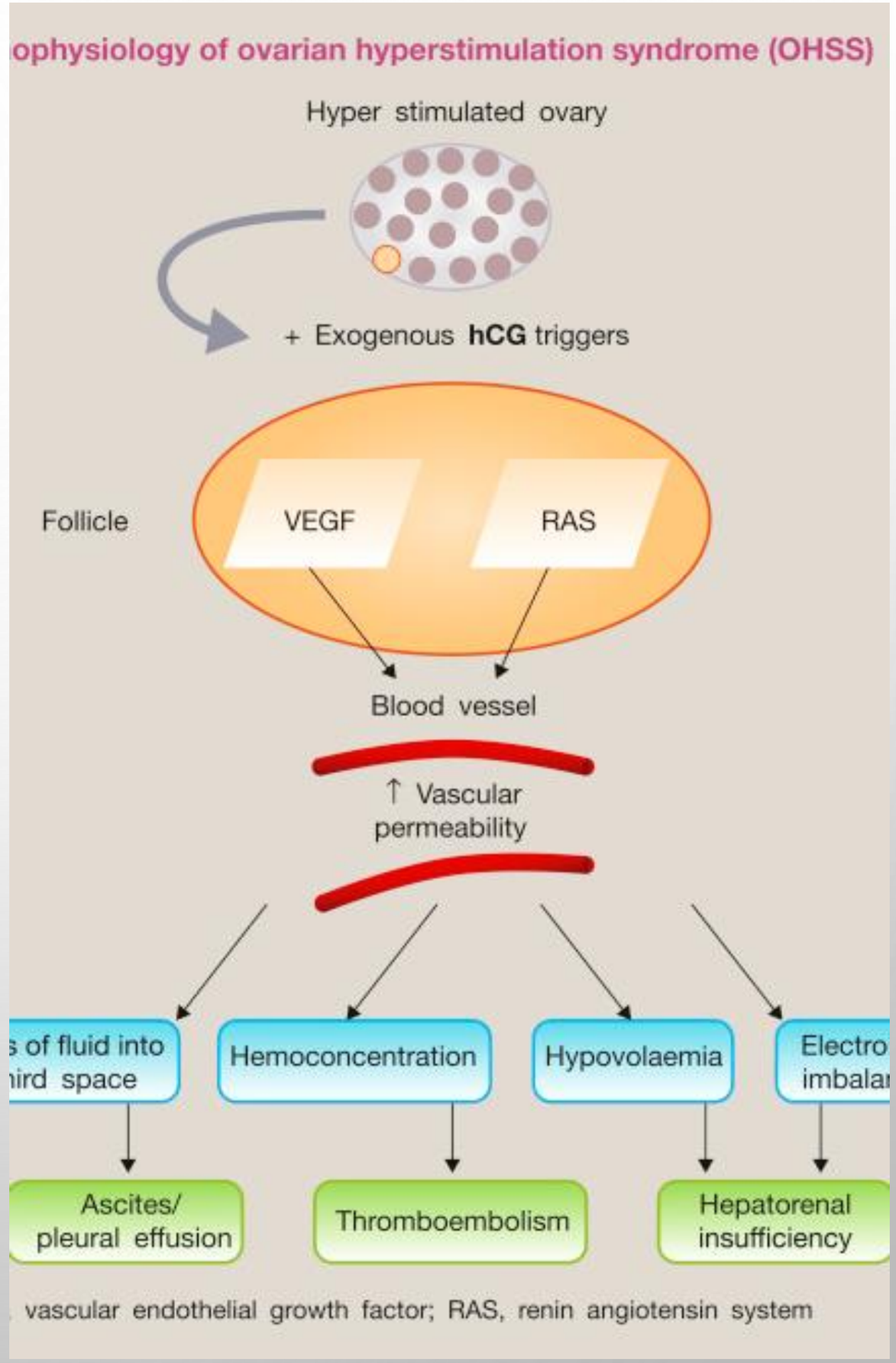


Risk factors present at baseline: Before gonadotropin administration
Previous OHSS
PCOS
Potential markers:
▪ Basal serum anti-müllerian hormone >3.3 ng/mL
▪ Antral follicle count >8
Single nucleotide polymorphisms (SNPs) in genes involved in follicular growth (*BMP15*)

Risk factors related to ovarian response
Multiple follicles >20 follicles larger than 10 mm
High or rapidly rising serum estradiol concentration (>3500 pg/mL [12,850 pmol/L] in COH)
High number of oocytes retrieved
hCG given for luteal phase supplementation
Elevated serum/follicular fluid VEGF levels
Pregnancy (increase in endogenous hCG)

