Ovulation Induction

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16.1 Introduction

About a third of women with infertility are found to have an ovulatory disorder. It often presents as menstrual irregularity from irregular menstrual cycles to complete amenorrhea. The most common underlying condition is polycystic ovarian syndrome (PCOS). A wide range of interventions are available for ovulation induction, starting from lifestyle changes to medications and historically surgery. Oral ovulation-inducing agents include selective estrogen receptor modulators and aromatase inhibitors. If unsuccessful, the next line of treatment is gonadotropin injection.

This chapter reviews the classification of ovulatory disorders, the indications for ovulation induction and the treatments, including their success rates and associated complications.

Clinical Case

A 29-year-old woman presents with a history of infertility. Her menstrual cycle length is typically 45–60 days. Her investigation shows mildly elevated testosterone, and normal FSH, thyroid studies, and serum prolactin. A tubal evaluation and semen analysis was normal.

16.2 Clinical Presentation and Classification of Ovulatory Disorders

The diagnosis of ovulatory disorder is often made with a good menstrual history. Oligomenorrhea or amenorrhea is both suggestive of ovulatory disorders. Tests to detect ovulation include basal body temperature measurement, mid-luteal serum level of progesterone, and documentation of ovulation by serial ultrasonography examinations.

Ovulatory disorders are classified by the World Health Organization as WHO Group I, II, and III.

16.2.1 WHO Group I: Hypogonadotropic Hypogonadal Anovulation

This group includes women with low to normal endogenous gonadotropins levels as well as low serum estradiol level. It is usually related to hypothalamic dysfunction resulting in inconsistent GnRH secretion. About 5–10% of anovulatory women are classified in this category. Examples of conditions presenting as hypogonadotropic hypogonadal anovulation are anorexia nervosa, excessive exercise, excessive weight loss, stress, and hypothalamic conditions such as Kallmann syndrome.

16.2.2 WHO Group II: Eugonadotropic Euestrogenic Anovulation

This group includes women with normal level of endogenous gonadotropins, sometimes elevated luteinizing hormone (LH) and normal estradiol level. Most of anovulatory women fall into this category. Examples of conditions include polycystic ovarian syndrome (PCOS, Fig. 16.1) or less commonly, late onset congenital adrenal hyperplasia (CAH).

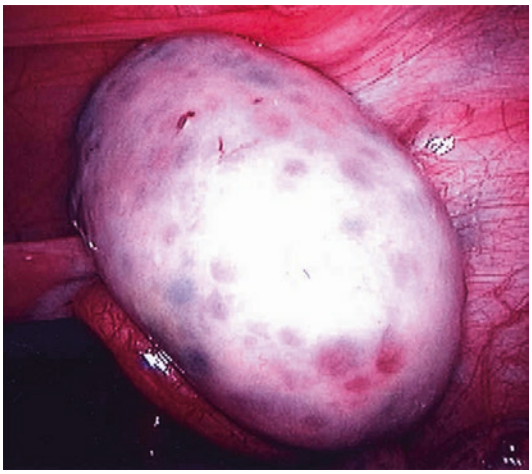

Fig. 16.1 Laparoscopic image of polycystic ovaries after transvaginal oocyte collection

16.2.3 WHO Group III: Hypergonadotropic Anovulation

This group includes women with elevated level of gonadotropins such as follicle stimulating hormone (FSH) and low or normal estradiol level. Typically, it is associated with amenorrhea, and accounts for about 10–20% of ovulatory disorders. Examples include idiopathic premature

ovarian failure (POF), as well as POF related to underlying conditions, such as Turner Syndrome and Fragile X carriers. Iatrogenic POF after treatment with gonadotoxic substances such as chemotherapy or pelvic radiation therapy is also included in this group.

An additional cause of anovulation that is not included in the above classification, but is sometimes considered a fourth group, is hyperprolactinemia. High prolactin level inhibits gonadotropin secretion and results in oligo or amenorrhea. Investigations and treatment of hyperprolactinemia is discussed in a different chapter.

