Induction of Ovulation

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INTRODUCTION

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 up to 40% of infertile women.[1,2] When anovulation is the only infertility factor, the prognosis for pregnancy is generally quite good because modern ovulation induction strategies are highly effective. When a specific cause of 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.

Clinicians caring for infertile couples must have a thorough understanding of the methods for treatment of anovulatory infertility. This chapter reviews the principles that guide the choice of treatment, the results achieved with different therapies, and their associated risks.

DIAGNOSIS OF ANOVULATION

The diagnosis of anovulation is generally not difficult to establish. **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, as discussed in Chapter 28 and summarized briefly here.

Ovulatory cycles are typically associated with a classic "biphasic" basal body temperature (BBT) pattern that is not difficult to recognize, when present.[3] **BBT recordings having no sustained interval of temperature elevation preceding the onset of menses strongly suggest anovulation**. Biphasic recordings exhibiting a short luteal phase (onset of menses <12 days 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.[2]

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 might naturally be expected.[4,5] A normal ovulatory cycle is 25 to 35 days in duration and exhibits a luteal phase lasting approximately 14 days. **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. Contrary to popular belief and practice, cycle day 21 is *not* always the best time to measure the serum progesterone concentration, and the threshold level indicating ovulation is *not* 10 ng/mL.** Cycle day 21 is a good choice for women with cycles lasting approximately 28 days but a poor choice for women with 35-day cycles. A serum progesterone concentration greater than 10 ng/mL suggests normal luteal function but not when the luteal phase is grossly short, and a level less than 10 ng/mL can be quite normal, because progesterone is secreted by the corpus luteum in distinct pulses,

temporally linked to pulsatile luteinizing hormone (LH) secretion[6]; random sampling can coincide with a transient nadir in serum levels. **If the menses does not commence 7 days after a serum progesterone reading of less than 3 ng/mL, it may be reasonable to repeat the test.**

Other simple tests of ovulation include monitoring urinary LH excretion. This has been simplified by the wide availability of home urine LH kits that are designed to detect a high LH value at the time of the LH surge. It should be noted that patients with polycystic ovary syndrome (PCOS) may have constantly elevated LH levels, leading to false-positive results, yet they would typically have oligomenorrhea.[2] More sophisticated tests available for home use also include a measure of rising estrogen production preceding the LH surge. Serial transvaginal ultrasonography can be useful but is unnecessary and not always accurate for the diagnosis of anovulation. Ruptured follicles can refill with fluid, and a nondominant follicle that has progressed in size can be mistaken for the missing follicle.

CLASSIFICATION OF OVULATORY DISORDERS

After evaluation of the causes of anovulation is completed, virtually all women can be classified according to the criteria adopted by the World Health Organization (WHO).[7] Hyperprolactinemic anovulation is considered as a fourth and specific category. Recently, the International Federation of Gynecology and Obstetrics proposed a more detailed classification of ovulatory disorders.[8] However, it has not been widely adopted at the moment, and the available evidence informing practice is currently based on the existing WHO classification, which will be followed in this chapter.

WHO Group I: Hypogonadotropic Hypogonadal Anovulation

The group accounts for approximately 5% to 10% of anovulatory women and includes 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. Women in the group may require hypothalamic–pituitary imaging to exclude a mass lesion.

WHO Group II: Normogonadotropic Normoestrogenic Anovulation

This group is the largest, including 75% to 85% of anovulatory women, and is characterized by normal serum FSH and estradiol levels and normal or elevated LH concentrations.[9] The most common examples are women with PCOS, some of whom ovulate at least occasionally. Women with PCOS should be assessed for cardiovascular disease risk factors and glycemic status.[10]

WHO Group III: Hypergonadotropic Anovulation

The group accounts for approximately 10% to 20% of anovulatory women and includes those with elevated serum FSH and low anti-Mullerian hormone (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.

Hyperprolactinemic Anovulation

Approximately 5% to 10% of anovulatory women have hyperprolactinemia, which inhibits gonadotropin secretion. Consequently, serum FSH concentrations are generally low or low-normal, and serum estradiol levels also tend to be relatively low. Most hyperprolactinemic women have oligomenorrhea or amenorrhea. When hyperprolactinemia cannot be confidently attributed to coexisting hypothyroidism or to medications, hypothalamic–pituitary imaging is indicated to exclude a mass lesion.

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, and obesity are all commonly associated with ovulatory dysfunction. Treatment should be directed at the underlying cause, when that can be determined, because specific treatment is more likely to succeed, and some conditions can have longer-term health consequences if not recognized and treated.

All anovulatory women deserve at least some preliminary evaluation, both to exclude important pathology that may require medical attention before ovulation induction begins and to identify the most likely successful form of treatment. Chapter 10 considers the causes and management of amenorrhea and galactorrhea. Chapters 11 and 12 discuss the pathophysiology and treatment of PCOS and hirsutism. Chapter 15 describes the evaluation of abnormal uterine bleeding. At a minimum, anovulatory women should be screened for thyroid disorders (serum thyroid stimulating hormone [TSH]) and hyperprolactinemia (serum prolactin) because both require further evaluation and specific treatment.[11–13] Depending on the menstrual history, endometrial sampling also merits consideration, because chronic anovulation is associated with increased risk for endometrial

hyperplasia. Persistently thick endometrium, prolonged amenorrhea, abnormal vaginal bleeding, or excess weight should be investigated for endometrial cancer in women with PCOS.[10] It is worth noting that endometrial biopsy is not required for the sole purpose of assessing ovulation.[2]

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/m2, a history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, a family history of diabetes mellitus type 2, hypertension, or high-risk ethnicity, oral glucose tolerance test (OGTT) is recommended.[10] **Even though OGTT is the preferred method of testing for impaired glucose tolerance and early type 2 diabetes, fasting plasma glucose or HbA1C levels can suffice for others.**[10] When OGTT is done, 2 hours after a 75 g oral glucose load, glucose concentrations between 140 and 199 mg/dL indicate impaired glucose tolerance, and levels of 200 mg/dL or greater indicate non–insulin-dependent diabetes.