OHSS CAN BE VIEWED AS AN EXAGGERATION OF A PHYSIOLOGIC PROCESS. THE SUCCESSIVE STAGES OF OHSS ARE :

1. Recruitment of a large number of small antral follicles into a functional cohort
2. Sustained development of numerous large antral follicles until ovulation (or luteinization)
3. Excessive production of vascular endothelial growth factor (VEGF) by the developing corpora lutea, after hcg administration
4. Exaggerated perifollicular neovascularization with some of the new blood vessels exhibiting increased permeability
5. Escape of follicular fluid and perifollicular blood containing large amounts of VEGF into the peritoneal cavity
6. Functional impairment of blood vessels (not only within the ovary)
7. Massive fluid shift from the intravascular to the third compartment, also known as "third spacing," resulting in intravascular hypovolemia concomitant with the development of edema, ascites, hydrothorax, diminished renal blood flow, and/or pericardial effusion
8. Impairment of cardiac, renal, pulmonary, and liver function



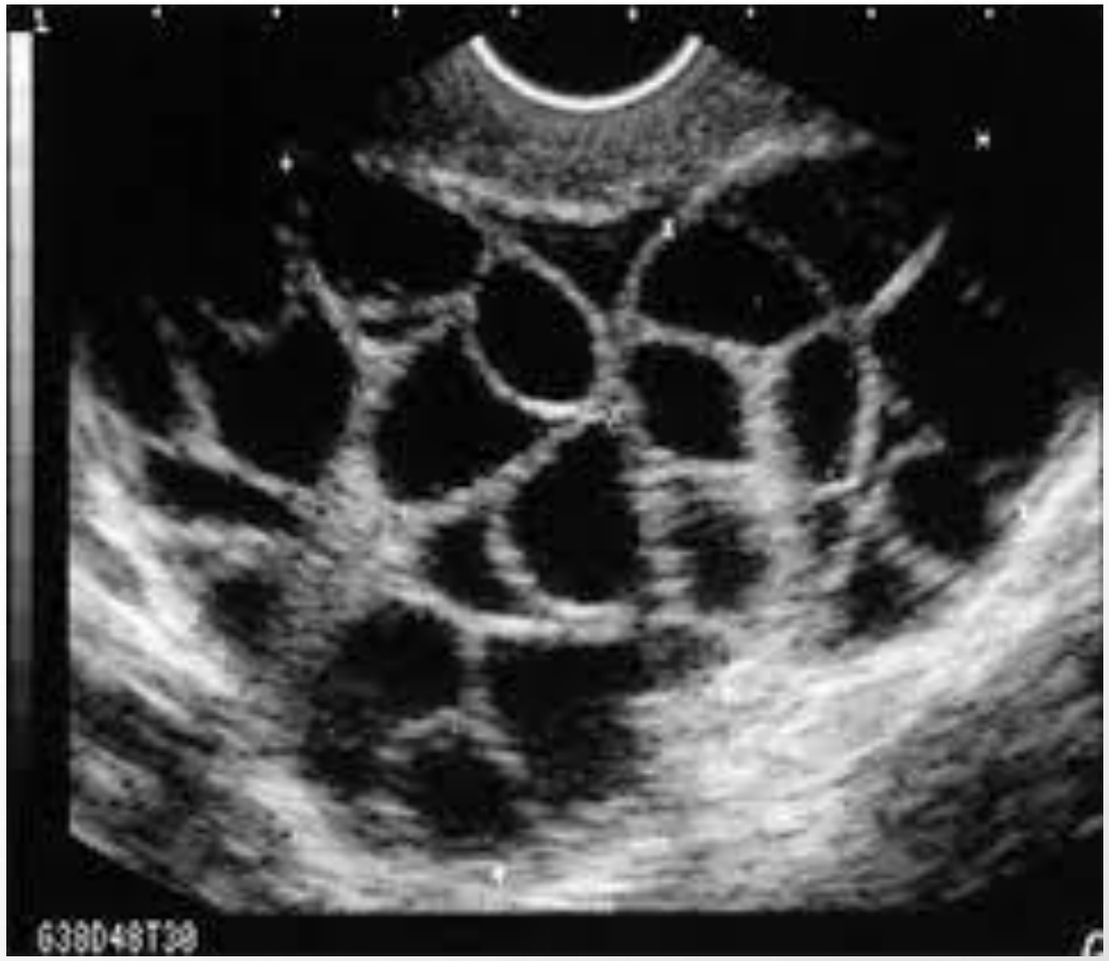
Classification of OHSS: Clinical and biochemical features[1]