16.3 Treatments for Ovulatory Disorders

Various options are available for the treatment of ovulatory disorders. The choice of treatment depends on the underlying cause of anovulation. A thorough history and physical examination of both partners should be first performed to rule out any underlying pathologies and determine the best course of action. As a general rule, the least invasive options with fewer side effects are used first and more invasive treatments with higher risks kept as a last resort. Interventions can be as simple as weight loss and exercise, followed by oral agents such as clomiphene citrate or aromatase inhibitors, with or without insulin-sensitizing agents. More aggressive therapies include gonadotropins injections. With the availability of in-vitro fertilization, surgery such as laparoscopic ovarian drilling or wedge resection has become outdated.

16.4 Lifestyle and Exercise

Metabolic syndrome and high body mass index is associated with anovulation, often due to polycystic ovarian syndrome (PCOS). PCOS is associated with insulin resistance, hyperandrogenism, oligo or amenorrhea and polycystic ovarian morphology on ultrasound. It is a very common cause of secondary amenorrhea in reproductive age female. There is good evidence that in overweight patient, lifestyle modifications including diet and exercise leading to weight loss can lead to spontaneous return of ovulation. The serum levels of testosterone and insulin decrease after weight loss in obese-PCOS women [1]. Clinical signs of hyperandrogenism such as hirsutism and acne subsequently improve [2]. In fact, weight loss by diet and exercise alone can lead to resumption of ovulation in overweight patients presenting with PCOS [3].

Another important aspect to consider in such patients is pregnancy-related morbidity including gestational diabetes, preeclampsia, hypertension, cesarean delivery and postpartum weight retention. Fetal and child morbidity and mortality are also more prevalent due to increased stillbirth, prematurity, congenital anomalies, macrosomia leading to possible birth injury and childhood obesity. Due to obesity, these patients might have difficulties with anesthesia during labor and increased wound infection. Initiation and sustainment of breastfeeding is also less likely in obese mothers [4].

The first line of treatment for overweight anovulatory women desiring pregnancy is therefore weight loss and exercise. It often leads to spontaneous resumption of ovulation and provides future mothers with the opportunity for a healthier pregnancy with less risk of complications.

16.5 Clomiphene Citrate

Clomiphene citrate is the first agent used for ovulation induction, first described in the 1950s [5]. It is given orally and cleared through the liver and then excreted in the stool. About 85% of a dose is eliminated after 6 days, however traces can remain in the circulation for much longer.

16.5.1 Pharmacology and Mechanism of Action

It is a selective estrogen receptor modulator (SERM) which acts as an agonist or antagonist on the estrogen receptors, depending on the target tissue. The currently manufactured product is a mixture of two isomers, in an approximate 3:2 ratio of enclomiphene and zuclomiphene. Enclomiphene seems to be the most potent isomer of the two, and the one responsible for the ovulation induction effect. It is usually cleared more rapidly than zuclomiphene, which does not seem to have any clinical relevance [6].

The mechanism of action of clomiphene citrate is believed to happen at the level of the hypothalamus, where it binds to the estrogen receptors and

depletes its concentration by interfering with the normal replenishing mechanism. This depletion of estrogen receptor is viewed by the hypothalamus as low circulating estrogen. It then triggers an alteration in GnRH pulsatility resulting in an increase of circulating gonadotropins stimulating the ovary. The subsequent increase in circulating levels of FSH and LH stimulates folliculogenesis and ovulation. It is expected to occur 5–12 days after clomiphene citrate administration [6].

16.5.2 Dosage and Administration

The usual starting dose of clomiphene citrate is 50–100 mg orally every day, for 5 days, starting on day 2–5 of the menstrual or induced cycle. The standard effective dose of CC ranges from 50 to 250 mg/days, although doses in excess of 100 mg/days are not recommended by the US Food and Drug Administration (FDA) and seem to add little to clinical pregnancy rates [6]. Response can be evaluated by ultrasound examination around day 10 of the cycle to view and measure the developing follicle. Urinary LH kits can also be used at midcycle to detect the presence of ovulation. A spontaneous menses at the expected timing of the cycle is also indicative of ovulation.