Anovulation offers an obvious potential explanation for infertility but is often not the only infertility factor. **Before ovulation induction begins, a screening semen analysis is prudent because male factors are an important contributing cause in 20% to 40% of infertile couples.**[14] Early recognition of a significant coexisting male factor helps avoid wasted time, effort, expense, and associated frustrations.

Additional preliminary evaluation with transvaginal ultrasonography and tubal patency testing with hysterosalpingography (HSG) or hysterosalpingo-contrast sonography (HyCoSy) merits serious consideration, particularly in women with a history of previous pelvic infection or surgery, ectopic pregnancy, inflammatory bowel disease, pelvic pain or other symptoms of endometriosis, or an abnormal physical examination. In the absence of such risk factors, the likelihood of tubal disease is low, and tubal patency testing can be deferred safely in young women and those who do not require complicated and costly forms of ovulation induction. In older women with a narrowing window of opportunity, it is generally wise to evaluate objectively all relevant infertility factors before treatment begins to ensure that time is used to the best possible advantage. In women who require ovulation induction with exogenous gonadotropins, the associated costs, logistics, and risks also justify a thorough preliminary evaluation. **Preliminary tubal patency testing 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 tubal patency testing or signs or symptoms of pelvic disease.

Lifestyle management with healthy eating and/or physical activity should be recommended to all women with PCOS, especially those with a BMI greater than 25 kg/m^2. A healthy lifestyle is important to optimize general health, quality of life, body composition, and weight management and may improve fertility, fertility treatment outcomes, and health during pregnancy.[10] While there are benefits of lifestyle management even in the absence of weight loss, **even modest weight loss (5–10% of body weight) often restores ovulatory cycles in obese anovulatory women with PCOS.**[15–21] In overweight and obese women with PCOS, unless age-related infertility is a concern, intensive lifestyle modification, including hypocaloric diet and exercise, with or without behavioral interventions, may be the first-line treatment for 3 to 6 months or until weight goal is achieved, to determine whether ovulation is resumed.[10] At a minimum, weight loss can increase sensitivity to ovulation-inducing drugs and decrease the complexity of treatment required. In one study, 60 of 67 obese anovulatory women (90%) who lost an average of 10 kg in a diet and exercise program resumed spontaneous ovulation, and 52 (78%) ultimately achieved pregnancy, 18 (27%) without other interventions.[21] In another study, 149 infertile women with PCOS were randomly allocated to (1) continuous oral contraceptive pills (OCP); (2) lifestyle modification consisting of caloric restriction with meal replacements, weight loss medication (either sibutramine or orlistat), and increased physical activity to promote a 7% weight loss; or (3) combined treatment with both OCP and lifestyle modification, for 16 weeks prior to four cycles of ovulation induction with clomiphene and timed intercourse.[22] Women receiving lifestyle modification or combined lifestyle modification with OCP achieved significant weight reduction (−6.2% and −6.4%, respectively) and had significantly higher cumulative ovulation rates than women receiving OCP (60%, 67%, and 46%, respectively).[22] Compared to similar women who received clomiphene right away in another randomized trial,[23] women receiving lifestyle modification in the aforementioned trial achieved significantly higher cumulative ovulation (lifestyle, RR = 1.4; 95% CI = 1.1–1.7; combined, RR = 1.4; 95% CI = 1.2–1.8) and significantly better live birth rates (lifestyle, RR = 2.5; 95% CI = 1.3–4.7 and combined, RR = 2.5; 95% CI = 1.3–4.8).[23,24]

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 obesity-related comorbidities.[10,25] Limited evidence, mostly from retrospective studies, reports that bariatric surgery improves anovulation, hirsutism, insulin resistance, sexual activity, libido and decreases obstetric risks, such as gestational diabetes and pregnancy induced hypertension, while whether fetal outcomes are improved remains uncertain.[10,26–29] A 2016 meta-analysis, including 13 case series with 2,130 patients who underwent bariatric surgery, reported that 12 months after surgery, the incidence of PCOS decreased to 6.8% from 45.6%, menstrual irregularity to 7.7% from 56.2%, and hirsutism to 38.6% from 67.0%.[26] A 2017 meta-analysis corroborated these findings and, furthermore, reported 96%

(CI = 88–100%) resolution rate for PCOS among 82 severely obese patients.[30] A 2022 meta-analysis, including 14 studies with 501 PCOS patients who underwent bariatric surgery, reported that abnormal menstruation was significantly decreased after surgery (odds ratio 0.03, 0.01–0.08), and 31 of the 32 patients attempting pregnancy had conceived; however, publication bias was noted, which could have affected estimates.[31]

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, developmental abnormalities and, possibly, neonatal mortality seem to increase after bariatric surgery.[32,33] 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.

While bariatric surgery appears superior to conventional weight loss treatments, introduction of a new class of antiobesity medications, including glucagon-like-peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) receptor agonists, which are more potent than other pharmaceutical interventions for weight loss, can require reconsideration of the role of bariatric surgery in the management of PCOS.