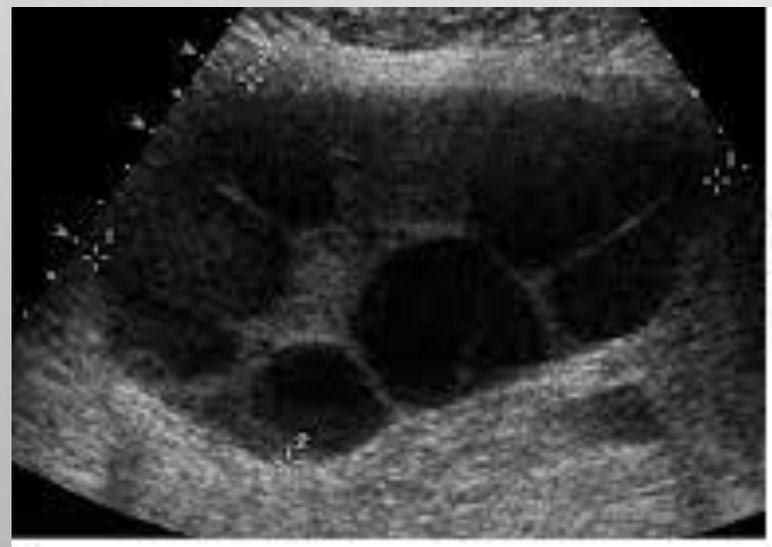
	Clinical features	Biochemical features
Mild	▪ Abdominal distention/discomfort ▪ Mild nausea/vomiting ▪ Diarrhea ▪ Enlarged ovaries	▪ No clinically important laboratory findings
Moderate	▪ Presence of mild features plus: • Ultrasonographic evidence of ascites	▪ Elevated Hct (>41%) ▪ Elevated WBC (>15,000/microL) ▪ Hypoproteinemia
Severe	▪ Presence of mild and moderate features plus: • Clinical evidence of ascites (can be tense ascites) • Severe abdominal pain • Intractable nausea and vomiting • Rapid weight gain (>1 kg in 24 hours) • Pleural effusion • Severe dyspnea • Oliguria/anuria • Low blood/central venous pressure • Syncope • Venous thrombosis	▪ Hemoconcentration (Hct >55%) ▪ WBC >25,000/microL ▪ Serum creatinine >1.6 mg/dL ▪ Creatinine clearance <50 mL/min ▪ Hyponatremia (Na^+ <135 mEq/L) ▪ Hyperkalemia (K^+ >5 mEq/L) ▪ Elevated liver enzymes
Critical	▪ Presence of severe features plus: • Anuria/acute renal failure • Arrhythmia • Pericardial effusion • Massive hydrothorax • Thromboembolism • Arterial thrombosis • ARDS • Sepsis	▪ Worsening of biochemical findings seen with severe OHSS

