

Induction Of Ovulation



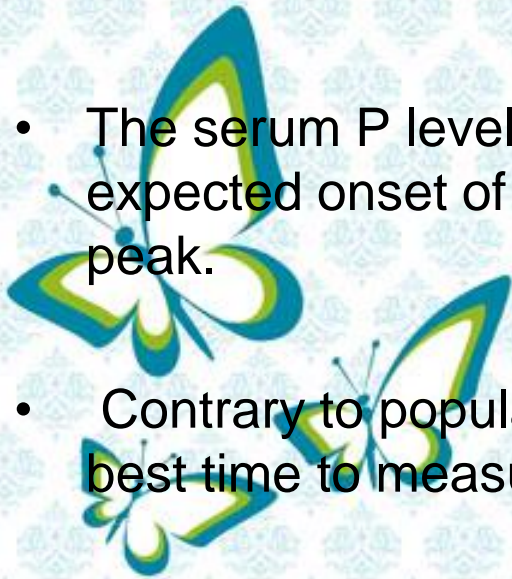
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- **Ovulatory disorders** can be identified in 18-25% of infertile women.
- When anovulation is the **only** infertility factor, the prognosis for pregnancy generally is quite **good** .
- When a **specific cause** for anovulation can be identified, treatment often restores **normal** cycle fecundity.

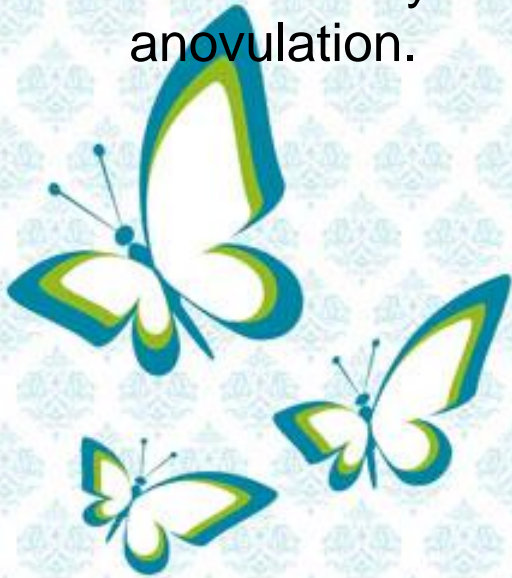


DIAGNOSIS OF ANOVULATION

- ***Women with irregular, unpredictable, or infrequent menses do not require specific diagnostic tests to prove what is already obvious.***
- A **serum P** measurement is the simplest, most common, objective, and reliable test of ovulatory function, as long as it is **appropriately timed**.
A **P concentration less than 3 ng/mL implies anovulation**.
- The serum P level should be drawn approximately **1 week before** the expected onset of menses, when the concentration is at or near its peak.
- Contrary to popular belief and practice, cycle **day 21 is not always** the best time to measure the serum P concentration .

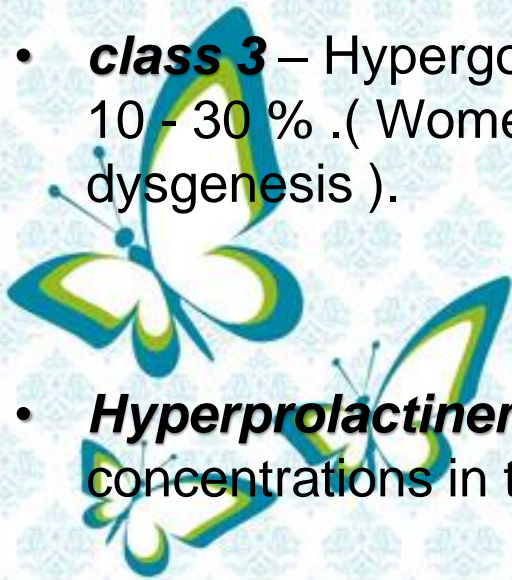


- Other simple tests of ovulation include monitoring **urinary LH excretion**.
- **Serial TVS** can be useful once **ovulation** has been achieved but is unnecessary and not always accurate for the diagnosis of anovulation.



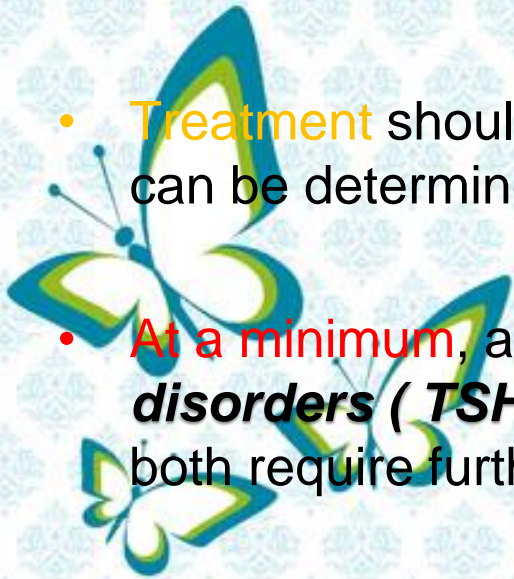
World Health Organization classification of anovulation

