OVULATION INDUCTION

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Ovulatory disorders can be identified in 18 to 25 percent of couples presenting with infertility .

most of these women have oligomenorrhea, arbitrarily defined as menstruation that occurs at intervals of 35 days to six months.

While ovulation may occasionally occur, spontaneous conception is unlikely.

- The clinical approach to ovulation induction requires an understanding of the causes of anovulation.

- Proper diagnosis of underlying conditions may not only be relevant for infertility treatment but may also have general health implications (such as bone health, brain health and wellbeing, sexual health, and long-term cardiometabolic health).

The four most common ovulatory disorders include :

- 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])

- Hyperprolactinemia did not have a separate WHO category.

Polycystic ovary syndrome

The polycystic ovary syndrome (PCOS) is an important cause of androgen excess, menstrual irregularity, and cardiometabolic dysfunction in women. The manifestations include irregular menstrual cycles, hirsutism, obesity, insulin resistance, and anovulatory infertility.

- Largest group of anovulatory women (70 to 85 percent of cases).
- Serum estradiol and FSH concentrations levels are normal.
- luteinizing hormone (LH) concentrations may either be normal or elevated .
- The criteria for diagnosis have been referred to as the "Rotterdam criteria" .

Ovulation induction for those pursuing pregnancy

Lifestyle changes

- ✓ Diet and exercise for weight reduction as **the first step for overweight and obese women with PCOS**.
- ✓ lifestyle interventions (diet, exercise, and behavioral interventions) are more effective than minimal treatment for weight loss and for improving insulin resistance and hyperandrogenism .

- ✓ Weight loss, which can restore ovulatory cycles and improve metabolic risk, is the first-line intervention for most women.

- ✓ Weight loss results in a decrease in serum androgen concentrations and, improvements in hirsutism.

Weight reduction

For anovulatory women with PCOS who are overweight or obese, weight loss is prior to initiating ovulation induction therapy.

weight-loss strategies :
calorie-restricted diets combined with exercise for women with PCOS and obesity.

Even modest weight loss (5 to 10 percent reduction in body weight) in women with PCOS may result in restoration of normal ovulatory cycles and improved pregnancy rates.
However, the response to weight loss is variable; not all individuals have restoration of ovulation or menses despite similar weight reduction .

Diet

- ✓ There is no good evidence that one type of diet is superior to another for women with PCOS.

- ✓ Low-carbohydrate diets have become very popular for women with PCOS, because less carbohydrate leads to less hyperinsulinemia and less insulin resistance.

However, a 12-week study of a high protein/low carbohydrate diet (30 percent protein, 40 percent carbohydrate, 30 percent fat) and a low protein/high carbohydrate diet (15 percent protein, 55 percent carbohydrate, 30 percent fat) were **equally effective** for weight loss, improvements in menstrual cyclicity, insulin resistance, dyslipidemia, and abdominal fat.

Treatment with insulin-sensitizing agents (metformin,thiazolidinediones,Dchiroinositol, and myoinositol) has been used in attempts to increase/improve ovulation rates.

Metformin

- ✓ Metformin has been used to promote ovulation either alone or in combination with clomiphene, but **clomiphene or letrozole** monotherapy appears to be **superior to metformin** monotherapy on live birth rates. Its role in treating infertility is limited .

- ✓ Metformin is a drug whose major effect is to reduce hepatic glucose output and thereby lower serum insulin concentrations.

- ✓ Current guidelines **recommend against** the routine use of metformin in obese women with PCOS (including ovulation induction), **except** in women with glucose intolerance who have failed lifestyle interventions .

Pretreatment evaluation

Before initiating therapy, the presence of ovulatory dysfunction must be established.

- ✓ The menstrual history alone may be diagnostic (ovulatory dysfunction is present in women with amenorrhea or irregular menses [>45 day intermenstrual interval]).
- ✓ It is possible that women with cycles in the 35- to 45-day range have intermittent ovulations.

these women must try to conceive on their own without therapy for several months.

If they are unsuccessful, they should be referred for ovulation induction.

If the diagnosis of ovulatory dysfunction is uncertain, additional testing should be performed. such as:

Basal body temperature and/or urinary luteinizing hormone (LH) monitoring& luteal phase serum progesterone level .