GLP-1 and GIP are produced by the L-cells in the gut upon food intake and stimulate insulin secretion in a glucose-dependent manner. They reduce appetite and delay gastric emptying. Increased satiety and reduced food intake bring about weight loss. They can also enhance glucose uptake and lipolysis as well as thermogenesis in adipose tissue.[34,35] Studies have shown that these medications can offer weight loss results comparable to those achieved by bariatric surgery. In 2023, the U.S. Food and Drug Administration (FDA) approved weekly injectable forms of these drugs for weight loss in patients without diabetes.[36] Meanwhile, animal studies have raised concerns about teratogenicity, an increased risk of early pregnancy loss, and reduced fetal weight. However, it remains unclear whether these fetal complications are due to an energy deficit or a direct effect of the drugs.[36] Pregnancy and lactation are contraindications for the use of these medications, while a 2023 review and a large retrospective study in 2024 did not suggest an increased risk of fetal malformations.[37] It is also noteworthy that the required interval between cessation of use and conception has not been established, and rapid weight gain upon cessation is a concern. In summary, reproductive effects of GLP-1 and GIP receptor agonists are presently not well understood, and long-term data are needed.

FIRST-LINE TREATMENT: ORAL ANTIESTROGENS

Clomiphene citrate has been the first choice for ovulation induction in WHO Group 2 patients for decades. Recent trials report significantly higher success rates with an aromatase inhibitor, letrozole, leading to prioritizing letrozole over clomiphene, where it is available and can be used for this indication.[10,38] However, it is noteworthy that despite evidence of effectiveness and safety in well-designed large randomized controlled trials, letrozole is still used off-label for ovulation induction in the United States, since it has not been approved by the FDA for this indication. The choice between letrozole and clomiphene should be made collaboratively with the patient, after thoroughly discussing the risks, benefits, efficacy, and costs of each option.[10] Other methods of ovulation induction, such as gonadotropins and laparoscopic ovarian drilling, are considered second-line treatments if letrozole or clomiphene fail to induce ovulation.

AROMATASE INHIBITORS

Aromatase inhibitors, which were used primarily in the treatment of postmenopausal breast cancer, emerged as a new class of ovulation-inducing agents. Even though the use of aromatase inhibitors for ovulation induction has been controversial since their first introduction in 2001,[39] letrozole is now considered the first-line therapy for ovulation induction in women with PCOS,[10] as it provides significantly higher live birth rates compared to clomiphene.[38]

Pharmacology and Mechanism of Action

Anastrozole and letrozole are triazole (antifungal) derivatives that act as potent, competitive, nonsteroidal inhibitors of aromatase,[40,41] the enzyme that catalyzes the rate-limiting step in estrogen production. They block estrogen production both in the periphery and in the brain, resulting in a compensatory increase in pituitary gonadotropin secretion that stimulates ovarian follicular development.[42–44] In this regard, their mechanism of action is similar to, but also distinct from, that of clomiphene. Although both stimulate increased gonadotropin secretion by decreasing the negative feedback effects of estrogen during treatment, clomiphene does so via depletion of central estrogen receptors, whereas aromatase inhibitors decrease estrogen production directly (**Figure 30.1**).

At least in theory, the different actions of aromatase inhibitors and clomiphene may have functional, and clinical, importance. 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.[23] Gonadotropin secretion is anticipated to promptly decrease due to negative feedback by rapidly rising estrogen production by growing follicles following the cessation of aromatase inhibitor. To the contrary, the lack of immediate negative feedback following cessation of clomiphene, due to the depletion of central estrogen receptors, results in a more sustained increase in

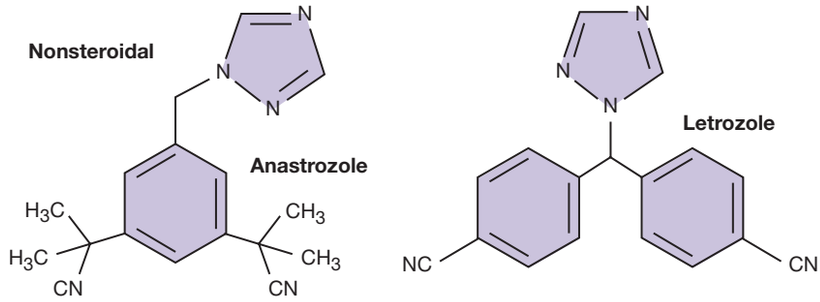

FIGURE 30.1

gonadotropin levels that is more likely to support multifollicular development. However, while the average number of growing follicles are lower with letrozole than clomiphene (25 randomized controlled trails (RCTs); standardized mean difference: −0.56; 95% CI: −0.96, −0.17), mono-ovulatory cycles are similar between women stimulated with clomiphene and letrozole.[45,46] Likewise, multiple pregnancy rates are also similar between letrozole and clomiphene-induced cycles.[38]

Peripheral Actions

Despite lower serum estradiol 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. Indeed, a 2024 systematic review comparing the effect of clomiphene citrate and letrozole on endometrial thickness in patients with PCOS reported significantly higher endometrial thickness in letrozole-induced cycles (39 RCTs; weighed mean difference, 1.45 mm; 95% CI = 0.98–1.92).[46] However, the results in individual studies demonstrated high heterogeneity and comprise low-quality evidence. Whether the effect of letrozole on endometrial thickness has a significant effect on treatment outcome in terms of pregnancy and live birth rates is controversial. Few studies investigated molecular markers or endometrial growth and receptivity in letrozole-stimulated cycles. In general, letrozole was found to be associated with a more favorable molecular profile than clomiphene.[47] Clomiphene is associated with significantly decreased protein expression of active B-catenin, inactive glycogen synthase kinase-3β, and estrogen receptor 1.[48] A retrospective study involving women undergoing in vitro fertilization (IVF) reported increased integrin αvβ3 expression following stimulation with letrozole.[49] However, whether integrin expression is different between letrozole- and clomiphene-stimulated cycles is controversial.[50]