- **class 1** – Hypogonadotropic hypogonadal anovulation is the **least common**, occurring in 5 - 10 % of cases. , (women with hypothalamic amenorrhea from functional etiologies such as excessive exercise or low body weight)
- **class 2** – Normogonadotropic normoestrogenic anovulation is the **most common**, accounting for 70 - 85 % of cases.(Women with PCOS)
- **class 3** – Hypergonadotropic hypoenestrogenic anovulation occurs in 10 - 30 % .(Women with primary gonadal failure (POF) or gonadal dysgenesis).
- **Hyperprolactinemic** anovulation is a separate category; gonadotropin concentrations in this condition are usually NI or ↓



PRETREATMENT EVALUATION AND TREATMENT

- The causes of anovulation are **many and varied** :
 - thyroid disease
 - hyperprolactinemia
 - adrenal disease
 - pituitary or ovarian tumors
 - eating disorders
 - extremes of weight loss or exercise
 - PCOS
 - obesity
- **Treatment** should be directed at the **underlying cause**, when that can be determined .
- **At a minimum**, anovulatory women should be **screened for thyroid disorders (TSH) and hyperprolactinemia (prolactin)** because both require further evaluation and specific treatment.



- Glycemic status should be assessed at baseline in all PCOS women.

- In high-risk patients , OGTT is recommended:

- BMI > 25 kg/m²
- Hx of impaired FBS
- impaired GTT or GDM
- family Hx of DM type 2, HTN

- FBS or HbA1C levels can suffice for others.



- **Anovulation** offers an obvious potential explanation for infertility but often **is not the only infertility factor**. Before ovulation induction begins, a **screening S/A** is prudent because male factors are an important contributing cause in 20-40% of infertile couples.
- Preliminary **HSG and TVS are recommended** when :
 - M Hx or Ph/Exam raises suspicion for coexisting uterine or tubal factors
 - for women age > 35 Y
 - when I/O requires Tx with exogenous gonadotropins
- Laparoscopy and hysteroscopy are unnecessary for most women but certainly appropriate for those with an abnormal HSG or signs or symptoms of pelvic disease.



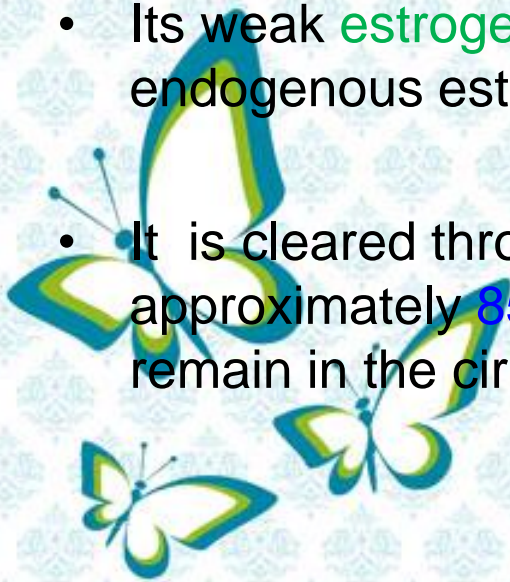
- **Lifestyle management** for weight loss is recommended for PCOS patients with a BMI >25 kg/m².
- Even **modest weight loss** (5-10% of body weight) often **restores ovulatory cycles** in obese anovulatory women with PCOS.
- In **overweight and obese** women with PCOS, **unless age related** infertility is a concern , hypocaloric diet and exercise , may be the **first-line treatment for 3-6 months**.
- At a minimum, weight loss can **increase sensitivity** to ovulation inducing drugs and **decrease the complexity** of treatment required.



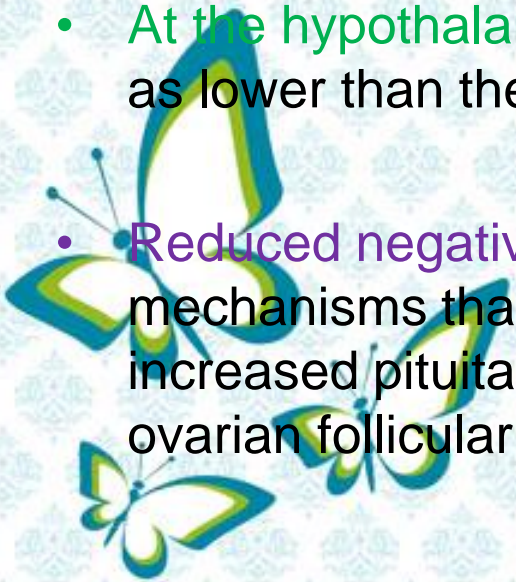
- **Bariatric surgery** can be considered as a **second-line treatment option** when :
 - significant obesity (BMI > 35 kg/m²)
 - anovulation are resistant to lifestyle intervention +/- pharmacotherapy
 - especially in the presence of obesity related comorbidities
- Bariatric surgery **improves** anovulation, hirsutism, insulin resistance, sexual activity, and libido .
- Bariatric surgery can cause malabsorption and eating disorders, which may adversely affect **maternal and neonatal health**(SGA , PTL , neonatal mortality).
- Therefore, ***it is recommended to avoid pregnancy during rapid weight loss and for at least 12 months after bariatric surgery.***
- In sum, bariatric surgery is considered an experimental therapy for infertility associated with PCOS.