Drugs & different regimens used for ovulation induction in women with ovulatory disorders:

- clomiphene citrate
- Aromatase inhibitors
- Gonadotropins

Ovulation induction medications

● Induction of ovulation in the women with pcos is aimed at inducing monofollicular development, subsequent ovulation, and, ultimately, pregnancy and birth of a healthy newborn.

●For oligo-ovulatory women with PCOS undergoing ovulation induction, letrozole is as first-line therapy over clomiphene citrate, regardless of the patient's BMI.

● Before starting letrozole, the clinician must discuss that this use of the drug is not approved by the US Food and Drug Administration (FDA) for this purpose and that there is an available alternative (clomiphene citrate).

●Clomiphene citrate had been the first-line drug for this population for many years, with metformin used as an alternative. However, both clomiphene and metformin appear to be less effective for live birth rates than letrozole .

● In women with PCOS, an ovulatory rate of 80 percent and a cumulative pregnancy rate of 30 to 40 percent can be expected. Cumulative pregnancy rate is dependent on patient BMI, with higher BMI levels associated with lower cumulative pregnancy rate.

Clomiphene citrate

- The most widely used treatment for fertility enhancement for the past 40 years. Clomiphene was a revolutionary advance in reproductive medicine and quickly became popular for induction of ovulation because of its ease of administration and minimal side effects.

- However, letrozole, an aromatase inhibitor, is also effective for ovulation induction in women with polycystic ovary syndrome (PCOS).

Available data suggest that live birth rates are higher with letrozole than clomiphene, and many experts now suggest letrozole as first-line therapy for anovulatory women with PCOS.

PHARMACOLOGY/MECHANISMS OF ACTION:

Clomiphene is a nonsteroidal triphenylethylene derivative distantly related to diethylstilbestrol.

- It acts as a selective estrogen receptor modulator (SERM), similar to tamoxifen and raloxifene.

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

The commercially available form of clomiphene is the dihydrogen citrate salt (clomiphene citrate).
It contains two stereoisomers: zu-clomiphene (38 percent) and en-clomiphene (62 percent), which were originally called the cis-isomer and trans-isomer.
En-clomiphene is cleared rapidly, while zu-clomiphene has a long half-life.

The two clomiphene isomers have mixed estrogenic and antiestrogenic effects that vary among species. En-clomiphene is the more potent isomer with greater antiestrogenic activity and the one primarily responsible for inducing follicular development .

Clomiphene is cleared through the liver and excreted in feces.

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.

Although this observation raises concerns about fetal exposure to clomiphene, most studies suggest that the frequency of congenital malformations is not increased

The ovarian actions of clomiphene are for the most part secondary to the effects of elevated FSH and LH on ovarian follicular development .
Clomiphene is an estrogen agonist in the absence of estrogen, thereby enhancing FSH stimulation of LH receptors in granulosa cells .

Clomiphene acts primarily as an antiestrogen in the uterus, cervix, and vagina. The following findings may explain why pregnancy rates are relatively low when ovulatory rates are so high in women administered clomiphene cycles:

The normal increase in uterine volume and endometrial thickening that occurs during spontaneous menstrual cycles is largely absent during clomiphene-induced cycles, despite higher estradiol levels.

Data on the effect of clomiphene on cervical mucus are conflicting.
In a meta-analysis, a detrimental effect was seen only with doses ≥100 mg/day .

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

Starting a cycle

Clomiphene citrate therapy for ovulation induction is typically started on the fifth day of a cycle, following either spontaneous or induced bleeding.

There are no laboratory or clinical parameters that predict the dose necessary to achieve ovulation.

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 100mg.

Thereafter, the dose is increased by increments of 50 mg to a maximum daily dose of 150 mg .

100 mg is the maximum dose approved by the US Food and Drug Administration [FDA], and ASRM suggests that doses >100 mg add little to clinical pregnancy rates) .

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.

Pregnancy rates are low after six cycles of treatment and that 12 or more cycles may increase the risk of ovarian neoplasms , ACOG has suggested that clomiphene treatment be limited to fewer than 12 cycles and that the number of gonadotropin cycles be minimized.

Further evaluation and/or a change in therapy for women who do not conceive after three to six ovulatory clomiphene citrate cycles

The incidence of miscarriage and congenital anomalies appears to be similar to spontaneous pregnancies, and the rate of ectopic pregnancy is probably not increased .

The risk of ovarian hyperstimulation syndrome is less than 1 percent.
But the risk of multiple gestations is increased .

