
بسم الله الرحمن الرحيم

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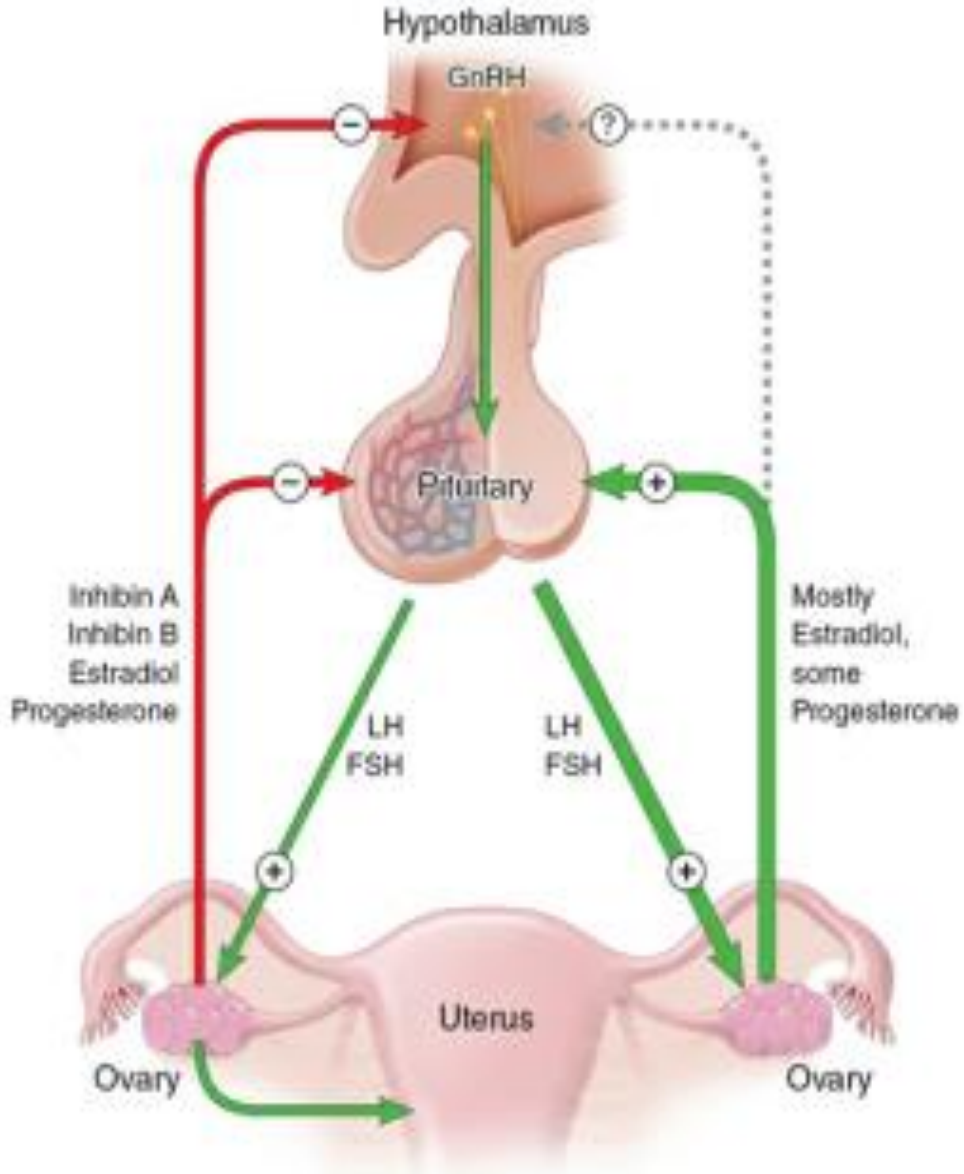
- **Infertility fellowship**