CLOMIPHENE CITRATE

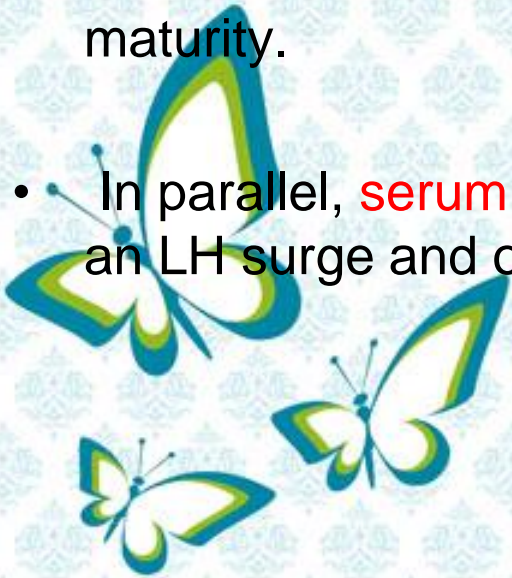
- Clomiphene is a nonsteroidal triphenyl ethylene derivative that acts as a selective estrogen receptor modulator (SERM), having both estrogen agonist and antagonist properties.
- *In almost all clinical circumstances, clomiphene acts purely as an antagonist or antiestrogen .*
- Its weak estrogenic actions are clinically apparent only when endogenous estrogen levels are very low.
- It is cleared through the liver and excreted in the stool; approximately 85% is eliminated within a week, but traces can remain in the circulation for a longer time .



- **Structural similarity to estrogen** allows clomiphene to compete with endogenous estrogen for nuclear estrogen receptors at sites throughout the reproductive system.
- Unlike estrogen, clomiphene binds to nuclear estrogen receptors for an **extended interval of time**.
- **At the hypothalamic level**, circulating estrogen levels are perceived as lower than they truly are.
- **Reduced negative estrogen feedback** triggers normal compensatory mechanisms that alter the pattern of GnRH secretion and stimulate increased pituitary gonadotropin release, which, in turn, drives ovarian follicular development.



- In the **pituitary**, clomiphene also may increase the sensitivity of gonadotrophs to GnRH stimulation .
- ***Serum levels of both FSH and LH rise during clomiphene treatment*** and fall again soon after the typical 5-day course of therapy is completed.
- In successful treatment cycles, **one or more follicles** emerge and grow to maturity.
- In parallel, **serum estrogen levels** rise progressively, ultimately triggering an LH surge and ovulation.

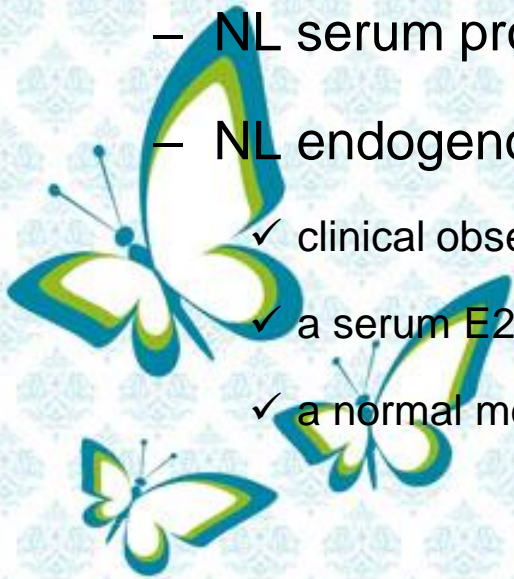


- **Impaired endometrial growth** has been reported in clomiphene-treated women.
- preovulatory endometrial thickness in clomiphene-induced cycles remains well within the range normally observed in spontaneous ovulatory cycles .
- ***It has little clinical importance, except in those individuals exhibiting grossly poor endometrial growth (peak preovulatory thickness <5-6 mm).***
- Clomiphene does not appear to have any clinically relevant direct effects on the **ovary or embryo**.

