Induction of Ovulation

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Induction of Ovulation

- Although it seems commonplace today, indeed even routine, the ability to induce ovulation and attain pregnancy in anovulatory infertile women remains one of the greatest achievements of reproductive endocrinology. Once limited to clomiphene citrate, the therapeutic armamentarium for ovulation induction now includes a wide variety of agents.
- 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 because modern ovulation induction strategies are highly effective.

Induction of Ovulation

- When a specific cause for anovulation can be identified, treatment often restores normal cycle fecundity
- Even when no specific cause can be found, as in most anovulatory women, empiric treatments with low costs and risks usually succeed. When those fail, other more complex forms of treatment are effective. One way or another, almost all anovulatory infertile women can be induced to ovulate. Unfortunately, many still do not conceive, often because there are other coexisting infertility factors.

DIAGNOSIS OF ANOVULATION

- Women with irregular, unpredictable, or infrequent menses do not require specific diagnostic tests to prove what is already obvious.
- When anovulation is suspected but uncertain, a variety of methods can be used to evaluate ovulatory function:
- “Biphasic” basal body temperature (BBT) pattern :

- BBT recordings having no sustained interval of temperature elevation preceding the onset of menses strongly suggest anovulation.

DIAGNOSIS OF ANOVULATION

- Biphasic recordings exhibiting a short luteal phasee (onset of

menses <12 after the midcycle rise in BBT) suggest a subtle, but still important, form of ovulatory dysfunction. Although uncommon, BBT recordings are not clearly biphasic in some ovulatory women.

Since BBT cannot reliably define the time of ovulation and can become tedious, it is not the method of choice for evaluating ovulatory function for most infertile women.

DIAGNOSIS OF ANOVULATION

- **Serum progesterone measurement:**
- A serum progesterone measurement is the simplest, most common, objective, and reliable test of ovulatory function, as long as it is appropriately timed.
- A progesterone concentration less than 3 ng/mL implies anovulation, except when drawn immediately after ovulation or just before the onset of menses, when lower levels naturally might be expected.
- Ideally, the serum progesterone level should be drawn approximately 1 week before the expected onset of menses, when the concentration is at or near its peak.

DIAGNOSIS OF ANOVULATION

- **Urinary LH excretion:**
- Other simple tests of ovulation include monitoring urinary LH excretion.
- More sophisticated test available for home use also includes a measure of rising estrogen production preceding the LH surge.
- **Serial transvaginal ultrasonography:**
- can be useful once ovulation has been achieved but is unnecessary and not always accurate for the diagnosis of anovulation.

CLASSIFICATION OF OVULATORY DISORDERS

- **WHO Group I:** Hypogonadotropic Hypogonadal Anovulation
- The group accounts for approximately 5-10% of anovulatory women
- Those with low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol levels, due to absent or abnormal hypothalamic gonadotropin-releasing hormone (GnRH) secretion or pituitary insensitivity to GnRH.
- Examples include women with hypothalamic amenorrhea relating to physical, nutritional, or emotional stress; weight loss; excessive exercise; anorexia nervosa and its variants; Kallmann syndrome; and isolated gonadotropin deficiency.

CLASSIFICATION OF OVULATORY DISORDERS

- **WHO Group II:** Normogonadotropic Normoestrogenic Anovulation
- This group is the largest, including 75-85% of anovulatory women
- Characterized by normal serum FSH and estradiol levels and normal or elevated LH concentrations.
- The most common examples are women with polycystic ovary syndrome (PCOS), some of whom ovulate at least occasionally.

CLASSIFICATION OF OVULATORY DISORDERS

- **WHO Group III:** Hypergonadotropic Anovulation:
- The group accounts for approximately 10-20% of anovulatory women
- Those with elevated serum FSH and low AMH concentrations; most, but not all, have amenorrhea.
- The classic example is premature ovarian insufficiency, due to follicular depletion, and few respond to treatment aimed at ovulation induction.

CLASSIFICATION OF OVULATORY DISORDERS

- **Hyperprolactinemic Anovulation:**
- Approximately 5-10% of anovulatory women have hyperprolactinemia, which inhibits gonadotropin secretion
- Consequently, serum FSH concentrations generally are low or low-normal, and serum estradiol levels also tend to be relatively low.
- Most hyperprolactinemic women have oligomenorrhea or amenorrhea.

PRETREATMENT EVALUATION

- **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, and obesity all are commonly associated with ovulatory dysfunction.
- Anovulation offers an obvious potential explanation for infertility but often is not the only infertility factor.