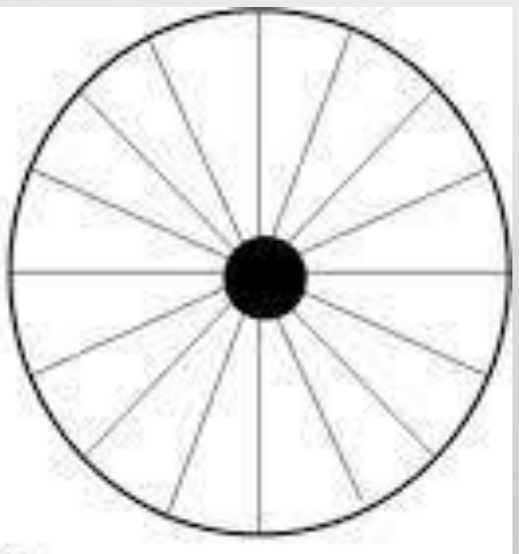
Diagnosis

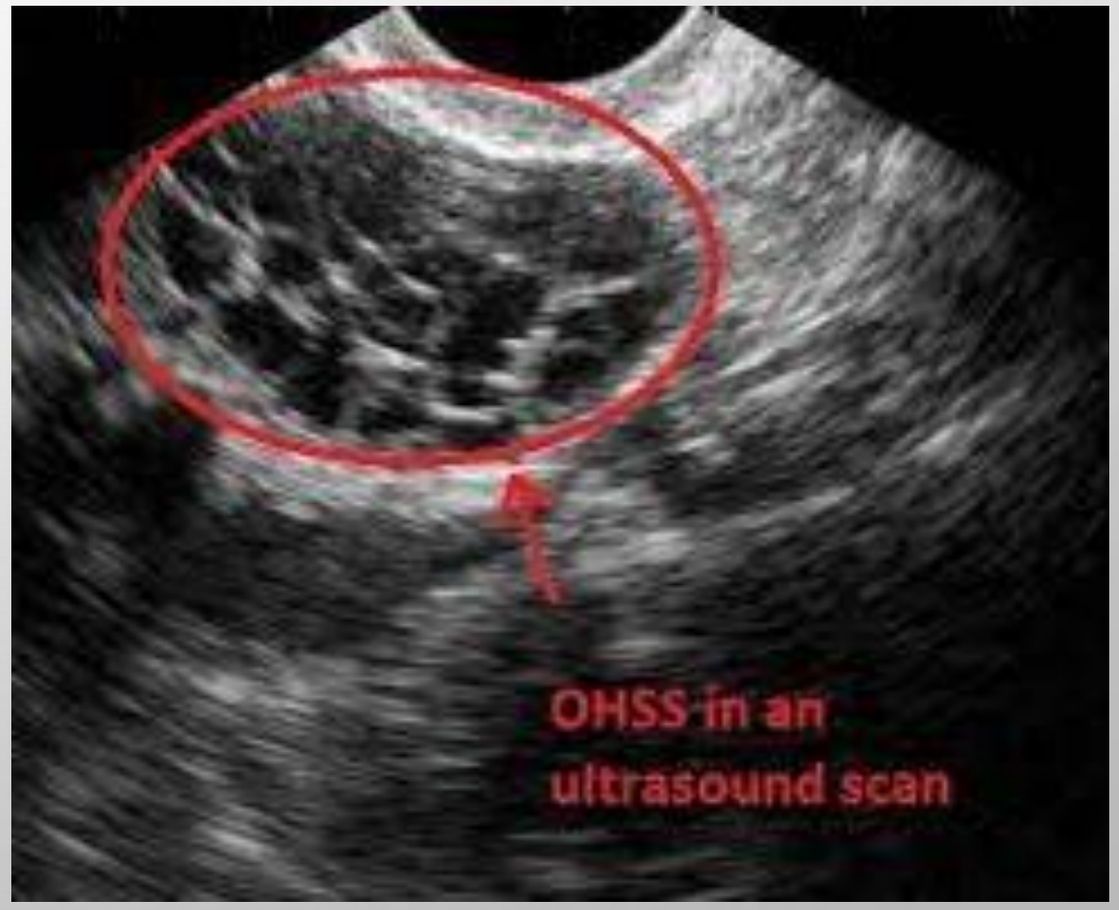
The diagnosis of ohss is made by :
1)clinical history/physical

2)abdominal/ transvaginal ultrasound (typically shows bilateral symmetric enlargement of ovaries (often >12 cm in size) ,multiple cysts of varying sizes, giving the classic spoke-wheel appearance)









Management :

Mild OHSS normally, these cases are self-limited and can be managed conservatively, with a goal of relieving symptoms by analgesics (acetaminophen rather than nonsteroidal anti-inflammatory drugs [nsaids]) and avoidance of heavy physical activity are usually enough

Moderate OHSS — recommendations include:

1. Oral fluid intake of 1 to 2 liters per day. Diuretics are contraindicated because they can worsen decreased intravascular volume.
2. Ambulate, but avoid other physical activity. Avoid sexual intercourse.
3. Bed rest is sometimes necessary
4. Daily weights, abdominal circumference measurements, and urinary output recordings.
5. Monitoring for signs of progression

Severe and critical OHSS

Hospitalization — hospitalization is mandatory in females with (OHSS) .

Medical treatment of severe OHSS is directed at :

1. Maintaining intravascular blood volume. Isotonic crystalloid solutions (eg, normal saline, ringer's lactate) are used.
2. Correcting the disturbed fluid and electrolyte balance, relieving secondary complications of ascites and hydrothorax
3. Preventing thromboembolic phenomena. Thromboprophylaxis indicated for **all** hospitalized patients

Critical ohss cases should be managed in an(icu) and patient monitored by :

1. Assessment of fluid balance (daily or more often)
2. Weights and measurement of abdominal circumference
3. CBC
4. Electrolytes, blood urea nitrogen (BUN), creatinine
5. Serum hcg measurements (to determine if patient has conceived)
6. Invasive monitoring of central venous pressure
7. Pelvic ultrasound as needed to evaluate ovarian size and ascites
8. Chest radiograph and echocardiogram when pleural or pericardial effusion is suspected (as often as needed