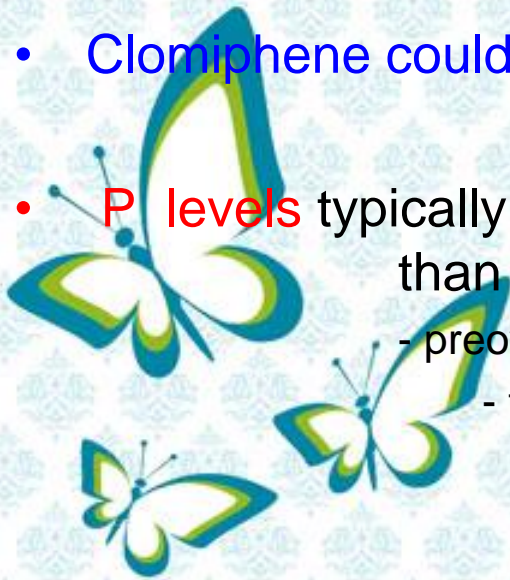


Clinical Indications

- **Before** the introduction of aromatase inhibitors, and large randomized controlled trials demonstrating higher live birth rates with letrozole, clomiphene citrate was the traditional **drug of choice for I/O in anovulatory infertile women with :**
 - NL thyroid function
 - NL serum prolactin levels
 - NL endogenous estrogen production, as determined by :
 - ✓ clinical observations (oligomenorrhea, estrogenic cervical mucus)
 - ✓ a serum E2 determination (> 40 pg / mL)
 - ✓ a normal menstrual response to a progestin challenge (WHO Group II)



- *clomiphene typically is ineffective in women with hypogonadotropic hypogonadism (WHO Group I).*
- Inadequate follicular development can be expected to predispose to **poor luteal function**, if ovulation still occurs.
- Indeed, the most obvious example of poor luteal function, a short luteal phase, is associated with **abnormally low follicular phase FSH levels**.
- Clomiphene could be both a logical and effective choice for treatment.
- **P levels** typically are **higher** in clomiphene-induced ovulatory cycles than in normal spontaneous cycles, because :
 - preovulatory follicular development is optimized
 - treatment often results in more than one corpus luteum

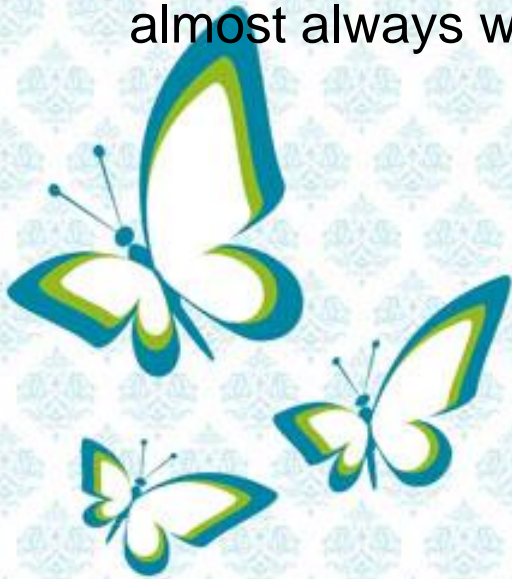


- **Clomiphene citrate treatment is for :**
 - women with ovulatory dysfunction
 - normally ovulating women whose infertility remains unexplained, (particularly in young women and short duration of infertility)
 - those unwilling or unable to pursue more aggressive treatments
- Efficacy of clomiphene treatment in women with **unexplained infertility** has been attributed to :
 - optimizing follicular development
 - superovulation of more than a single ovum
- Clomiphene alone **does not significantly improve** live birth rates or time to pregnancy compared to expectant management in unexplained infertility.
- Empiric clomiphene treatment for **unexplained infertility** is most effective when **combined with IUI**, in an effort to increase the numbers of both ova and sperm

Clomiphene Treatment Regimens

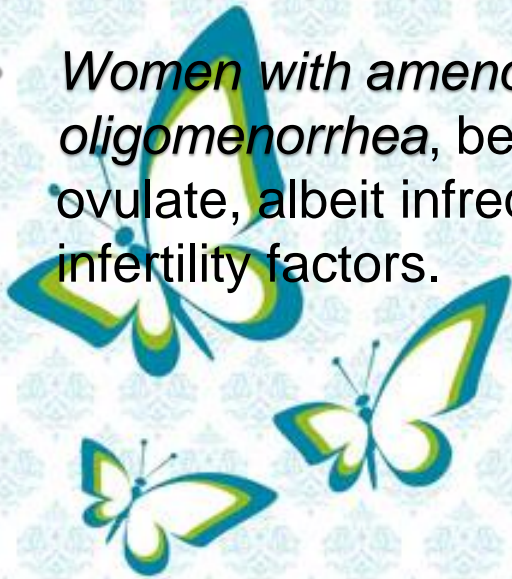
- Clomiphene is administered orally, typically beginning on the 3 – 5 day after the onset of a spontaneous or progestin-induced menses.
- Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 2 and 5.
- In women with amenorrhea, treatment can begin immediately, without inducing endometrial shedding, if pregnancy has been excluded.
- The dose of clomiphene required to induce ovulation correlates with body weight .
- *No clinical or laboratory parameter has proven utility for predicting the dose of clomiphene needed to induce ovulation .*
- Treatment usually starts with a single 50-mg tablet daily for a 5-day interval and, if necessary, increases by 50 mg increments in subsequent cycles until ovulation is achieved.