16.5.3 Side Effects and Risks

In general, clomiphene citrate is well tolerated. Common side effects include mood swings and hot flushes, but are rarely persistent or severe enough to discontinue the treatment. These side effects are temporary and short lived. Visual symptoms such as blurred or double vision, scotomata, and light sensitivity are rare and reversible. Yet, there have been reports of persistent visual symptoms and severe complication such as optic neuropathy [7]. If such visual disturbances occur, CC should be discontinued. Other less specific side effects include pelvic discomfort, breast tenderness, and nausea, observed in 2–5% of patients treated with clomiphene citrate [6].

Treatment with CC is associated with the risks of multiple pregnancies and rarely ovarian hyperstimulation syndrome (OHSS). Multiple pregnancies are due to multifollicular development, and usually results in twin pregnancies. The rate of twin pregnancies is around 8% in anovulatory women and 2.6–7.4% in those with unexplained infertility. The rate of high order multiple pregnancy is much lower (0.08–1.1%) [6]. Ovarian hyperstimulation syndrome rarely occurs with CC. There is no good evidence that the use of clomiphene citrate per se increases the risk of miscarriage, congenital malformations, or ovarian cancer [6].

However, clomiphene citrate can have a negative effect on estrogen responsive tissue such as the endometrium and the cervix. It can result in a thin endometrium and luteal phase defect [8]. Ovulation trigger with hCG or progesterone supplementation may improve the luteal phase. Strategies to avoid a thin endometrium include starting clomiphene citrate on day 1 of the cycle, lowering the dose to 25 mg daily, or supplementation with exogenous estrogen near the time of ovulation [9].

16.5.4 Effectiveness

About 75–80% of patients with PCOS will ovulate with clomiphene citrate treatment. The conception rate per cycle in ovulatory women after clomiphene citrate treatment is up to 22% [10]. Over a half of the patients will ovulate with 50 mg daily dose. Those who do not ovulate with 50 mg may ovulate at higher doses using a step-up regimen with doses escalation by 50 mg with each anovulatory cycle (22% with 100 mg, 12% with 150 mg, 7% with 200 mg, and 5% with 250 mg). Higher doses sometimes required in patients with increased BMI [6].

16.6 Aromatase Inhibitors

Aromatase inhibitors were first developed to lower estrogen levels in the context of breast cancer treatments. The application of this medication for ovulation induction in WHO Group II anovulatory patients, mainly in PCOS was first described in 2001 [11].

16.6.1 Pharmacology and Mechanism of Action

This compound is a cytochrome P450 inhibitor of the aromatase enzyme complex, which results in downregulation of estrogen production. Lower

circulating estrogen levels inhibit the negative feedback loop to the hypothalamus, which results in stronger GnRH pulses release. This further stimulates the pituitary gland to produce more FSH, which induces development of follicles in the ovaries.

The lack of depletion of estrogen receptors by aromatase inhibitors offers a few potential advantages over clomiphene citrate. First, because the estrogen receptors are intact at the level of the hypothalamus, the normal negative feedback loop is also intact. As the growing dominant follicle produces more estrogen, it leads to normal atresia of the smaller follicles and produces monofollicular growth and lower risk of multiple pregnancy. Aromatase inhibitors have less anti-estrogenic effect on the endometrium and cervix than clomiphene citrate [12].

The most commonly use aromatase inhibitor for ovulation induction is its third generation, such as letrozole. It has a relatively short half life of 45 h, offering the advantage of being cleared from the system rapidly, often even before conception occur, therefore limiting the exposure of the potential early pregnancy [13].