COMPLICATIONS OF OHSS

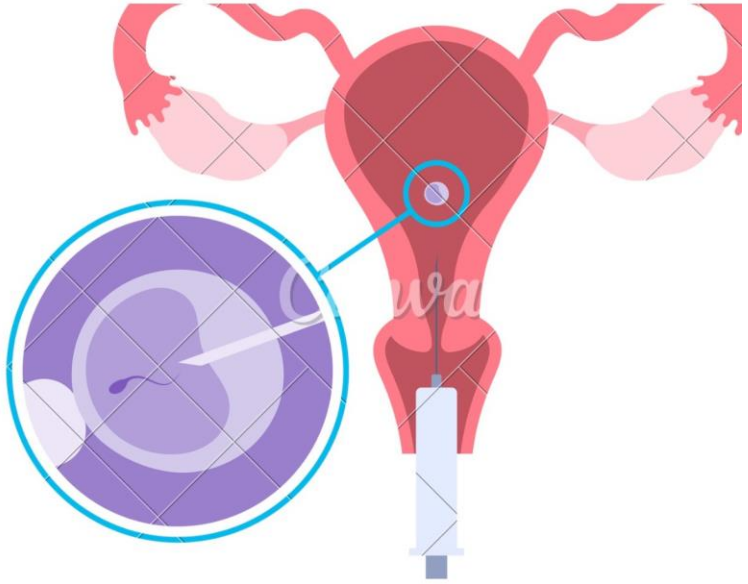
1. Deep vein thrombosis
2. Pulmonary embolism
3. Arterial thrombosis
4. Internal jugular vein thrombosis and stroke
5. Cerebral oedema; ovarian torsion
6. Renal failure
7. Ascites abnormal build-up of fluid in the abdomen
8. Ileus

2)MULTIPLE PREGNANCY

Multiple pregnancy occurs in 8-10% of clomiphene conceptions, with less than 1% of cases exceeding twins. Multiple gestation occurs in 20-30% of hmg conceptions, and 5% of these conceptions are multiple births of more than two. Ultrasonic monitoring reduces this risk if the hcg is withheld in the presence of an excessive number of mature follicles. **Current use of a lower-dose regimen of hmg or pure FSH reduces the overall risk of multiple pregnancy to about 5%.**

In vitro fertilization (IVF)

Assisted reproductive technology



Abdullah Al reqib, Sawsan Sweilmeen , Lian Hyari, Orayb Siam, Hazim alkousheh, Dana Sawalha, Soad alsuwait
C1

Introduction:

Assisted reproductive technology (ART) – ART includes:
"all interventions that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction".

This includes:
in vitro fertilization (IVF) and embryo transfer (ET), intracytoplasmic sperm injection (ICSI), embryo biopsy, preimplantation genetic testing (PGT), assisted hatching, gamete intrafallopian transfer, zygote intrafallopian transfer, gamete and embryo cryopreservation, semen, oocyte and embryo donation, and gestational carrier cycles and more.

Terminology :

- **Medically assisted reproduction** (MAR) -the reproduction brought about through various interventions, procedures, surgeries, and technologies to treat different forms of fertility impairment and infertility. These include ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures (This is a broader phrase compared with ART)

- **Infertility**: In ability to conceive after (1-2) years of regular unprotected intercourse.

- **Intracytoplasmic sperm injection (ICSI)** – ICSI is "a procedure in which a single spermatozoon is injected into the oocyte cytoplasm(This procedure is typically used for severe male factor infertility)

In Vitro Fertilization

- a complex procedure designed to overcome infertility and produce a livebirth as a direct result of the intervention; it is one type of assisted reproductive technology (ART).

- In general, IVF involves stimulating ovaries and retrieving oocyte(s) fromovarian follicles. The retrieved oocytes fertilized in the laboratory (ie, in vitro) to create embryos then the resultant embryo(s) are transferred into the uterine cavity.

- These steps typically occur over approximately a two-week interval of time.

Indications :

Fertility issues

Other uses :

Fertility issues:

Diminished ovarian reserve /

Primary ovarian insufficiency/

Age related

Tubal factor

male factor infertility

All other causes of infertility that have not responded to less invasive therapies

Endometriosis(moderate to severe) /

Ovulatory dysfunction

Other uses:

- **Preimplantation genetic testing (PGT)**
- **Sex selection and/or balanced family planning**
- HIV-positive serodiscordant couples
- Fertility preservation in cancer patients

IVF/ICSI cycle

Consists of:

1. Down-regulation of gonadotrophins.
2. Controlled ovarian stimulation.
3. Maturation of oocytes.
4. Oocytes retrieval.
5. Fertilization and incubation of the gametes.
6. Embryo transfer.
7. Luteal phase support.