- The **same methods** used for diagnosis of anovulation can be used to evaluate the response to treatment (serum P , LH kits , TVS) .
- In clomiphene-induced ovulatory cycles in anovulatory women, the **LH surge** occurs 5-12 days after treatment ends, most often on cycle day 16 or 17 when clomiphene is administered on days 5-9.
- **Ovulation** generally occurs 14-26 hours after surge detection and almost always within 48 hours .



Results of Clomiphene Treatment

- Clomiphene will induce **ovulation** successfully in **70-80%** of selected women.
- In anovulatory women the likelihood of **response decreases with** :
 - ↑ age
 - ↑ BMI
 - hyperandrogenemia.
- *Women with amenorrhea are more likely to conceive than those with oligomenorrhea*, because infertile women who menstruate also likely ovulate, albeit infrequently, and are more likely to have other coexisting infertility factors.

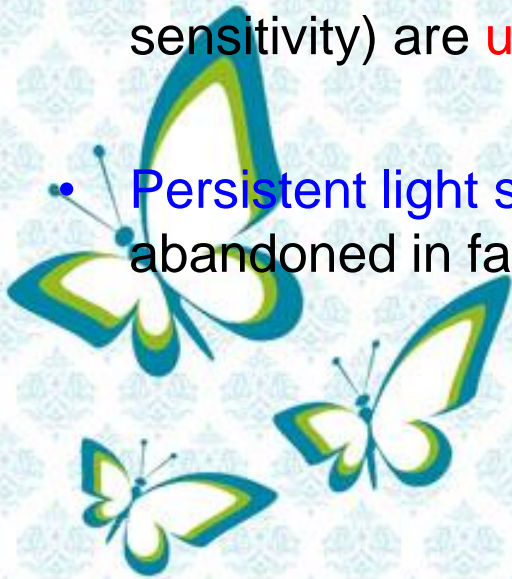


- When pregnancy is not achieved within **3-6** clomiphene-induced **ovulatory cycles** ;
 - the infertility investigation should be expanded to exclude other infertility factors not yet evaluated,
 - the overall treatment strategy should be modified if evaluation is already complete.
- *Prolonged treatment with clomiphene is inappropriate, particularly for women >35 y .*



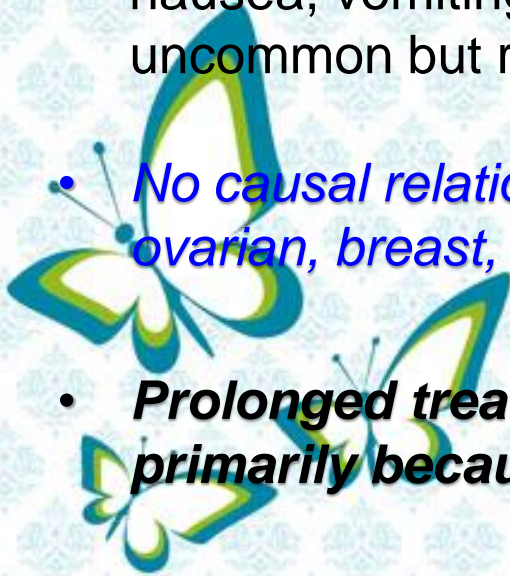
Side Effects

- **Minor** side effects are relatively **common** but rarely are persistent or severe enough to require that treatment be discontinued.
- Transient hot flashes, headache, breast tenderness, pelvic pressure or pain, and nausea .
- **Visual disturbances** (blurred or double vision, scotomata, light sensitivity) are **uncommon** (1-2%) and **reversible**.
- **Persistent light sensitivity (photophobia)** dictates that treatment be abandoned in favor of **alternative methods** for ovulation induction.



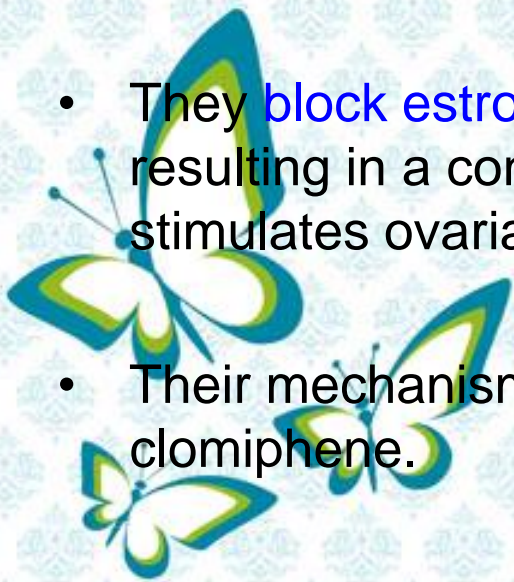
Risks

- The **principal risk** associated with clomiphene treatment is an increased risk for conceiving a **multiple pregnancy** (7-10%) .
- There is **no evidence** that clomiphene treatment increases the overall risk of **birth defects** , **developmental delay** or **learning disability** in children conceived during clomiphene treatment.
- **Mild symptoms of OHSS** (transient abdominal discomfort, mild nausea, vomiting, diarrhea, and abdominal distention) are not uncommon but require only expectant management.
- *No causal relationship between ovulation-inducing drugs and ovarian, breast, or endometrial cancer has been established .*
- ***Prolonged treatment with clomiphene should be avoided, primarily because it has little hope of success.***