- **Ovulatory disorders** can be identified in 18 to 25 percent of couples presenting with infertility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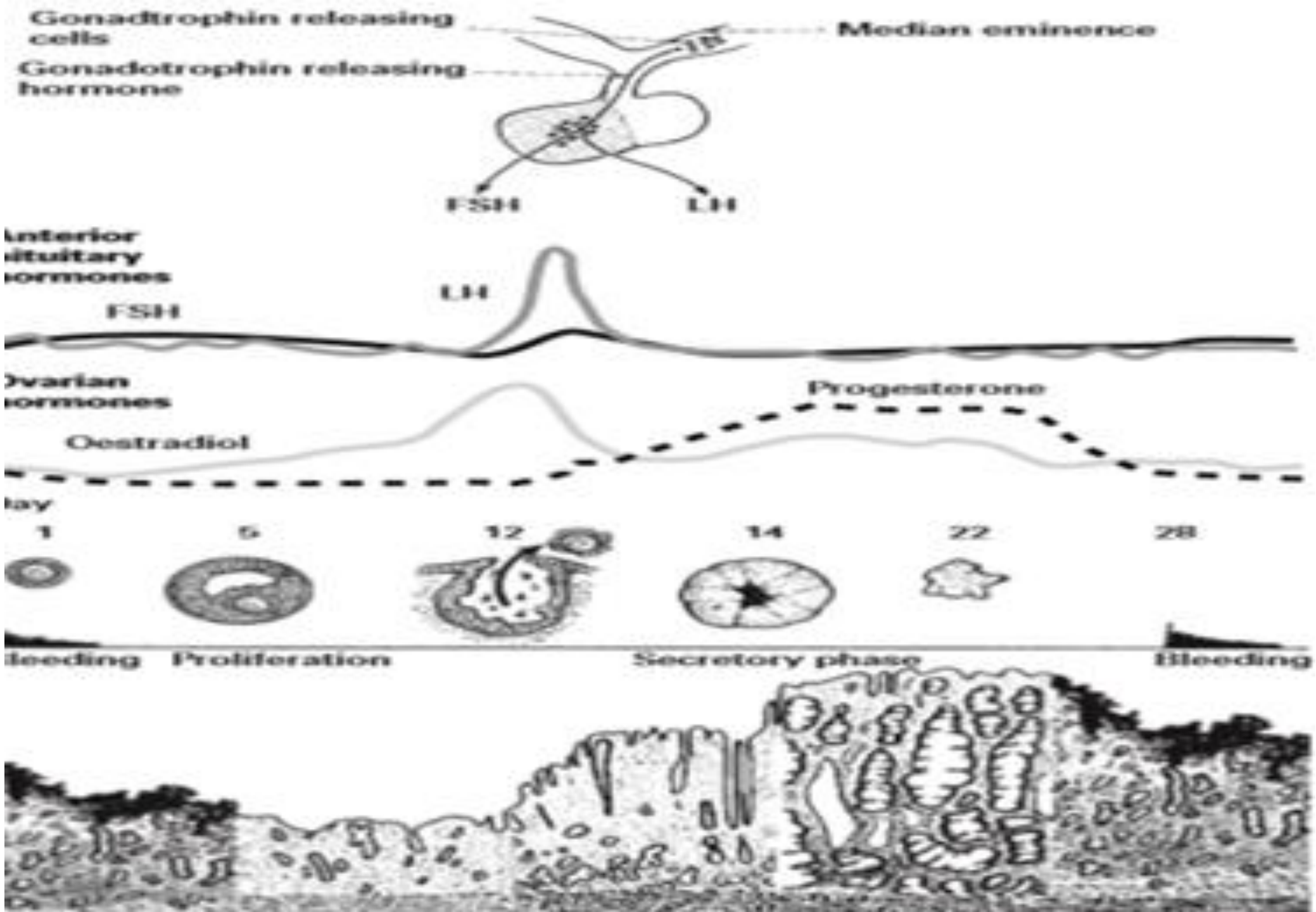
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WHO class 1 – **Hypo**gonadotropic **hypo**gonadal anovulation

- hypothalamic amenorrhea 5 to 10 percent of anovulatory women

○ eating disorders (such as anorexia nervosa),
○ exercise
○ Stress
○ congenital GnRH deficiency kallman syndrome
○ Many infiltrative diseases and tumors of the hypothalamus and pituitary

●**WHO class 2** – Normogonadotropic normoestrogenic anovulation
almost all women in this category have PCOS most common cause

●**WHO class 3** – **Hyper**gonadotropic **hypo**estrogenic anovulation
○ primary ovarian insufficiency
○ premature ovarian failure

Hyperprolactinemia did not have a separate WHO category.

- AMH levels are increased in PCOS
- AMH levels are decreased in WHO class 1 and 3.

goals of ovulation induction in women withanovulatory infertility are:

- Induce monofollicular rather than multifollicular development
- a singleton pregnancy and birth of a healthy newborn

- Focus on cumulative outcomes over a given period of time, rather than per cycle outcomes.
- Start with the least invasive, simplest, and cheapest treatment option; subsequent options should depend upon ovarian response (ovulation and number of follicles)
- Minimize the risk of OHSS in women undergoing **gonadotropin therapy**, particularly those with PCOS
- This could mean canceling the cycle and refraining from intercourse in case of multiple follicle development

- **Preconception counseling** refers to the process of identifying social, behavioral, environmental, and biomedical risks to a woman's fertility

  and pregnancy outcome

  reducing these risks through education, counseling, and appropriate intervention.