The ovulatory rate is **lower** with **increasing age, body mass index (BMI), insulin resistance, and free androgen index**

Higher doses — High-dose clomiphene citrate (200 to 250 mg daily) may be given for 8 to 10 days in women who are refractory to standard doses.
This extended regimen of clomiphene is sometimes used for women who cannot receive exogenous gonadotropins, but the overall experience is limited.

Adverse effects:

- Hot flashes
- Problems related to the hyperestrogenic environment
- Nausea and vomiting
- Breast discomfort
- Visual disturbances
- Endometrial effects

Cancer risks:

The use of clomiphene citrate for ovulation induction does not appear to be associated with an excess risk of ovarian or breast cancer.

Letrozole

letrozole

letrozole, the most effective aromatase inhibitor, for ovulation induction in women with PCOS and as an adjunct to gonadotropin therapy for controlled ovarian hyperstimulation (COH) in women with ovulatory infertility.

Although Clomiphene citrate is the most commonly used pharmacologic agent to induce ovulation in these women, some women fail to conceive with this therapy.

During the past decade, aromatase inhibitors have been explored as an option for ovulation induction in women who fail to conceive with clomiphene citrate.

Aromatase inhibitors are a class of drugs that block estrogen biosynthesis, thereby reducing negative estrogenic feedback at the pituitary.

PHARMACOLOGY AND PHYSIOLOGY

Aromatase is a microsomal cytochrome P450 hemoprotein-containing enzyme , that catalyzes the rate-limiting step in the production of estrogens: the conversion of androstenedione and testosterone via three hydroxylation steps to estrone and estradiol.

Aromatase activity is present in many tissues, including the ovaries, brain, adipose tissue, muscle, liver, and breast.

Aromatase inhibitors are widely used as adjuvant endocrine therapy for postmenopausal women with breast cancer. They have been used off-label in the treatment of patients with anovulatory infertility such as polycystic ovary syndrome (PCOS), and for increasing the number of ovarian follicles recruited in ovulatory women undergoing controlled ovarian hyperstimulation (COH) .

- ✓ 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 follicle-stimulating hormone (FSH) (due to release from the negative feedback effect of estradiol), follicular development, and estradiol production (as the effect of the aromatase inhibitor diminishes).

- ✓ As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally because aromatase inhibitors do not deplete estrogen receptors in the brain .

- ✓ 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, which is associated with an increased risk of multiple gestation.

Letrozole is drug of choice for ovulation induction in women with PCOS.

Clomiphene citrate has been the first-line drug for this population for many years, with metformin used as an alternative. However, both clomiphene and metformin appear to be less effective for live birth rates than letrozole.

Letrozole regimen :

If an aromatase inhibitor is prescribed for ovulation induction in a patient with PCOS, it suggests that **letrozole** is over anastrozole as letrozole .

- ✓ 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**.
- ✓ If ovulation did not occur, the dose could be increased in the subsequent cycle.

- ✓ Sequential dose escalation of 2.5, 5, and 7.5 mg if ovulation does not occur on lower doses is widely used by reproductive endocrinologists.

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

Two proof-of-concept studies have reported that a single-dose regimen (20 mg) may also be effective , but the studies do not suggest this approach at this time, as data are limited and further studies are underway.

Comparison with clomiphene

Potential advantages of letrozole over clomiphene citrate include :

●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), which would predict a lower risk of teratogenicity.

●No direct antiestrogenic adverse effects on the endometrium, due to an absence of peripheral estrogen receptor blockade and the shorter half-life.

●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

BMI had a significant impact on live birth rates:

- For women with a BMI ≤30.3 kg/m2, the cumulative live birth rate (approximately 30 percent) was similar in the clomiphene and letrozole groups.

- For women with a BMI ≥30.3 kg/m2, the cumulative live birth rate was significantly higher with letrozole when compared with clomiphene (20 versus 10 percent).

- The obese women in both treatment groups had lower live birth rates than nonobese women,(a negative impact of obesity on fecundity).

- Miscarriage rates were similar with the two therapies .

- There were no differences in birth weights or rates of neonatal complications (including anomalies).

- The twin pregnancy rate was lower with letrozole .

Suggested approach

For anovulatory women with PCOS who are overweight or obese, it seems that weight loss,is prior to initiating ovulation induction therapy.

The approach to obesity management is the same as that for patients without PCOS, starting with lifestyle interventions (diet and exercise), followed by pharmacotherapy .