Limited data suggest that letrozole does not have a clinically relevant direct effect on oocytes or embryos. In a mouse model of PCOS, superovulation with letrozole was not found to affect meiotic spindle assembly or blastocyst development, compared with FSH-stimulated superovulation.[51] A randomized controlled trial of letrozole cotreatment during ovarian stimulation for assisted reproductive technology (ART) reported similar number of oocytes retrieved, similar fertilization, blastulation, clinical pregnancy and cumulative pregnancy rates as compared to placebo cotreatment, suggesting the lack of a negative effect of letrozole administration on oocytes.[52]

Clinical Indications

Following the publication of large randomized controlled trials demonstrating higher live birth rates with letrozole than with clomiphene, it is now regarded the drug of choice for ovulation induction in anovulatory infertile women with PCOS.[10] The drug has also been tested in ovulatory women with unexplained infertility (in combination with IUI).[53]

Letrozole is ineffective in women with hypogonadotropic hypogonadism (WHO Group 1), who already have low serum estrogen concentrations and a dysfunctional hypothalamic–pituitary–ovarian axis.

Aromatase Inhibitor Treatment Regimens

In almost all studies conducted to date, letrozole (2.5–7.5 mg daily) and anastrozole (1 mg daily) have been administered for a 5-day interval. Early on, a phase II randomized controlled trial comparing a single-dose therapy with anastrozole and 5-day course of clomiphene reported significantly lower ovulation rates with anastrozole, and the sponsoring company stopped the development of the drug.[54] Thus, 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. Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 3 and 5.[55] 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/d fails to induce ovulation, the dosage can be increased

by 2.5 mg increments up to a maximum of 7.5 mg/d for 5 days. Dose increments can be done in the same cycle without inducing bleeding, also known as the stair-step protocol.[56–58] Longer durations of letrozole treatment (7–10 days) can succeed when standard 5 days treatment does not. A retrospective study comparing outcomes with letrozole 2.5 mg/d for 5 days, 2.5 mg/d for 10 days, 5 mg/d for 5 days, and 5 mg/d for 10 days observed that patients who received 5 mg/d or 10-day-long regimens achieved significantly higher ovulation rates, ovulated significantly earlier, had shorter time to pregnancy despite similar multifollicular development rates.[59] Ovulation rates were 45.2% with 2.5 mg/d for 5 days, 88.2% with 2.5 mg/d for 10 days, 73.7% with 5 mg/d for 5 days, and 83% with 5 mg/d for 10 days letrozole regimens.[59] Another retrospective study also reported a cumulative ovulation rate of 92.75% with extension of an anovulatory 5 mg/d 5 days' course first to 7 and then to10 days' course.[60]

Results of Treatment With Aromatase Inhibitors

Several trials have compared letrozole and clomiphene in anovulatory women without documented clomiphene resistance. The largest involved 750 patients who were randomized to receive letrozole (2.5 mg daily increased up to a maximum of 7.5 mg/d in case of anovulation) or clomiphene (50 mg daily increased up to a maximum of 150 mg/d), without ovulation trigger, up to five treatment cycles. In the letrozole group, a significantly higher proportion of women achieved ovulation (88.5% vs 76.6%, RR = 1.16; 1.08–1.24), and the proportion of ovulations over total treatment cycles was significantly higher (61.7% vs 48.3%, RR = 1.28; 1.19–1.37). Cumulative pregnancy (27.3% vs 21.5%) and live birth (27.5% vs 19.1%, RR = 1.44; 1.10–1.87) rates were also significantly higher with letrozole treatment.[23] One randomized trial, which recruited 100 anovulatory women with PCOS who had never received ovulation induction, also reported significantly higher ovulation (60% vs 32%) and a nonsignificant increase in pregnancy rate (26% vs 14%) with letrozole (5 mg/d) than clomiphene (100 mg/d).[61] A 2022 systematic review reported significantly higher live birth rates with letrozole than clomiphene (OR = 1.79; 1.42–2.25) based on high-certainty evidence.[38] The beneficial effect of letrozole seems independent of body mass index, that is, despite decreasing overall live birth rates with increasing BMI, letrozole outperforms clomiphene across categories of BMI, although the difference falls short of significance in patients with a BMI <25 kg/m^2 (OR = 1.49; 0.98–2.25) in the meta-analysis.[23,38] Miscarriage per pregnancy (OR = 0.94; 0.63–1.42) and multiple pregnancy rates (OR = 0.69; 0.35–1.34) are also similar between letrozole- and clomiphene-induced cycles.[38] **Available evidence suggests that letrozole should be considered the first-line agent for ovulation induction in anovulatory women with PCOS**.

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 (20%) and dizziness (12%) than women on clomiphene.[23] However, hot flushes are less common with letrozole (20.3% vs 33.0%).[23]

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.[38] The risk of multiple pregnancy is about 1%.[38] While the vast majority of multiples are limited to twins, a case of sextuplets has been reported following ovulation induction with letrozole at a dose of 7.5 mg/d.[62] It would be prudent to monitor ovarian response and cancel cycles when the patient is regarded to be at risk of multifollicular development, for example, with prior multifollicular development or requiring a high dose of letrozole.

Given the mechanism of action, ovulation induction with aromatase inhibitors is not considered a risk factor for female reproductive tract or breast cancer.