16.6.2 Dosage and Administration

Letrozole is given for 5 days starting on day 3–7 of the menstrual cycle. The dose used varies from 2.5 to 7.5 mg orally per day, administration of a single dose of 20 mg on day 3 of the menstrual cycle has also been described [13]. It appears that the optimal dose is 5 mg daily for 5 days [14].

16.6.3 Side Effects and Risks

Despite growing evidence for its effectiveness and safety, FDA and Health Canada do not approve its use for ovulation induction. The concern about congenital malformations in offspring born after letrozole treatment is unfounded [3, 12, 15]. In general, side effects of letrozole use for ovulation induction are mild and limited. These include hot flushes, dizziness, and fatigue [3].

The risk of multiple pregnancy with letrozole is lower than that with clomiphene citrate. In a randomized trial, the multiple pregnancy rate after letrozole was 3.4% versus 7.4% in the clomiphene citrate group [3].

16.6.4 Effectiveness

In a recent randomized study, the cumulative live birth rates were significantly higher at 27.5% in the letrozole group and 19.1% in the clomiphene group (relative risk [RR] 1.44, 95% CI 1.10–1.87). The cumulative ovulation rate was also higher with letrozole, at 62% versus 48% with clomiphene citrate (RR 1.28, 95% CI 1.19–1.37) [16]. A Cochrane review on the subject reported a higher live birth rate with letrozole (275 per 1000) than with clomiphene (188 per 1000) and a higher clinical pregnancy rate (262 per 1000 for letrozole and 202 per 1000 for clomiphene). The miscarriage rates were similar between the two groups (123 per 1000 for letrozole and 134 per 1000 for clomiphene). There was no case of OHSS reported in any of the above-mentioned study [12].

Letrozole is as effective as and maybe more effective than clomiphene citrate for ovulation induction in PCOS patients. However, patients should be informed of the risks and benefits of both options, and be aware that letrozole use is off label for such indication.

16.7 Gonadotropins

Exogenous gonadotropins were first derived from the urine of menopausal women, and their initial clinical use was in the 1950s. Today, purified versions of these gonadotropins are available, as well as recombinant forms [17]. These compounds consist of either FSH or LH alone, or a combination of both and could be administered intramuscularly or subcutaneously.

16.7.1 Pharmacology and Mechanism of Action

Gonadotropins act by directly stimulating the FSH and LH receptors on the granulosa and theca cells of the ovary, resulting in proliferation of one or more follicles. Ovulation induction with gonadotropin is usually accompanied by ovulation trigger with hCG. HCG and LH share the same alpha-subunit, making hCG able to bind to LH receptor and to mimic the endogenous LH surge. Since recombinant and human hCG is readily available, easy to administer, less expensive and requires smaller doses than recombinant LH, it is the most common

used compound to trigger ovulation. GnRH agonist could also be used to trigger ovulation, using the "flare effect" of gonadotropins at the initial use to mimic the LH surge. However, this would not be efficacious in women with hypothalamic amenorrhea who have an endogenous low LH and FSH.

Gonadotropins are effective agents for ovulation induction in WHO Group I (hypogonadotropic hypogonadal anovulation) by supplementing lack of FSH and LH to the HPO axis. In such patients, choosing a preparation containing LH, or adding recombinant LH to the regimen is important, as there is no endogenous production of LH. LH stimulation of the theca cells will produce androgens, which will then be used as a substrate for granulosa cells to produce the estrogen necessary for proper follicular maturation. Gonadotropins are also effective in WHO Group II (eugonadotropic euestrogenic anovulation patients) by augmenting the level of endogenous FSH and LH present.

16.7.2 Dosage and Administration

Gonadotropin is usually started between day 2 and 5 of the menstrual or progesterone-induced cycle. In women with hypothalamic anovulation, the treatment can be started any time. A baseline ultrasound examination should be first done to exclude other ovarian pathology and to evaluate the endometrial thickness, especially in anovulatory PCOS patients. Dosage is based on patient's age, ovarian reserve, and previous response to gonadotropins, but is usually started at a relatively low dose, and increased as needed according to the patient's response.