AROMATASE INHIBITORS

- ***letrozole is now considered the first-line therapy for ovulation induction in women with PCOS, as it provides significantly higher live birth rates compared to clomiphene .***
- Anastrozole and letrozole are triazole (antifungal) derivatives that act as potent, competitive, nonsteroidal **inhibitors of aromatase, the enzyme that catalyzes the rate-limiting step in estrogen production.**
- They **block estrogen production both in the periphery and brain,** resulting in a compensatory \uparrow in pituitary gonadotropin secretion that stimulates ovarian follicular development .
- Their mechanism of action is similar to, but also distinct from, that of clomiphene.



- ↓ E2 levels and ↑ luteal phase P levels attained in letrozole-stimulated cycles than clomiphene-stimulated cycles may be the mechanism behind ↑ LBR with letrozole.
- Similar to clomiphene, ***letrozole is ineffective in women with hypogonadotropic hypogonadism (WHO Group 1)***.



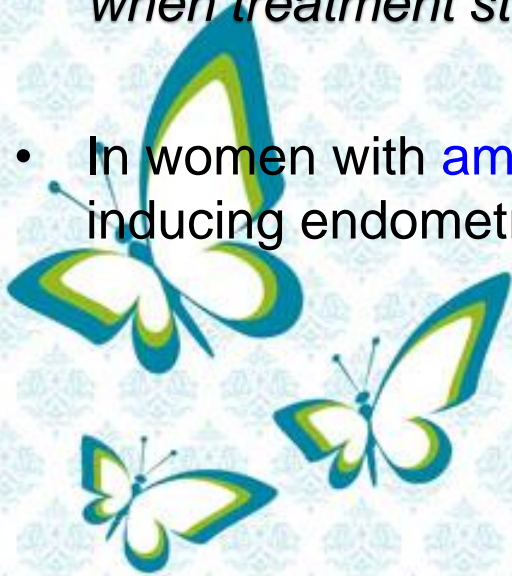
Peripheral Actions

- Despite ↓ serum E2 levels in letrozole-stimulated cycles than in clomiphene-stimulated cycles, *letrozole could have been expected to have less of an adverse effect on endometrial growth*, since it *does not block estrogen receptors*.

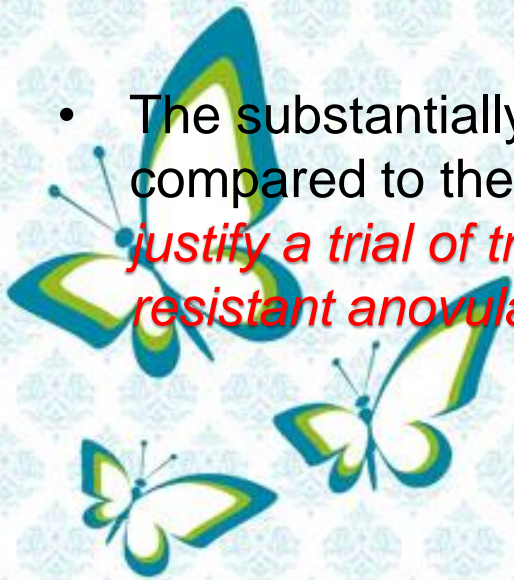


Aromatase Inhibitor Treatment Regimens

- letrozole (2.5-7.5 mg daily) and anastrozole (1 mg daily) have been administered for a 5-day interval.
- Letrozole is administered orally, typically beginning on the 3 – 5 day after the onset of a spontaneous or progestin-induced menses.
- *Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 3 and 5.*
- In women with amenorrhea, treatment can begin immediately, without inducing endometrial shedding; however, pregnancy must be excluded.

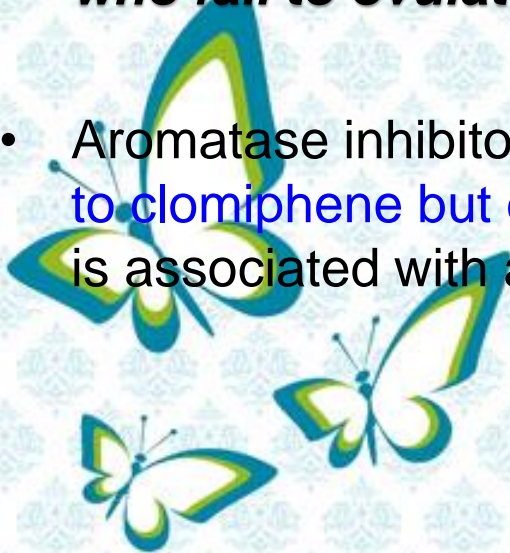


- ***The starting dose for letrozole is 2.5 mg a day for 5 days.***
- If 2.5 mg/day **fails to induce ovulation**, the dosage can be increased by 2.5 mg increments up to a Max of 7.5 mg/day for 5 days.
- The **same methods** used for diagnosis of a spontaneous or clomiphene-induced **ovulation** can be used to determine the response to letrozole.
- The substantially lower complexity, risks, and costs of treatment, compared to the alternative of gonadotropin therapy, ***make it easy to justify a trial of treatment with an aromatase inhibitor for clomiphene-resistant anovulatory women.***