Despite initial concerns regarding increased risk of fetal anomalies following ovulation induction with aromatase inhibitors, there is no evidence suggesting letrozole is any more teratogenic than clomiphene. One case series comparing the incidence of congenital malformations in 911 newborns of women who conceived after treatment with letrozole (14/514, 2.4%) or clomiphene (19/397, 3.0%) found no difference.[63] Another comparing the incidence of birth defects in children born to mothers treated with letrozole or clomiphene to that in pregnancies conceived without treatment also observed no difference.[64] A 2021 systematic review that investigated risk of fetal harm with letrozole, included 46 studies and corroborated former findings.[65] The risk of congenital malformations or pregnancy loss was not increased with letrozole in comparison to clomiphene or natural conceptions.

The risk of clinically significant ovarian hyperstimulation syndrome (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.

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.

CLOMIPHENE CITRATE

Clomiphene citrate was first synthesized in 1956, introduced for clinical trials in 1960, and approved for clinical use in the United States in 1967.[66,67] In early clinical trials, 60% to 80%

of anovulatory women treated with clomiphene achieved ovulation, and half of those who ovulated also conceived.[66–68] The collected clinical experience gained in the years since remains consistent with those early observations.

Pharmacology and Mechanism of Action

Clomiphene is a nonsteroidal triphenylethylene derivative that acts as a selective estrogen receptor modulator (SERM), having both estrogen agonist and antagonist properties.[69] However, 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. Clomiphene 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.[70] Clomiphene is a racemic mixture of two different stereoisomers, enclomiphene (62%, originally known as *cis*-clomiphene) and zuclomiphene (38%, originally known as *trans*-clomiphene).[69,71] Enclomiphene is the more potent isomer and the one responsible for its ovulation-inducing actions.[69,72] The half-life of enclomiphene is relatively short, so serum concentrations rise and fall quickly during and after treatment.[70,73] Zuclomiphene is cleared much more slowly; serum levels remain detectable for weeks after a single dose[70] and may even accumulate gradually over a series of cycles, but there is no evidence that residual zuclomiphene has any important clinical effects or consequences.[73]

Structural similarity to estrogen allows clomiphene to compete with endogenous estrogen for nuclear estrogen receptors at sites throughout the reproductive system. However, unlike estrogen, clomiphene binds to nuclear estrogen receptors for an extended interval of time and thereby depletes receptor concentrations by interfering with receptor recycling.[69] At the hypothalamic level, estrogen receptor depletion prevents accurate interpretation of circulating estrogen levels; 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 may also increase the sensitivity of gonadotrophs to GnRH stimulation (**Figure 30.2**).[74]

When administered to already ovulatory women, clomiphene increases GnRH pulse frequency.[75] In anovulatory women with PCOS who already exhibit an increased GnRH pulse frequency, clomiphene increases only pulse amplitude.[76] 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.[77] 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. In sum, clomiphene works primarily by stimulating the normal endocrine mechanisms that define the hypothalamic–pituitary–ovarian feedback axis. The importance of other effects it may have on insulin-like growth factors (decrease in IGF-I concentrations) and sex hormone–binding globulin (increase in serum levels) is uncertain.[78,79]

Peripheral Actions

In addition to its desirable central actions, clomiphene can exert less desirable antiestrogenic effects at peripheral sites in the reproductive system, which some have suggested might

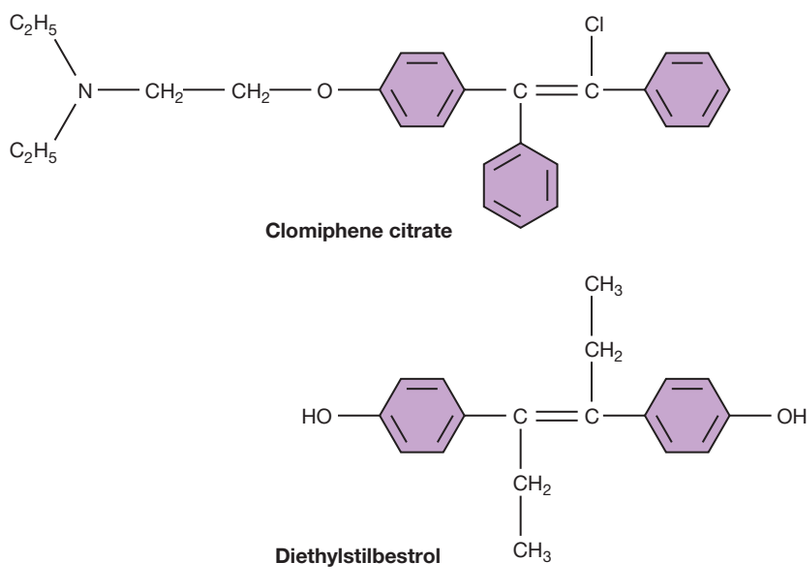

FIGURE 30.2

IV

explain the difference between ovulation and pregnancy rates achieved with clomiphene treatment. **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.**

On balance, the weight of evidence from controlled trials suggests that the quality and quantity of **cervical mucus production** can be decreased in clomiphene treatment cycles. Whereas some have observed no significant changes in mucus characteristics during treatment,[80] others have found clomiphene has dose-dependent adverse effects.[81,82] The conflicting results have several possible explanations. The effect may be more apparent when the interval between the end of treatment and ovulation is short.[81] The effect might often be negated by higher serum estradiol levels resulting from clomiphene-induced multifollicular development.[83] It is also possible that some individuals may be more sensitive to the effect.[84] Regardless, any adverse effect that clomiphene may have on cervical mucus does not prevent pregnancy (Chapter 28). In recent years, even the evaluation of cervical mucus has all but disappeared from clinical practice because controlled trials have demonstrated that postcoital testing (the traditional test of cervical factors) has little or no predictive value[85,86] and because modern advanced treatment regimens for persistent infertility now routinely incorporate intrauterine insemination (IUI), which bypasses the cervix altogether.[87,88]