In addition, cryopreservation choice is offered if good quality embryos are available.

1. Down-regulation of gonadotrophins:

- Given to avoid premature LH surge and spontaneous ovulation
- Either GnRH agonist protocol or GnRH antagonist protocol. But always use GnRH antagonist protocol in women with high risk of OHSS.
- Commonly started in the mid-luteal phase or overlapped with an oral contraceptive.

2. Controlled ovarian stimulation:

- Refers to "pharmacologic treatment with the intent of inducing development of multiple ovarian follicles".
- After ovarian suppression, ovaries are stimulated by urinary or recombinant FSH and/or HMG on the second or third day of the next cycle.
- The dose depends on age, BMI, presence of PCO and ovarian reserve.
- Monitoring of follicle is done by TVUS or E2 levels.

3. Maturation of oocytes:

- Trigger of ovulation is done by urinary or recombinant hCG, 36 hours before oocyte retrieval.
- An injection of hCG (usually 10,000 U) is given on the basis of follicular size and estradiol levels to induce the resumption of meiosis and completion of oocyte maturation.
- the ovarian follicles are judged to be mature when two or more follicles with a mean diameter of 16 to 18 mm, depending on the protocol utilized. And, in some centers, a serum estradiol level of 200 pg/mL [734 pmol/L] per codominant follicle).

4. Oocyte retrieval:

- 36 hours after the hCG injection (ovulatory trigger), multiple oocytes are aspirated under transvaginal ultrasonic guidance.

5. Fertilization and incubation of the gametes:

- After a further period of in vitro maturation, washed sperm are added or a single sperm is injected (ICSI) into each oocyte. Fertilization may be identified 14 to 18 hours after insemination by the visualization of two pronuclei.
- Typical fertilization rates with IVF are around 70-80%.

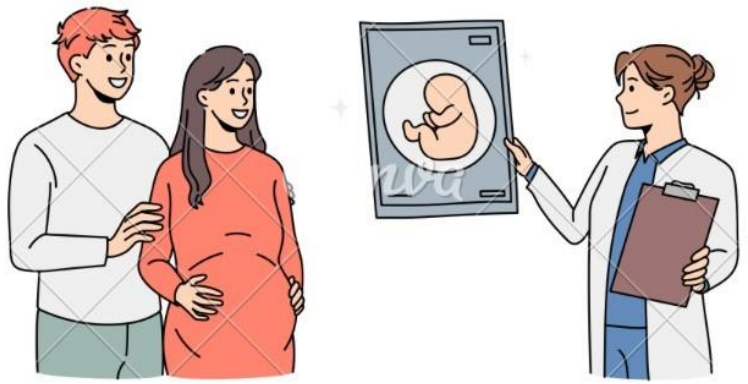
6. Embryo transfer:

- The conceptus is transferred to the uterine cavity 2-4 days after oocyte retrieval (early transfer) or at 5-6 days (blastocyst stage) by means of a tiny catheter via the cervix, under ultrasound guidance, they are placed 1 to 2 cm from the top of the uterine cavity.
- In some cases, the hatching process is aided by making an artificial opening in the zona pellucida ("assisted hatching").
- The number of embryos transferred is influenced by maternal age, the number of oocytes retrieved, and availability of embryos for cryopreservation, but in general one to two embryos are transferred (SET or DET).

7. Luteal phase support:

- Should offer support with progesterone till 8 weeks of gestation.
- Different form of progesterone with different routes of administration are available, RCT are taking place comparing efficacy of different forms.

Generally, success rates lie between 40% and 60% per cycle.



Cryopreservation

Cryopreservation of semen, oocytes or embryos should be offered to anyone who may undergo treatment that may affect his/her fertility. (e.g.: chemotherapy for cancer).

For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment. And do not use a lower age limit for cryopreservation.

In addition, surplus embryos not transferred at the time of the IVF treatment can be frozen, stored, and transferred in a later menstrual cycle in the event of failure or for additional pregnancies.