For women who are unable to lose weight, start ovulation induction for PCOS anovulatory women with aromatase inhibitors .

● letrozole : first-line therapy over clomiphene citrate.
The starting dose is 2.5 mg administered days 3 to 7; this can be titrated up to a maximum dose of 7.5 mg/day if ovulation has not occurred. However, before starting letrozole, the clinician must discuss with the patient that this is use of the drug is not FDA approved and that there is an alternative (clomiphene citrate) that is FDA approved.

● letrozole ,such as clomiphene citrate,is not associated with an increased risk of congenital malformations.

●Based on the half-life of letrozole, administration in the early follicular phase should result in clearance of letrozole before implantation takes place. Nevertheless, as with any ovulation induction agent, one must confirm that the patient is not pregnant before starting therapy. We suggest a blood pregnancy test before administering letrozole.

GONADOTROPINS

- Gonadotropin products for human use derive from urinary extracts or recombinant technology and all have similar effectiveness and safety .

- A systematic review found no evidence of a difference in either live-birth or OHSS rates among women with PCOS who were treated with urinary or recombinant gonadotropins.

GONADOTROPIN REGIMENS FOR OVULATION INDUCTION

- Gonadotropin therapy has more risks and is more expensive than oral ovulation induction agents and should only be used by clinicians having the requisite training and experience.

- Exogenous FSH stimulates proliferation of granulosa cells and follicular growth and together with LH ; stimulates estradiol production.
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- LH stimulates the production of androgens in thecal cells that are subsequently aromatized to estrogen by granulosa cells .

- The goal of ovulation induction is to promote the growth and development of a single mature follicle

- Women with PCOS may begin ovulation induction after a menses induced by brief treatment with an exogenous progestin. However, data suggest that progestin withdrawal bleed may decrease pregnancy rates in these women ; ovulation induction may be induced without a withdrawal bleed when pregnancy has bee excluded.

- Baseline ultrasonography should be performed to exclude ovarian cysts that might be confused with new follicular growth.

- Exogenous FSH alone can induce ovulation in women with PCOS, because endogenous LH levels are adequate, although added LH does not appear to be harmful .

- No significant advantage for using any specific gonadotropin preparation.
- outcomes of treatment with human menopausal gonadotropins (hMG) or FSH alone were similar .
- outcomes of treatments with recombinant FSH or urinary FSH yields similar results .
- The recommended approach in the first dose-finding cycle is to begin with a low dose of gonadotropin, typically 37.5–75 IU/day, and increasing in small increments after 7 days or more if no follicle >10 mm has developed.
- Pen devices allow more finely tuned incremental dosing.

- In subsequent cycles, treatment generally begins at the threshold of response previously determined. Although 7–12 total days of treatment is typical,longer durations of treatment may be required. Once a mature follicle has developed, exogenous hCG is administered to stimulate ovulation .

- In women with hypothalamic amenorrhea, optimal clinical results are achieved by administering a combination of FSH and LH .

- This can be accomplished by administration of hMG or a combination of FSH with either recombinant LH or low-dose hCG .

- In addition to stimulating the production of androgens, which provide the substrate for estrogen production that enhances oocyte and endometrial development, LH activity promotes development of larger follicles .

- There are no established superior gonadotropin regimens or doses for ovulation induction in patients with hypothalamic amenorrhea.

- Patients with profound hypothalamic dysfunction may require a prolonged period of gonadotropin treatment to achieve follicular growth.

Monitoring of Ovulation Induction

- The safety and efficacy of gonadotropin treatment dependson careful monitoring with serial transvaginal ultrasonography and estradiol measurements .

- Ultrasonography provides a structural measure of follicular development and generally should be performed after the first 4–5 days of treatment and at subsequent intervals of 1–3 days according to response . Endometrial thickness and appearance provide an indirect measure of endometrial development and have some prognostic value for implantation .
- Measurement of serum estradiol in conjunction with ultrasonography provides an accurate gauge of response to treatment and informs treatment management .

- The presence of multiple follicles as small as 10–12 mm at the time of ovulation can increase the risk of multiple gestation

Inducing Ovulation

- The final stages of oocyte maturation and release can be induced by injection of human chorionic gonadotropin (hCG).
- The trigger injection can be 5,000–10,000 IU of urinary hCG or 250 mg of recombinant hCG, which corresponds to approximately 6,000–7,000 IU urinary hCG .
- Ovulation is expected to occur 36-48 hours after trigger, so intercourse or intrauterine insemination should be appropriately timed to occur prior to ovulation

- Although most women will respond to ovulation induction with oral medications, some will not.