Impaired **endometrial growth** has also been reported in clomiphene-treated women. However, preovulatory endometrial thickness in clomiphene-induced cycles remains well within the range normally observed in spontaneous ovulatory cycles in the large majority of women.[87,89–94] Other subtle differences in endometrial morphology have been attributed to the effects of clomiphene, but their clinical relevance, if any, is uncertain.[95,96] It is likely that clomiphene inhibits endometrial growth, at least in some women,[97] for the same reasons that it may inhibit cervical mucus production, but the same caveats apply; the effect is inconsistent, may be offset by the higher estrogen levels in clomiphene-induced cycles, and probably has little clinical importance, except perhaps 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**. Although clomiphene can inhibit steroid hormone production by cultured avian,[98] ovine,[99] and human granulosa/luteal cells in vitro,[100] serum estrogen and progesterone concentrations in clomiphene-induced cycles are typically higher, not lower, than in spontaneous ovulatory cycles. Adverse effects on mouse ovum fertilization and embryo development have been observed in vitro,[101] but studies in women indicate that serum concentrations of enclomiphene and zuclomiphene never approach the levels required to induce such effects, even after several consecutive treatment cycles.[73]

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 ovulation induction in anovulatory infertile women with normal thyroid function, normal serum prolactin levels, and normal endogenous estrogen production, as determined by clinical observations (oligomenorrhea, estrogenic cervical mucus), a serum estradiol determination (approximately $>$40 pg/mL), or a normal menstrual response to a progestin challenge (WHO Group II).[102,103] Although the drug also is frequently used empirically to stimulate multifollicular development in ovulatory women with unexplained infertility (in combination with IUI),[88,104–107] the focus here is on ovulation induction in anovulatory women; empiric clomiphene and other treatments for unexplained infertility are discussed in detail in Chapter 28.

Given its mechanism of action, it is not surprising that clomiphene is typically ineffective in women with hypogonadotropic hypogonadism (WHO Group I). Together, low or low-normal FSH levels and low serum estrogen concentrations indicate that the hypothalamic–pituitary–ovarian axis is not functioning normally in women with hypothalamic amenorrhea; if it were, FSH levels would be high because estrogen concentrations are low. If low endogenous estrogen concentrations cannot stimulate increased FSH secretion, there is little reason to think that a clomiphene-induced decrease in the level of negative estrogen feedback will succeed, and it rarely does. Alternative treatments that directly stimulate the pituitary (pulsatile exogenous GnRH) or the ovary (exogenous gonadotropins) are usually required.

Because the corpus luteum derives from the ovulatory follicle, its functional capacity depends, in part, on the quality of preovulatory follicular development. Logically, inadequate follicular development can be expected to cause or 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.[108,109] Consequently, clomiphene could be both a logical and an effective choice for treatment.[110–113] Progesterone levels are typically higher in clomiphene-induced ovulatory cycles than in normal spontaneous cycles, likely because preovulatory follicular development is optimized and because treatment often results in more than one corpus luteum.[113,114]

Clomiphene citrate treatment is generally limited to women with demonstrated ovulatory dysfunction but has also been offered to normally ovulating women whose infertility remains unexplained, particularly when they are young and infertility is of short duration, and those unwilling or unable to pursue more aggressive treatments. The putative efficacy of clomiphene treatment in women with unexplained infertility has been attributed to optimizing follicular

development or to the "superovulation" of more than a single ovum. However, clomiphene alone does not seem to significantly improve live birth rates or time to pregnancy compared to expectant management in unexplained infertility.[104] **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** (Chapter 28).[88,104,115] **On the contrary, in anovulatory women with PCOS treated with clomiphene, IUI is not considered superior to timed intercourse, when the semen analysis is within the normal range.**[10,116]

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. Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 2 and 5.[117] In women with amenorrhea, treatment can begin immediately, without inducing endometrial shedding, if pregnancy has been excluded. Indeed, available evidence suggests that progestin-induced endometrial shedding is associated with a longer treatment cycle, lower conception and live birth rates, and longer time to pregnancy.[118,119] The dose of clomiphene required to induce ovulation correlates with body weight but cannot be predicted confidently for an individual woman.[120,121] Although obese women often require higher doses of clomiphene treatment, the results achieved are ultimately similar to those observed in lean women.[122,123] No clinical or laboratory parameter has proven utility for predicting the dose of clomiphene needed to induce ovulation (**Figure 30.3**).[120,123]

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. **Most women who respond to clomiphene will respond to either 50 mg (52%) or 100 mg (22%).**[124,125] 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.[126] Although not approved by the FDA, higher doses of clomiphene (150–250 mg daily) can sometimes succeed when lower doses fail (150 mg, 12%; 200 mg 7%; 250 mg 5%).[124,125] We believe that treatment with doses up to 150 mg is reasonable before considering alternatives and recommend against the use of higher doses.[124] Longer durations of clomiphene treatment (7–10 days) can succeed in some women when standard treatment does not and may occasionally be useful when there are no practical alternatives.[121,127,128]