- medical history and physical examination,

- **preconception assessment**
- laboratory assessment based upon individual risk factors and local guidelines.
- genetic carrier testing

- **Functional hypothalamic amenorrhea**
- unlikely to respond to clomiphene citrate
- one course of clomiphene prior to initiating pulsatile GnRH or gonadotropin therapy.
- For those who ovulate, clomiphene citrate can then be continued.
- For those who do not ovulate, we suggest pulsatile GnRH as first-line therapy in countries where it is available.
- If pulsatile GnRH is unavailable, gonadotropin therapy

Polycystic ovary syndrome (PCOS) –

- **exercise and weight loss**,
- Letrozole is best
- Metformin –
- reduce hepatic glucose output
- and lower serum insulin concentrations, has been used to promote ovulation
- recommendation against the routine use of metformin except in women with glucose intolerance

●**Gonadotropins** – Gonadotropin therapy is only considered who have either not ovulated or not conceived after treatment with initial therapies (weight loss, clomiphene, letrozole

●**Laparoscopic ovarian drilling** in who fail to ovulate despite an adequate trial of clomiphene citrate.

- **Clomiphene**
- Sixty to 85 percent of anovulatory women, typically with PCOS, ovulate in response to clomiphene citrate.
- Of those who ovulate, approximately 50 percent do so at a dose of 50 mg daily for five days,
- Twin and triplet gestations occur in approximately 7 to 9 and 0.3 percent, respectively, of clomiphene-induced pregnancies.
- miscarriage not increased
- spontaneous pregnancies not increased
- ectopic pregnancy is probably not increased.
- The risk of OHSS is less than 1 percent

- **Dopamine agonists** — A dopamine agonist is the treatment of choice for women with hyperprolactinemic anovulation

- Bromocriptine is still often used to restore ovulation in women with hyperprolactinemia.
-
- cabergoline, are associated with fewer side effects.

- The fetal safety of bromocriptine is better established than cabergoline, but cabergoline appears to be safe as well.

- Treatment should be stopped once pregnancy

CANCER RISKS

- **Ovarian cancer** nulliparous women with refractory infertility may harbor a particularly high risk of epithelial ovarian cancer,

irrespective of their use of fertility drugs

- **Breast cancer** do not increased

Other cancers do not increased

- **Risk in offspring** does not increased with oral ovulation induction

letrozole

- **PHARMACOLOGY AND PHYSIOLOGY**
- Aromatase inhibitors

Aromatase activity is present in

ovaries

brain

adipose tissue

muscle

liver

breast.

- Aromatase inhibitors are widely used as adjuvant endocrine therapy for postmenopausal women with breast cancer.
- They are completely absorbed after oral administration
- and have a mean terminal half-life of approximately 45 hours
- clearance is mainly hepatic

- Administration of an aromatase inhibitor to premenopausal women on days 3 to 7 of the menstrual cycle results in suppression of ovarian estradiol secretion, a rise in FSH
- As the dominant follicle grows and estrogen levels rise
- FSH is then suppressed, and the smaller-growing follicles become atretic, resulting in monofollicular ovulation in most cases.
- The potential for monoovulation represents a theoretical advantage over clomiphene citrate,

- When prescribing letrozole, the starting dose is 2.5 mg/day, cycle days 3 to 7, following a spontaneous menses or progestin-induced bleed.
- If the cycle is ovulatory, but pregnancy has not occurred, the same dose should be used in the next cycle.

- If ovulation does not occur, the dose should be increased to 5 mg/day, cycle days 3 to 7, with a maximal dose of 7.5 mg/day.

- Higher doses (7.5 mg) appear to be associated with a thinning of the endometrium similar to that seen with clomiphene citrate

Comparison with clomiphene

- A high rate of monofollicular development, which should theoretically reduce the risk of multiple pregnancies.
- A shorter half-life (48 hours versus two weeks for clomiphene citrate
- No direct antiestrogenic adverse effects on the endometrium.
- Lower serum estradiol levels – This is a particular advantage for women with **breast cancer** and possibly for women with **endometriosis** undergoing in vitro fertilization (IVF

Outcomes

- For women with a BMI ≥30.3 kg/m^2, the cumulative live birth rate was significantly higher with letrozole when compared with clomiphene (20 versus 10 percent).
- The twin pregnancy rate was lower with letrozole than with clomiphene (6 of 81 [7.4 percent

- **Side effects**
- common side effects included hot flashes in 33 percent of women receiving clomiphene and fatigue and dizziness in 22 and 12 percent
- mild side effects with short-term use of letrozole for ovulation induction,

- musculoskeletal symptoms in postmenopausal women with breast cancer has been associated with in at least one-third of patients

- **Controlled ovarian hyperstimulation**
- **Unexplained infertility**
- Letrozole has also been used alone or as an adjunct to gonadotropin therapy in women with unexplained infertility.
- **Women with breast cancer**

- **Women with endometrial cancer**

The strategy of combining letrozole and FSH therapy to avoid high serum estradiol concentrations described for women with breast cancer undergoing ovarian stimulation for cryopreservation of embryos or oocytes prior to gonadotoxic therapy or definitive surgery has also been used for women with **endometrial carcinoma**.