Results of Treatment with Aromatase Inhibitors

- The beneficial effect of letrozole seems independent of BMI , that is, despite ↓ overall LBR with ↑ BMI .
- Miscarriage per pregnancy and multiple pregnancy rates are also similar between letrozole and clomiphene-induced cycles.
- ***Aromatase inhibitors can also be effective in anovulatory women who fail to ovulate in response to clomiphene treatment.***
- Aromatase inhibitors also might be considered for women who respond to clomiphene but exhibit grossly poor endometrial proliferation. letrozole is associated with a significantly thicker endometrium.



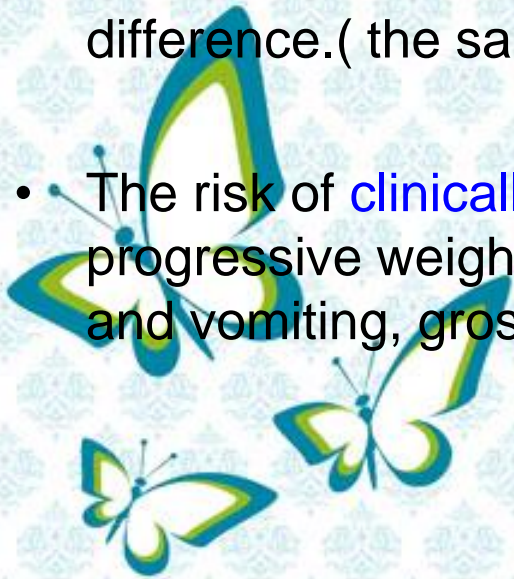
Side Effects

- Letrozole is generally well tolerated, and the **most common** side effects of letrozole are **headaches and cramps**.
- Women on letrozole report **more fatigue and dizziness** than women on clomiphene.
- **Hot flushes** are ↓ common with letrozole .



Risks

- The **major risk** of ovulation induction is the occurrence of a **multiple pregnancy**.
- There is **no evidence** suggesting letrozole is any more **teratogenic** than clomiphene.
- The incidence of **congenital malformations** in newborns of women who conceived after treatment with letrozole or clomiphene found no difference.(the same as pregnancies without treatment) .
- The risk of **clinically significant OHSS** (massive ovarian enlargement, progressive weight gain, severe abdominal pain, intractable nausea and vomiting, gross ascites, oliguria) **is very low** with letrozole .



- ***In sum, the available data suggest that letrozole is more effective than clomiphene as a first-line treatment for ovulation induction in anovulatory women with PCOS, without a significant increase in complications or side effects.***



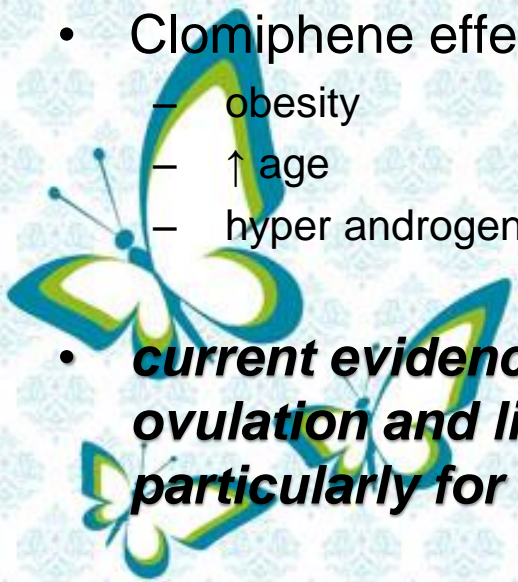
Ovulation Induction & Super ovulation

- The goal of **ovulation induction** refers to the therapeutic restoration of the release of **one egg per cycle** in a woman who either has not been ovulating regularly or has not been ovulating at all .
- The explicit goal of **super ovulation** for women with unexplained infertility is to cause **more than one egg** to be ovulated, thereby increasing the probability of conception .