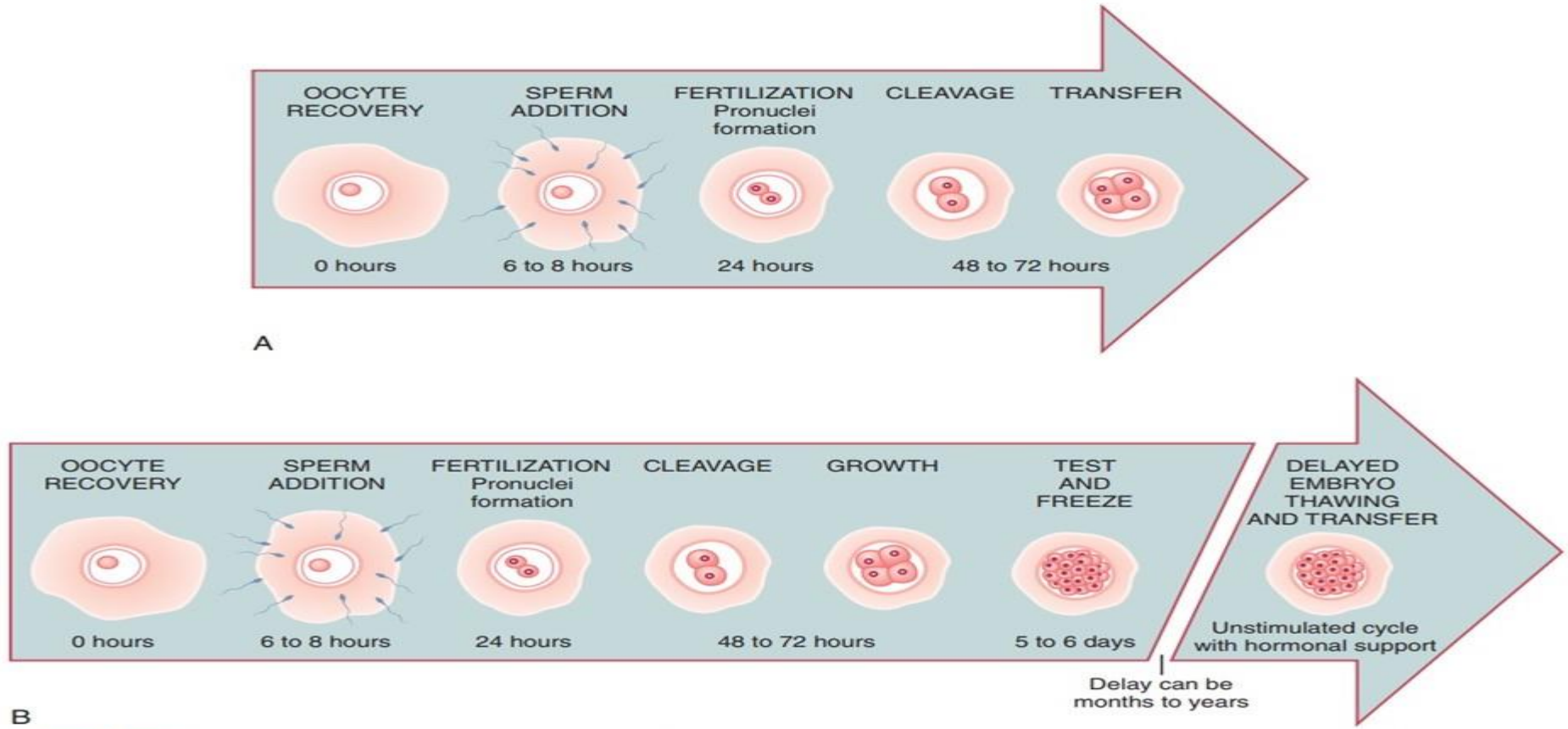


FIGURE 34-6 Approximate time-course for in vitro fertilization and embryo transfer in same cycle as stimulation **(A)** or delayed after embryo freezing and thawing **(B)**.

FACTORS IMPACT IVF SUCCESS

Age of the woman is considered the major determinant of the success of IVF.

the diminished success is due to:

Decreased ovarian responsiveness to gonadotropin stimulation, which results in a decreased number of oocytes available for IVF.

Decreased implantation rate per embryo transferred due to poor egg quality.

In addition, the risk of pregnancy loss (ie, miscarriage or spontaneous abortion) and chromosomal abnormality rises with increasing female age.

Quality of Eggs and Sperm: The quality of both eggs and sperm plays a crucial role in the success of IVF. High-quality eggs and healthy sperm increase the likelihood of successful fertilization and implantation.

Underlying Causes of Infertility: The cause of infertility can also impact IVF success. Some conditions, such as blocked fallopian tubes or male factor infertility, may be more amenable to IVF treatment than others.