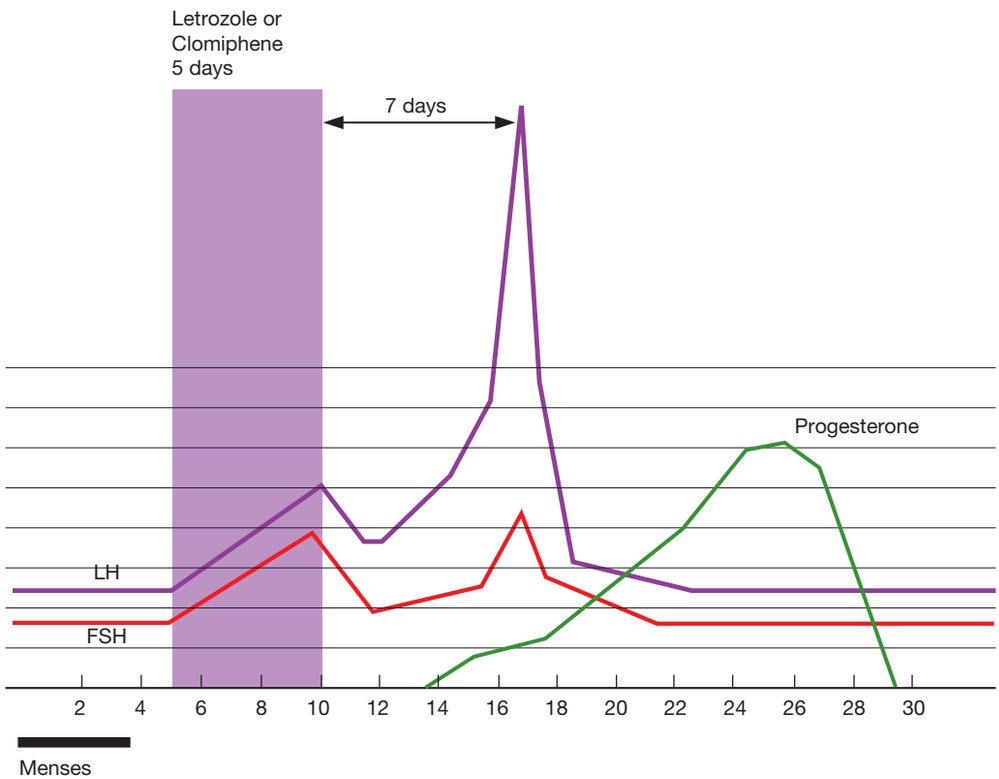

FIGURE 30.3

IV

Results of Clomiphene Treatment

Clomiphene will induce ovulation successfully in 70% to 80% of properly selected women.[129,130] The likelihood of response decreases with increasing age and body mass index and with the extent of any associated hyperandrogenemia in anovulatory women. Interestingly, women with amenorrhea are more likely to conceive than those with oligomenorrhea,[129] possibly because infertile women who menstruate also likely ovulate, albeit infrequently, and are more likely to have other coexisting infertility factors.

Among anovulatory infertile women who respond to clomiphene treatment, the overall cycle fecundability is approximately 15%. In women with no other infertility factors, cycle fecundability may reach as high as 22%, comparable to that observed in normal fertile couples after discontinuation of barrier contraception and those with male factor infertility receiving therapeutic donor inseminations.[129] **Cumulative pregnancy rates of 70% to 75% can be expected over six to nine cycles of treatment.**[131,132] Thereafter, cycle fecundability falls substantially. **When pregnancy is not achieved within three to six clomiphene-induced ovulatory cycles, the infertility investigation should be expanded to exclude other infertility factors not yet evaluated, or the overall treatment strategy should be modified if evaluation is already complete. Prolonged treatment with clomiphene is inappropriate, particularly for women over age 35.**

Side Effects

Clomiphene treatment is generally very well tolerated. Minor side effects are relatively common but are rarely persistent or severe enough to require that treatment be discontinued.

Transient hot flashes, usually limited to the short interval of treatment, occur in 10% to 20% of women.[133] Considering that clomiphene causes a central misperception that endogenous estrogen levels are low, vasomotor symptoms are not difficult to understand. Other mild and less common side effects include headache, breast tenderness, pelvic pressure or pain, and nausea (2–5%). Visual disturbances (blurred or double vision, scotomata, light sensitivity) are uncommon (1–2%) and reversible, but reports of persistent "afterimages" (palinopsia) and light sensitivity (photophobia) make them nonetheless unnerving[134]; when such symptoms appear, prudence dictates that treatment be abandoned in favor of alternative methods for ovulation induction.

Risks

Clomiphene treatment has risks, but serious complications are rare. Inevitably, questions arise concerning the risks for multiple pregnancy, congenital anomalies, and other potential adverse outcomes associated with clomiphene treatment.

The principal risk associated with clomiphene treatment is an increased risk for conceiving a **multiple pregnancy**. The clomiphene-induced increase in FSH secretion is only transient, so normal selection mechanisms still operate to yield only a single mature follicle in most treatment cycles in anovulatory women. **Nevertheless, multifollicular development is relatively common and the overall risk of multiple pregnancy is increased to approximately 7% to 10%.**[135–137] The large majority of multiple pregnancies conceived in clomiphene-induced cycles are twins; the risk for triplets is 0.3% to 0.5%, for quadruplets 0.3%, and for quintuplets 0.1%.[67,138] **The higher risk of multifetal gestation is another reason to treat with the lowest effective dose of clomiphene; higher doses do not improve results and only increase the risk of superovulation and multiple pregnancy, with all of the attendant antenatal and neonatal complications.**

There is no evidence that clomiphene treatment increases the overall risk of birth defects or of any one anomaly in particular.[139] Several large series have examined the question and have drawn the same conclusion.[135–137,139,140] In a series of 1,034 pregnancies resulting from clomiphene treatment, 14.2% ended in miscarriage, 0.5% in ectopic pregnancy, 0.1% in molar pregnancy, and 1.6% in stillbirth, and among 935 live born infants, malformations were detected in 21 (2.3%).[139] Earlier suggestions that the risk of neural tube defects might be higher in pregnancies conceived after clomiphene treatment were not confirmed in later investigations.[141,142] A small study of pregnancy outcomes in women exposed inadvertently to clomiphene during the first trimester of pregnancy found no evidence of teratogenicity.[143] There is also no evidence that clomiphene treatment increases the risk of **developmental delay or learning disability** in children conceived during clomiphene treatment.[144]