Typical starting doses are between 37.5 and 75 IU per day. Ultrasound examination is performed after 4–5 days of injection and then every 1–3 days depending on each individual's response. When a mature follicle has developed, usually around size 16–18 mm, exogenous hCG is given to trigger ovulation. Response to gonadotropins can also be followed with estradiol level. It is usually not measured routinely, but can be helpful in cases of atypical or prolonged responses to gonadotropins. Estradiol concentrations generally range between 150 and 300 pg/mL per dominant follicles [18].

To reduce the occurrence of multiple pregnancy, ovulation should not be triggered if multiples follicles are present. Ideally, hCG is given when no more than two mature follicles of 16–18 mm are observed. HCG is administered in a single intramuscular or subcutaneous injection of 5000–10,000 IU. Recombinant hCG is given at a dose of 250 mg subcutaneously, which corresponds to 6000–7000 IU of human hCG. As ovulation can be expected between 24 and 48 h after the hCG injection, intercourse or intrauterine insemination is usually scheduled 24–36 h after trigger [18].

16.7.3 Side Effects and Risks

The most common complication of gonadotropin treatment is multiple pregnancy. It occurs in up to 20% of gonadotropin-induced pregnancies. If numerous follicles are growing, cancellation or conversion to IVF with elective single blastocyst transfer can be offered. In case of high order multiple pregnancies, fetal reduction could be offered. Other risk of gonadotropin treatment is ovarian hyperstimulation syndrome. In the presence of multiple developing follicles, the cycle could be cancelled, converted to IVF with or without agonist trigger and freeze all embryos, or use a lower dose of hCG for trigger [18].

Minor and common side effects include injection-site reaction such as erythema and discomfort. These are usually self-limited and spontaneously resolve. There have been concerns that ovulation induction may be associated with an increased risk for ovarian cancer mainly borderline tumor and breast cancer. Results of studies on this subject have been mixed [18].

16.7.4 Effectiveness

Overall pregnancy rate after ovulation induction with gonadotropins is in the range of 15–20% per cycle. This is dependent on the underlying pathology and individual prognosis factors including age. Women who are obese or insulin resistant may require increased amounts of gonadotropins per cycle to achieve ovulation [18].

16.8 Combination of Gonadotropins and Oral Agents

The addition of clomiphene citrate or letrozole to gonadotropins for ovulation induction in insemination cycle has been used in some centers. It is

associated with reduced total dose of gonadotropins needed to achieve ovulation and the duration of treatment [19–21]. Because lower doses of gonadotropins are needed, patients achieve a reduced rate of monofollicular growth, and less cancellation for ovarian hyperstimulation [20]. In addition, the clinical pregnancy rate appears similar when the combination of oral agents and gonadotropins for ovulation induction is compared to gonadotropin alone [19].

16.9 Insulin-Sensitizing Agents

PCOS is associated with obesity, insulin resistance, and hyperinsulinemia. For this reason, insulin-sensitizing agents have been used to treat ovulatory dysfunction in these patients. The most commonly used compound is a biguanide, metformin, which improves peripheral sensitivity to insulin through stimulated glucose uptake by the tissues. As first line treatment, metformin alone offers no advantage over clomiphene citrate [22]. Combined metformin and clomiphene citrate may increase clinical pregnancy rates, but not live birth rates [23]. Yet, in clomiphene citrate resistant patients, the addition of metformin improves ovulation rate, clinical pregnancy rates but not live birth rates.

Gonadotropins in this specific population may offer an improved live birth rate over adding metformin to clomiphene citrate [22]. Current evidence shows that the rate of spontaneous abortion in PCOS patient does not seem to be reduced with addition of metformin [22]. ESHRE/ASRM guidelines state that "metformin appears to be useful in patients with normal BMI who have infertility due to anovulatory PCOS" and that "metformin, in combination with clomiphene citrate, is the treatment of choice in clomiphene-resistant patients with anovulatory PCOS" [24].