- Exogenous gonadotropin treatment for ovulation induction may be indicated in women with PCOS who fail to respond to lifestyle modifications and oral agents.

- However, gonadotropins are associatedwith significantly increased risks of ovarian hyperstimulation syndrome (OHSS) and multiple-gestation pregnancy .

- Accordingly, low-dose gonadotropin regimens are strongly advised , or considerations of other strategies as in vitro fertilization (IVF).

PRETREATMENT EVALUATION

- Pretreatment evaluation generally should exclude abnormalities of thyroid function and hyperprolactinemia and should include evaluation of the uterine cavity, fallopian tubes, and semen analysis.
- While evaluation for hyperprolactinemia is not indicated in the general infertility workup, it is indicated in anovulatory women.
- Women with ovarian insufficiency should generally not be considered candidates for ovulation induction with exogenous gonadotropins .

Luteal-Phase Progesterone Support

- High estradiol levels routinely produced by ovulation induction with gonadotropins are associated within adequate progesterone levels in the luteal phase .

- Some clinicians recommend progesterone luteal support in all patients undergoing ovulation induction with gonadotropins.

This includes women with hypothalamic amenorrhea whose endogenous LH secretion may be inadequate to support normal luteal function.

- In women with unexplained infertility undergoing ovulation induction with gonadotropins,luteal support with progesterone demonstrated a higher live-birth rate .

- Currently, there are insufficient data on women with PCOS to recommend luteal support with progesterone.

SUMMARY

- The goal of gonadotropin treatment for ovulation induction is to promote the development of a single mature follicle.
  Monofollicular development sometimes can be difficult to achieve.

- Monofollicular development decreases the risk of multiple gestation and OHSS.

- Patients should be counseled on the risks of ovulation induction with gonadotropins prior to cycle start.
  Gonadotropins should be started at a low dose of 37.5–75 IU a day and cautiously increased as needed for monofollicular
  development.
- Cycle cancellation should be considered if more than two follicles R16 mm develop or if three or more
  follicles develop.

- Luteal support is beneficial in women with hypothalamic amenorrhea.
- While luteal support also may be beneficial following ovulation induction with gonadotropins in women with PCOS, there is insufficient evidence to make a recommendation.

hMG and FSH

The degree to which the type of follicle-stimulating hormone (FSH) compound employed may influence outcome of ovulation induction has been controversial.

- There were no differences in clinical pregnancy or live-birth rates for rhFSH and urinary-derived gonadotropins.

- There also were no differences between hMG preparations and urinary FSH-P.

- After pooling the data, there were no differences in the rates of ovarian hyperstimulation syndrome (OHSS) between rhFSH and urinary-derived gonadotropins.

- The evidence for all outcomes was of very low quality.

- Purified uFSH has some LH activity, but rhFSH does not.

- The experience with rhFSH in hypogonadotropic hypogonadal women indicates that those women who have very low serum LH concentrations (<0.5 IU/L) need exogenous human chorionic gonadotropin (hCG) (or 75 IU/day subcutaneous recombinant LH) to maintain adequate estradiol biosynthesis and follicle development .

Most ovulation induction strategies for women with primary ovarian insufficiency (premature ovarian failure) are unsuccessful .

These women should be offered the option of in vitro fertilization with donor oocytes.

No suggestion for a trial of clomiphene citrate ,letrozol or gonadotropins in these women

Monitoring

The response to treatment should be monitored.

Determination of the ovulatory LH surge by urinary LH kits is what most clinicians recommend in practice.

Urinary LH monitoring also provides information on appropriate timing of intercourse during a given cycle .

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 and almost always within 48 hours .

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

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

In many institutions, hCG is routinely used to induce ovulation and to time IUI. However,accurate studies do not suggest routine administration of exogenous hCG for women in whom an endogenous LH surge can be detected .

A progressive rise in the serum estradiol concentration is also evidence for advancing follicular development and maturation, but **serial transvaginal ultrasound** to monitor follicle size is **superior** and should be used to time hCG administration.
Ovulation occurs approximately 36 to 44 hours after the injection.

THANKS FOR YOUR ATTENTION