EVALUATION

- Before ovulation induction begins, a screening semen analysis is prudent because male factors are an important contributing cause in 20-40% of infertile couples.
- At a minimum, anovulatory women should be screened for thyroid disorders (serum TSH) and hyperprolactinemia (serum prolactin) because both require further evaluation and specific treatment.
- Depending on the menstrual history, endometrial sampling also merits consideration, because chronic anovulation is associated with increased risk for endometrial hyperplasia

EVALUATION

- **Glycemic status** should be assessed at baseline in all women with PCOS. In high-risk patients, that is, with a BMI greater than 25 kg/m^2, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension, or high-risk ethnicity, oral glucose tolerance test is recommended.[9] Even though OGTT is the preferred method of testing for impaired glucose tolerance and early type 2 diabetes, fasting plasma glucose or HbA1C levels

EVALUATION

- Preliminary **HSG and transvaginal ultrasonography** are recommended when the medical history or physical examination raises suspicion for coexisting uterine or tubal infertility factors, for women over age 35, and when ovulation induction requires treatment 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.

TREATMENT

- **Lifestyle changing:**
- Lifestyle management for weight loss is recommended for PCOS patients with a BMI greater than 25 kg/m^2.
- Intensive lifestyle modification, including hypocaloric diet and exercise, with or without behavioral interventions, may be the first-line treatment for 3-6 months, to determine whether ovulation is resumed.
- Even modest weight loss (5-10% of body weight) often restores ovulatory cycles in obese anovulatory women with PCOS.

TREATMENT

- At a minimum, weight loss can increase sensitivity to ovulationinducing drugs and decrease the complexity of treatment required.
- **Bariatric surgery:**
- Bariatric surgery can be considered as a second-line treatment option when significant obesity (BMI > 35 kg/m^2) and anovulation are resistant to lifestyle intervention and/or pharmacotherapy, especially in the presence of obesityrelated comorbidities.[9]

REATMENT

- Bariatric surgery can cause malabsorption and eating disorders, which may adversely affect maternal and neonatal health. Risks of small-for-gestational-age babies, preterm delivery, and, possibly, neonatal mortality seem to increase after bariatric surgery. Therefore, it is recommended to avoid pregnancy during rapid weight loss and for at least 12 months after bariatric surgery.

CLOMIPHENE CITRATE

- Clomiphene is a nonsteroidal triphenylethylene derivative that acts as a selective estrogen receptor modulator (SERM), having both estrogen agonist and antagonist properties
- Clomiphene works primarily by stimulating the normal endocrine mechanisms that define the hypothalamic-pituitary-ovarian feedback axis
- Clomiphene typically is ineffective in women with hypogonadotropic hypogonadism (WHO Group I)

Peripheral Actions

- Adverse effects of clomiphene on the endocervix, the endometrium, the ovary, the ovum, and the embryo have been described, but there is no compelling evidence to indicate that such effects have important clinical consequences in most women.

Clomiphene Treatment Regimens

- Clomiphene is administered orally, typically beginning on the third to fifth day after the onset of a spontaneous or progestin-induced menses
- In women with amenorrhea, treatment can begin immediately, without inducing endometrial shedding, if pregnancy has been excluded
- 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.

Clomiphene Treatment Regimen

- Lower doses (12.5-25 mg daily) deserve consideration for women who prove highly sensitive to the drug or develop large ovarian cysts that prevent continued treatment
- Higher doses of clomiphene (150-250 mg daily) sometimes can succeed when lower doses fail
- Most women who respond to clomiphene will respond to either 50 mg (52%) or 100 mg (22%)

Stairstep treatment protocol

- A “stairstep” treatment protocol is an alternative that can shorten the time required to achieve ovulation :
- The regimen involves treatment with clomiphene (50 mg) on cycle days 5-9 after a spontaneous or induced menses, ultrasonography on days 11-14, immediate treatment at the next higher-dose level (100 mg) if no dominant follicle (≥15 mm) has emerged, repeated ultrasonography 1 week later, and, if still no dominant follicle is observed, immediate treatment at the highest dose level (150 mg) and ultrasonography again 1 week later

Risks

- The principal risk associated with clomiphene treatment is an increased risk for conceiving a multiple pregnancy.
- There is no evidence that clomiphene treatment increases the overall risk of birth defects or of any one anomaly in particular.
- **OHSS**
- No causal relationship between ovulation-inducing drugs and ovarian, breast, or endometrial cancer has been established, but prolonged treatment with clomiphene nonetheless should be avoided, primarily because it has little hope of success.