Side effects of metformin include nausea, vomiting, diarrhea, flatulence, GI upset, and rarely lactic acidosis. Metformin is in FDA category B if continued during pregnancy, which implies that "animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women." Clinical evidence of the use of metformin in first trimester of pregnancy is reassuring, as there does not seem to be an increase in congenital malformation in offspring [22].

16.10 Pulsatile GnRH and Dopamine Agonist

Pulsatile GnRHa can be administered to women with WHO Group I. However, its use is not practical and is rarely used today. Women with hyperprolactinemia can be treated with dopamine agonists. Although ovulation will resume, dopamine agonists are not considered ovulation-inducing agents.

16.11 Laparoscopic Ovarian Drilling or Wedge Resection

Ovarian surgery for ovulation induction in PCOS patient includes ovarian wedge resection and ovarian drilling by diathermy or laser [25]. This intervention is believed to be effective due to the destruction of the ovarian androgen-producing tissue. A fall in serum LH and androgen levels has been demonstrated after ovarian drilling, as well as an increase in serum FSH levels. It results in a change from the adverse androgen-dominant intrafollicular milieu to an estrogenic one, which restores the normal hormonal environment by correcting the ovarian-pituitary feedback mechanism. Consequently, both these local and systemic effects promote follicular recruitment, maturation and ovulation [26].

Potential complications of this procedure include the usual surgical and anesthetic risks, as well as post-operative formation of adhesion and diminution of the ovarian reserve by destruction of the healthy follicular pool. In order to limit the latter two, laparoscopic ovarian drilling is often preferred to wedge resection. The typical indication for surgical treatment is clomiphene citrate resistance in patients with anovulatory PCOS. Given the availabilities of other effective methods of ovulation induction and in vitro fertilization for such patients without the risk of affecting the ovarian reserve, surgery should be used very sparingly.

In any event, the procedure is effective and usually results in monofollicular ovulation. Pregnancy rates and live birth rates are comparable when compared to gonadotropin use for CC-resistant patients; however, the multiple pregnancy rate is significantly higher with gonadotropins [10]. The procedure may be best suited for patients in whom frequent ultrasound monitoring is impractical, or in milieu with limited

Table 16.1 Treatment approaches to infertility secondary to anovulation from PCOS

	Intervention	Advantages	Disadvantages
First line	Lifestyle changes including weight control and exercise	– Low cost – Low risk of complications during treatments and pregnancy – Better response to ovulation induction – No increase in risk of multiple pregnancy	– None
	Ovulation induction with oral agents clomiphene citrate or letrozole (off-label in North America)	– Low cost – Easy administration – Limited monitoring	– Side effects – Risk of multiple pregnancy
Second line	Ovulation induction with gonadotropins	– Efficacious when first line treatment fail	– Higher cost – Close ultrasound monitoring required – Administered by injection – High risk of multiple pregnancy – Side effects
	Laparoscopic ovarian drilling	– One time procedure needed – No increase in risk of multiple pregnancy – No monitoring required afterwards	– Surgical risks – High cost – Risk of damaging ovarian reserve
Third line	In vitro fertilization	– High pregnancy rates – Risk of multiple pregnancy can be controlled by elective single embryo transfer	– Risks of procedure (including OHSS) – High cost

resources [10]. In our institution, laparoscopic ovarian drilling or ovarian wedge resection is not performed anymore.

16.12 Conclusion

Anovulation is a common cause of infertility and usually presents as menstrual irregularity. A complete evaluation of the couple is mandatory to exclude systemic illnesses and other infertility factors. The first line treatment for ovulatory disorder should include lifestyle changes if applicable followed by treatment with ovulatory-inducing agents according to the underlying pathology in a stepwise approach (Table 16.1). If conventional treatment is unsuccessful, patient can be treated with controlled ovarian hyperstimulation and in vitro fertilization.

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