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.***

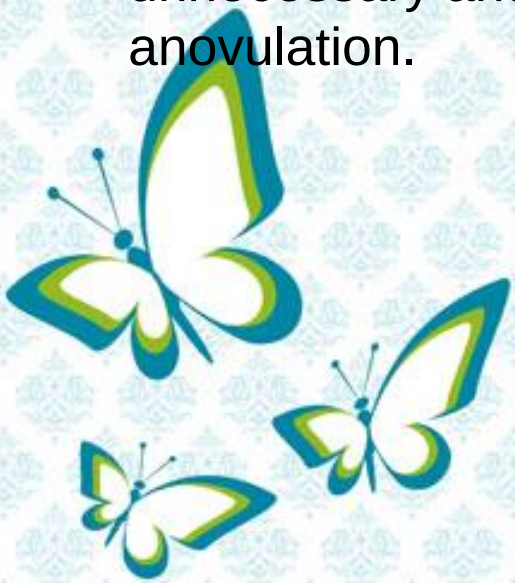
- A serum P measurement is the simplest, most common, objective, and reliable test of ovulatory function, as long as it is appropriately timed. A P concentration less than 3 ng/mL implies anovulation.

- 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 hypoestrogenic 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 Nl 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/m^2
  - 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

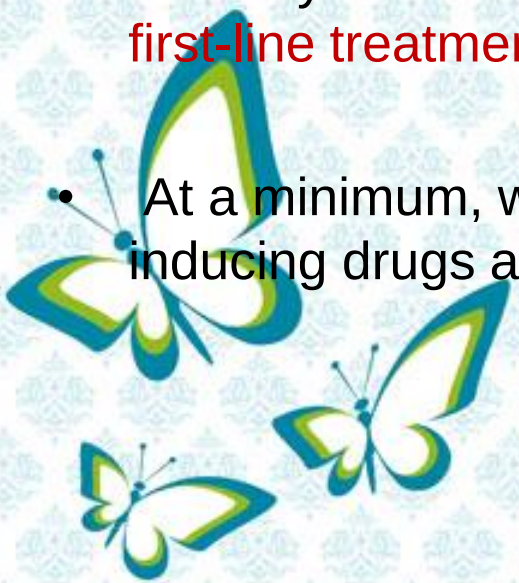
- Laparoscopy and hysteroscopy are unnecessary for most women but certainly appropriate for those with an abnormal HSG or signs or symptoms of pelvic disease.

- Lifestyle management for weight loss is recommended for PCOS patients with a BMI >25 kg/m^2.

- 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/m^2)
  - 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.

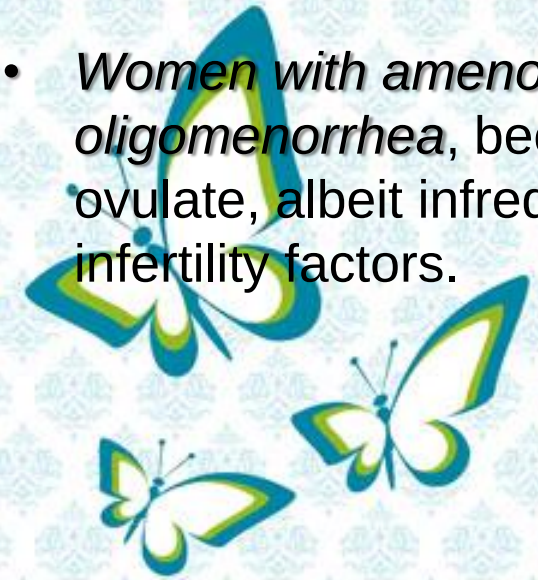
- Ovulation generally occurs 14-26 hours after surge detection and almost always within 48 hours .

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 ↑ 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.

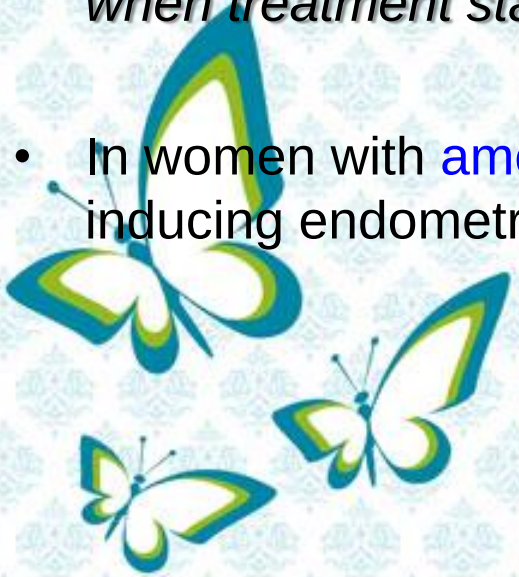
Aromatase Inhibitor Treatment Regimens

- 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 × 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 .

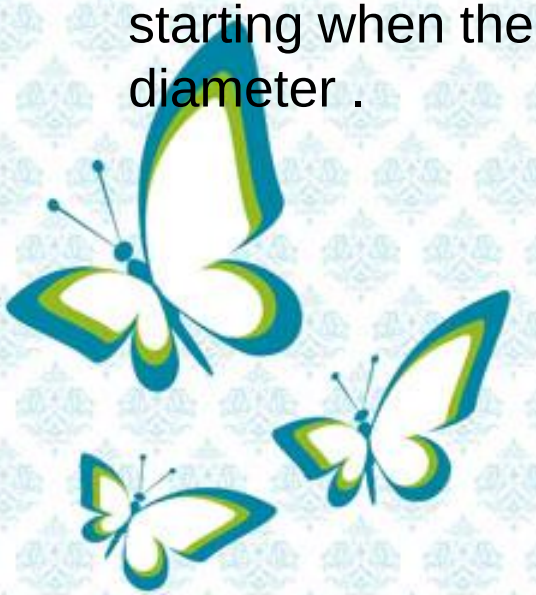
- The urinary LH surge may be detected 5 - 12 days after treatment is completed .

- 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