Adjuvant and Combination Treatments

- **Clomiphene and Glucocorticoids:**
- Combined treatment with clomiphene and a glucocorticoid can successfully induce ovulation in many who fail to respond to clomiphene alone
- Both continuous and more limited follicular phase treatment regimens (cycle days 5-14) have been described, using either prednisone (5 mg daily) or dexamethasone (0.5-2.0 mg daily).

Adjuvant and Combination Treatments

- **Exogenous Hcg:** can be useful for the few women who require IUI but repeatedly fail to detect the LH surge despite other objective evidence of successful ovulation induction.
- When the LH surge can be detected, adjuvant hCG treatment has no value and only adds unnecessary expense and inconvenience.
- In clomiphene-induced ovulatory cycles in anovulatory women, the LH surge typically occurs 5–12 days after treatment ends, most often on cycle day 16 or 17 when clomiphene is administered on days 5–9.

Adjuvant and Combination Treatments

- **Metformin and clomiphene**
- Insulin resistance and hyperinsulinemia are common features of PCOS and an important contributing cause of the hyperandrogenism and chronic anovulation that characterize the disorder. Anovulatory infertile women with PCOS and hyperinsulinemia also are typically more resistant to clomiphene treatment. Recognition of the pathophysiologic importance
- Combined treatment with metformin and clomiphene deserves consideration in women who prove to be clomiphene resistant.
- The attempt in combining the two medications can be justified for women having few alternatives besides ovarian drilling or treatment with exogenous gonadotropins.

Adjuvant and Combination Treatments

- **Preliminary Suppressive Therapy :**
- An interval of preliminary suppressive therapy might help to restore harmony and ovulatory function, at least temporarily.
- Combined suppressive therapy with a GnRH agonist and an estrogen-progestin contraceptive (3–6 months) achieves a greater and longer-lasting reduction in serum LH and androgen concentrations than treatment with estrogen-progestin contraception alone and also prevents the otherwise inevitable estrogen deficiency symptoms associated with the use of a GnRH agonist.

AROMATASE INHIBITORS

- Aromatase inhibitors, which were used primarily in the treatment of postmenopausal breast cancer, emerged as a new class of ovulation-inducing agents.
- 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.**
- **Lower estradiol levels** and **higher luteal phase progesterone levels** attained in letrozole-stimulated cycles than clomiphene-stimulated cycles may be the mechanism behind higher live birth rates with letrozole.

AROMATASE INHIBITORS

- Number of growing follicles and mono-ovulatory cycles are similar between women stimulated with clomiphene and letrozole
- Multiple pregnancy rates are also at least as low in letrozole as in clomiphene-induced cycles.
- **Peripheral Actions:**
- Despite lower serum estradiol levels in letrozole-stimulated cycles than in clomiphenestimulated cycles, letrozole could have been expected to have less of an adverse effect on endometrial growth, since it does not block estrogen receptors
- Endometrial thickness in women with WHO group 2 anovulation reported significantly higher endometrial thickness in letrozole-induced cycles

Aromatase Inhibitor Treatment Regimes

- letrozole is the most studied and the most commonly used aromatase inhibitor in ovulation induction.
- Letrozole is administered orally, typically beginning on the third to fifth day after the onset of a spontaneous or progestin-induced menses.
- The starting dose for letrozole is 2.5 mg a day for 5 days
- Despite the absence of published evidence with letrozole, dose increments can be done in the same cycle without inducing bleeding, like the stair-step protocol with clomiphene

Risks

- The major risk of ovulation induction is the occurrence of a multiple pregnancy. Even though a rapid decline in serum FSH level is anticipated following the cessation of letrozole, the incidence of monofollicular development and the risk of multiple pregnancy are similar with clomiphene. The risk of multiple pregnancy is about 3-7%. While the vast majority P.
- 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 when letrozole is used cautiously in an incremental manner

LAPAROSCOPIC OVARIAN DRILLING

- Laparoscopic ovarian drilling can be an effective therapeutic option for anovulatory infertile women who are resistant to oral ovulation induction agents, but the temporary effects of treatment, the risk of postoperative adhesions, and the theoretical risk of adverse effects on ovarian
- Reserve deserve careful consideration and discussion. The procedure is perhaps best reserved for women who are unable or unwilling to accept the costs and risks associated with gonadotropin therapy.

EXOGENOUS GONADOTROPINS

- Exogenous gonadotropins have been used to induce ovulation in gonadotropin-deficient women and those who fail to respond to other, less complicated forms of treatment for nearly 50 years.
- They are highly effective but also very costly and associated with substantial risks including multiple pregnancy and OHSS
- Consequently, exogenous gonadotropins should be used only by clinicians having the training and experience necessary to provide safe and effective treatment.