Clomiphene

It acts as a SERM similar to tamoxifen and raloxifene.

All three drugs are competitive inhibitors of estrogen binding to estrogen receptors and have mixed agonist and antagonist activity, depending upon the target tissue

Clomiphene appear in the feces up to six weeks after administration.

Clomiphene citrate binds to ERs and exerts its major effects on the **hypothalamus, pituitary, ovary, and uterus**.

Unlike estrogen, **clomiphene citrate binds nuclear ERs** for a **prolonged period** and depletes them.

the primary site of clomiphene action is the hypothalamus

blocking the negative feedback effect of circulating endogenous estradiol

This results in an increase in hypothalamic GnRH pulse frequency and increased serum concentrations of FSH and LH

- Clomiphene acts primarily as an antiestrogen in the uterus, cervix, and vagina.
- Abnormal luteal phase endometrial morphology has been found in some

- Predictors of ovulation

Of those who ovulate, 30 to 40 percent conceive.

predictors of pregnancy with clomiphene included

- younger age,
- low BMI,
- low FAI oligomenorrhea rather than amenorrhea.

- **Ovulatory triggers**
- recombinant hCG 250 mcg
- urinary hCG (5000 to 10,000 units)
- recombinant LH,

- Its use in ovulatory infertility and for men with hypogonadism separately.

pretreatment evaluation

- **Monitoring** —
- Determination of the ovulatory LH surge by urinary LH kits

The LH surge typically occurs 5 to 12 days after clomiphene administration is completed.

Ovulation generally occurs 14 to 26 hours after the detection of the urinary LH surge.

- the interval of highest fertility is the day of the LH surge and the following two days.

- A basal body temperature chart,
- as the temperature rise occurs one to five days after the midcycle LH surge and up to four days after ovulation.

- A mid-luteal serum progesterone concentration greater than 3 provides reliable evidence that ovulation has occurred..

- serial transvaginal ultrasound to monitor the number and size of developing follicles and to time hCG administration if necessary.

- Some advocate ultrasound monitoring of just the first clomiphene cycle in order to exclude hyper-response .

- However, adding ultrasonographic monitoring is costly and does not appear to improve pregnancy rates significantly.

- **Starting a cycle**
- clomiphene is started on cycle day 2, 3, 4, or 5

- The initial dose, empirically, is 50 mg daily for five days
- starting with a higher dose does not result in higher pregnancy rates.
- If ovulation does not occur in the first cycle of treatment, the dose is increased to 100 mg.
- maximum daily dose of 150 mg
- Once ovulation is achieved, 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.

- Because of the observations that pregnancy rates are low after six cycles of treatment and that 12 or more cycles may increase the risk of ovarian neoplasms

- We suggest further evaluation and/or a change in therapy for women who do not conceive after three to six ovulatory clomiphene citrate cycles.

- **Clomiphene citrate**
- **Ovulatory and pregnancy rates** —There is no benefit to increasing the clomiphene dose in subsequent cycles once ovulation occurs. .

- Failure to conceive despite ovulatory cycles, particularly at higher doses, may be due to clomiphene's antiestrogenic effects on the quantity and quality of cervical mucus and on the endometrium, impairing implantation

- **Multiple gestation** —The risk may be reduced by
- ultrasound monitoring and withholding human chorionic gonadotropin (hCG), intrauterine insemination (IUI), or intercourse if more than two follicles >15 mm diameter are seen.

- **Role of modified regimens**
- **Addition of ovulatory dose hCG** It is given when transvaginal ultrasonography shows that the leading follicle has reached 18 to 20 mm in diameter

- It should be noted that premature administration of hCG acts like a premature LH surge and may result in follicular atresia.

- hCG is routinely used to induce ovulation and to time IUI.

- However, we do not suggest routine administration

- it does not enhance the efficacy of clomiphene-IUI treatment

- Ovulation occurs approximately 36 to 44 hours after the injection.

Other

- conception and live birth rates may be lower in women after a spontaneous period or progestin-induced withdrawal bleed compared with anovulatory cycles without progestin withdrawal

- Progesterone supplementation may also be used for luteal phase support in women treated with clomiphene citrate, although a benefit has not been demonstrated

- Addition of IUI does not appear to improve pregnancy rates (without male factor infertility)