Ovulation Induction Outcomes

- Ovulation induction is **first-line** treatment for **anovulatory** infertility .
- Over the course of **6 months**, in women with anovulatory infertility, clomiphene is associated with :
 - 49% ovulation
 - 23.9% pregnancy
 - 22.5% live birth rates
- Clomiphene effectiveness is ↓ by :
 - obesity
 - ↑ age
 - hyper androgenic states
- ***current evidence suggests that letrozole results in higher ovulation and live birth rates compared with clomiphene, particularly for obese (BMI >30) women.***



Monitoring Ovulation Induction Therapy

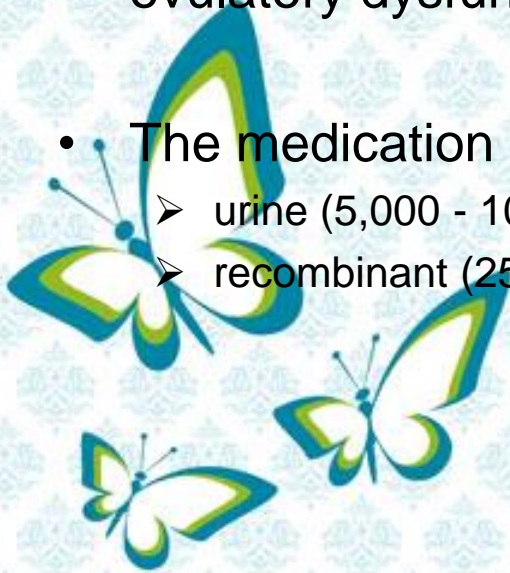
- If preovulation monitoring is not performed, patients should be instructed to have intercourse every 2 - 3 days following the last day of therapy and check serum P weekly \times 5 weeks before inducing a withdrawal bleed or increasing the dose of the ovulation induction agent .
- Although **no clear advantage** has been demonstrated for any ovulation monitoring technique, **regular contact** should be maintained with patients to review response to therapy .
- The **urinary LH surge** may be detected 5 - 12 days after treatment is completed .
- When clomiphene or letrozole is given on cycle days 5 - 9, the **surge** typically occurs on cycle days 16 - 17 and can be confirmed by midluteal serum P testing 7 days later .

- With **US monitoring**, treatment should be withheld if large cysts are seen on baseline testing.
- Following ovulation induction use, follicles typically reach a preovulatory diameter of 19 - 25 mm by US, but may be as large as 30 mm.
- A combination of LH testing and US can be used, with LH kits starting when the largest US-measured follicle reaches 14 mm in diameter .



Human Chorionic Gonadotropin

- If a dominant follicle develops, but there is no spontaneous LH surge, hCG can be used to induce final follicular maturation , with ovulation occurring approximately 40 hours following administration .
- Although administration of hCG at mid-cycle does not appear to improve conception chances in most infertility patients using clomiphene citrate , it may be useful for patients with known ovulatory dysfunction or for IUI.
- The medication may be derived from :
 - urine (5,000 - 10,000 IU - IM)
 - recombinant (250 µg - SC, equivalent to 5,000 to 6,000 IU urinary)

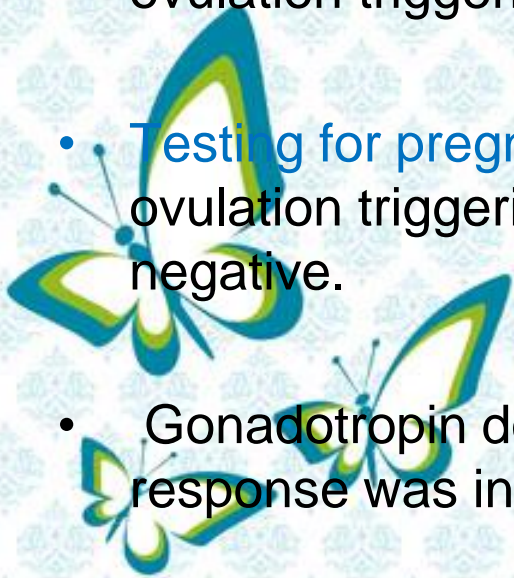


Gonadotropin Therapy

- Anovulatory PCOS patients who fail to ovulate or conceive with oral agents may be considered for ovulation induction with exogenous gonadotropin injections .
- Typical protocols monitor at baseline, 4 - 5 days after treatment initiation, and every 1 - 3 days until follicular maturation.
- Expected follicle growth is 1 - 2 mm daily after achieving 10 mm diameter .
- Given the goal of promoting growth of a single mature follicle, low initial gonadotropin doses of 37.5 – 75 IU / day are generally recommended, with increases in doses by 50% of the previous dose after 7 days if no follicle >10 mm is observed .



- Ovulation **triggering** with hCG is recommended for gonadotropin cycles and is used when 1 - 2 follicles are 16 to 18 mm diameter and the E2 level per dominant follicle is 150 to 300 pg/mL .
- Ovulation is expected 24 - 48 hours after the hCG trigger.
- **Intercourse** should be recommended within 24 - 48 hours of ovulation triggering or **IUI** 24 - 36 hours after triggering .
- **Testing for pregnancy** is performed within 15 - 16 days after ovulation triggering and the cycle reviewed if pregnancy testing is negative.
- Gonadotropin dosage in future cycles should be altered if the prior response was inadequate or excessive.



Thanks all with best wishes