Gonadotropin Preparations

- Gonadotropin preparations have evolved gradually over the years, from relatively crude urinary extracts to more highly purified urinary extracts to the recombinant preparations in common use today.
- For almost 30 years, the only exogenous gonadotropins available were human menopausal gonadotropins (hMG, menotropins), an extract prepared from the urine of postmenopausal women containing equivalent amounts (75 IU) of FSH and LH per ampule or vial and requiring intramuscular injection
- More purified urinary FSH preparations (urofollitropin) were developed by removing LH from urinary extracts using immunoaffinity columns containing polyclonal anti-hCG antibodies.

Indications for Gonadotropin Treatment

- **Hypogonadotropic Hypogonadism:**
- Women with hypogonadotropic hypogonadism (hypothalamic amenorrhea, WHO Group I)
- In women with hypogonadotropic hypogonadism, ovulation induction regimen must contain both FSH and LH
- Women with hypogonadotropic hypogonadism may respond to relatively low doses of gonadotropin stimulation, although treatment must nonetheless be carefully monitored and adjusted according to response.

Indications for Gonadotropin Treatment

- **Oral Antiestrogen-Resistant Anovulation:**
- In many who are exquisitely sensitive, the therapeutic range is extremely narrow; doses that are only slightly higher than those proving ineffective can cause hyperstimulation

- **Unexplained Infertility**

Gonadotropin Treatment Regimens

- “Low-slow” treatment regimen involving low doses (37.5-75 IU daily), small increments, and a longer duration of stimulation
- “Step-up” treatment regimen designed to define the effective threshold of response. After 4-7 days of stimulation, a serum estradiol level, with or without transvaginal ultrasonography, provides the first measure of response
- “Step-down” treatment regimen is designed to more closely approximate the pattern of serum FSH concentrations observed in spontaneous ovulatory cycles.

Gonadotropin Treatment Regimens

- Two approaches can be effectively combined, first gradually increasing the dose of gonadotropins until a response is observed and then decreasing the dose once a dominant follicle has emerged.
- **Sequential treatment with clomiphene and gonadotropins**: The typical cycle involves a standard course of clomiphene treatment (50-100 mg daily), followed by lowdose FSH or hMG (75 IU daily) beginning on the last day of clomiphene therapy or the next day; treatment is monitored

Monitoring Gonadotropin Therapy

- **Serum Estradiol Levels:**
- With existing gonadotropin stimulation regimens, best results generally are obtained when estradiol concentrations peak between 500 and 1,500 pg/mL; pregnancies are uncommon at levels below 200 pg/mL.
- **Ultrasonography:**
- **Baseline ovarian ultrasonography** is prudent between consecutive cycles of stimulation with exogenous gonadotropins. In the absence of any significant residual ovarian cysts or gross enlargement, treatment can begin again immediately without the need for an intervening rest cycle.

Mnitoring Gonadotropin Therapy

- **Ultrasonography:**
- Monitoring the number and size of follicles
- Studies of endometrial growth

Risks of Gonadotropin Treatment

- **Multiple Pregnancy**
- **Ovarian Hyperstimulation Syndrome**
- **Breast and Ovarian Cancer**

No causal relationship between exogenous gonadotropin treatment and breast or ovarian cancer has been established, although longer-term studies are warranted and prolonged treatment is best avoided, especially when there is little hope for success.

PULSATILE GONADOTROPINRELEASING HORMONE

- Once established, the method is relatively simple to use, requires no extensive and costly monitoring, and is associated with low risks for both multiple pregnancy and ovarian hyperstimulation.
- However, because GnRH therapy requires maintenance of an indwelling intravenous catheter for an interval of 2-3 weeks or longer, many women fear needle displacement or other technical problems and are reluctant to use the method or reject the option outright. Pulsatile GnRH therapy is currently unavailable in the United States and is not used widely elsewhere in the world.

DOPAMINE AGONISTS

- The two most common dopamine agonists in clinical use are bromocriptine and cabergoline
- Cabergoline has widely replaced bromocriptine as the first-choice treatment because it seems more effective in decreasing serum prolactin concentration and has a better side effect profile
- Dopamine agonists are the treatment of choice for hyperprolactinemic infertile women with ovulatory dysfunction who wish to conceive.
- Up to 30% of women with PCOS can exhibit mild hyperprolactinemia Consequently, dopamine agonists also have been advocated as adjuvant therapy for hyperprolactinemic anovulatory women with PCOS who require exogenous gonadotropin treatment.