FACTORS IMPACT IVF SUCCESS

Negative effect

- Poor ovarian reserve
- Hydrosalpinx
- Tobacco and substance use

Minimal or unclear effect

- Leiomyoma
- Endometrioma and endometriosis
- Previous pregnancy history
- Previous unsuccessful IVF cycle
- Obesity
- Diet
- Stress

No proven effect

- Aspirin, Heparin
- Acquired or inherited thrombophilia
- Endometrial thickness
- COVID-19 Infection or vaccination

NEGATIVE EFFECT

I. Poor ovarian reserve.

- Individuals with poor ovarian reserve have a lower likelihood of achieving a live birth using their own oocytes; other forms of therapy (eg, oocyte donation) should be offered.

II. Hydrosalpinx

- Studies have consistently shown that the presence of a hydrosalpinx is associated with poor IVF outcome.
- Salpingectomy prior to IVF in women with hydrosalpinges improves pregnancy rates, and therefore should be recommended.

III. Tobacco and substance use

- Cigarette smoking reduces IVF success rates (fewer ova retrieved) and is associated with numerous adverse effects on general health

MINIMAL OR UNCLEAR EFFECT

I. Leiomyoma

- The effect of leiomyomas on IVF depends on their location: submucosal myomas decrease the chance of success, whereas subserosal myomas do not appear to have any effect.

II. Endometrioma and endometriosis

III. Previous pregnancy history

- A previous live birth is associated with higher likelihood of successful IVF, but a history of one or more miscarriages does not substantially reduce the likelihood of success

IV. Previous unsuccessful IVF cycle

- Lack of success in an IVF cycle does not appreciably decrease success rates during subsequent treatment until approximately the fourth IVF cycle

MINIMAL OR UNCLEAR EFFECT

V. Obesity

- Patients with overweight or obesity have lower pregnancy and live birth rates following IVF as well as increased obstetric risks.

VI. Diet

- Healthy dietary patterns have been associated with improved outcomes of fertility treatment. Improved outcomes may result from a decrease in pregnancy loss in individuals who adhere to a healthy/Mediterranean diet.

VII. Stress

- The impact of stress on IVF outcome is unclear as the data are mixed

NO PROVEN EFFECT

I. Aspirin, acupuncture, heparin

- Meta-analyses have not demonstrated a statistical improvement in clinical pregnancy rates with use of aspirin, acupuncture or heparin anytime during the IVF cycle.

II. Acquired or inherited thrombophilia

- the presence of anticardiolipin or lupus anticoagulant antibodies alone or one of the common inherited thrombophilia's does not appear to adversely impact IVF success rates.

III. Endometrial thickness

- Endometrial thickness was a poor predictor of pregnancy occurrence after IVF and should not be used as a criterion for cycle cancellation, freezing of all embryos, or refraining from further IVF treatment.

IV. COVID-19 Infection or vaccination

- no deleterious effects of either viral infection or vaccination on fertility or IVF cycle outcomes

Pregnancy outcome

- The outcome of pregnancies conceived via assisted reproductive technology (ART) has been generally good and the vast majority of babies born are normal
- However, there are complications related can be seen more in pregnancies via ART compared to unassisted pregnancies

WHAT ARE THE RISKS OF THE IVF PROCEDURE?

- Procedure risks :

✓ Morbidity and mortality rates directly related to IVF are low.

✓ Complications are predominantly due to hormonal stimulation and egg retrieval, and include ovarian hyperstimulation syndrome (OHSS), thromboembolism, pelvic infections, abdominal bleeding, adnexal torsion, allergic reaction, and anesthetic complications .

- # Pregnancy-related risks :

1. Multiple gestation

2. Ectopic pregnancy – occurs in approximately 1.5 to 2 percent of patients.

3. Heterotopic pregnancy - increases in incidence to 1 in 100 to 1 in 1000 for IVF-conceived pregnancies compared with in 1 in 3000 to 1 in 30,000 for unassisted pregnancy

4. Stillbirth and perinatal mortality (appear to be increased as much as fourfold when compared with births from unassisted conception)

5. preterm birth and LBW (≤2500 g)

Frozen embryo transfer, rather than fresh embryo transfer, is associated with reduced risks of low birth weight and spontaneous preterm birth

6. preeclampsia/eclampsia (50% higher than unassisted)

7. Gestational diabetes

8. Placental disorders - including placenta previa and placenta accreta spectrum (PAS), as well as placental pathology appear to be increased in pregnancies conceived with IVF

9. venous thromboembolism


THANK
YOU