Early studies suggested that the incidence of spontaneous **miscarriage** in pregnancies resulting from clomiphene treatment might be increased, but a number of others have observed miscarriage rates no different from those in pregnancies conceived without treatment.[124,131,132,145,146]

The incidence of **ovarian hyperstimulation syndrome** (OHSS) in clomiphene-induced cycles is difficult to determine confidently because definitions of the syndrome vary widely among studies. In general, mild symptoms of ovarian hyperstimulation (transient abdominal discomfort, mild nausea, vomiting, diarrhea, and abdominal distention) are not altogether uncommon but require only expectant management. When induction of ovulation proceeds in the recommended incremental fashion to establish the minimum effective dose, the risk of clinically significant OHSS (massive ovarian enlargement, progressive weight gain, severe abdominal pain, intractable nausea and vomiting, gross ascites, oliguria) is remote.

The incidence of **ovarian cancer** is decreased among parous women and those using hormonal contraception for prolonged intervals, suggesting that "incessant ovulation" (repeated epithelial disruption and repair) predisposes to the development of ovarian cancer and that treatment with

ovulation-inducing drugs might increase the risk.[147] The results of case-control studies conducted in the 1990s lent credence to the notion and raised considerable concern,[148,149] although their conclusions were challenged because of important methodologic flaws. One study compared infertile treated women to fertile women rather than to infertile untreated women, even though infertility and nulliparity were known risk factors for ovarian cancer.[148] Another included cancers of all types and tumors of low malignant potential despite their differing pathophysiology.[149] Since then, numerous studies have confirmed that the incidence of ovarian cancer is increased in infertile women but have failed to find any substantive evidence that ovulation-inducing drugs increase the risk,[150–160] and a 2023 systematic review, including 14 case control studies and 20 cohort studies, found that fertility drug use among nulliparous subfertile women was associated with an increased incidence of borderline serous ovarian tumors (OR = 1.49; CI = 1.03–2.15) but not with any invasive cancers (OR = 1.55, CI = 0.94−2.57).[161] It should be noted that the observed risk did not demonstrate a linear relationship with the number of ovulation induction cycles, rendering a causal relationship less likely.[161] In 2013, a large US study, including 9,825 women, with an average follow-up time of 17.6 years for ovarian cancer cases and 26.2 years for noncases, found that while ever use of clomiphene was not associated with ovarian cancer, women who remained nulligravid were found to have an increased risk of breast cancer with ever use of clomiphene (RR = 3.63, 95% CI = 1.36–9.72).[162]

Clomiphene does not seem to increase the risk of breast cancer.[163,164] While the observational and retrospective nature of the studies leave some room for skepticism, the data are so far reassuring. It is noteworthy that studies on women considered to be at higher risk of breast cancer, such as those with a family history or BRCA mutations, also report no perceivable increase in the risk of breast cancer with clomiphene.[165,166]

A 2021 meta-analysis reported no association between clomiphene exposure and **endometrial cancer** among subfertile women treated with clomiphene alone (OR = 1.47; 95% CI = 0.95–2.28) or in combination with human menopausal gonadotropins (hMG) (OR = 1.11; 95% CI = 0.65–1.87).[167] It should be noted that a former meta-analysis reported some increased risk of endometrial cancer with high dosage (>2,000 mg) (RR = 1.69, 95% CI = 1.07–2.68) and at a high number of cycles (RR = 1.69, 95% CI = 1.16–2.47). However, whether the association is due to the underlying conditions requiring clomiphene or the drug itself is uncertain.[168]

Overall, the available data are quite reassuring. **No causal relationship between ovulation-inducing drugs and ovarian, breast, or endometrial cancer has been established, but prolonged treatment with clomiphene should nonetheless be avoided, primarily because it has little hope of success**.

MONITORING RESPONSE TO TREATMENT WITH ANTIESTROGENS

The most effective and cost-efficient way to assess response to ovulation induction with oral antiestrogens has been extensively studied. A great wealth of data accumulated in cycles using clomiphene due to its decades-long use as an ovulation induction agent. More recently, studies with aromatase inhibitors also became available. Most findings from these studies, whether using clomiphene citrate or aromatase inhibitors, can be used interchangeably in making a decision regarding the best way to monitor response to treatment in individual patients.

The same methods used for diagnosis of anovulation can be used to evaluate the response to treatment. BBT recordings are simple and inexpensive but can become tedious over time. **A serum progesterone level greater than 3 ng/mL provides reliable evidence that ovulation has occurred[4,5] but must be timed appropriately for confident and correct interpretation.** Measuring the serum progesterone concentration 7 to 10 days after anticipated ovulation will minimize the risk of incorrect sampling, immediately after ovulation (occurring as late as cycle days 19–20 in cycles lasting up to 35 days) or before menses, when levels less than 3 ng/mL might be observed and misinterpreted.

Commercial test kits can detect the midcycle urinary LH surge and help determine not only whether ovulation occurred but when and to accurately define the length of the luteal phase.[169] In clomiphene-induced ovulatory cycles in anovulatory women, the LH surge typically occurs 5 to 12 days after treatment ends, most often on cycle day 16 or 17 when clomiphene is administered on days 5 to 9.[170] Ovulation generally occurs 14 to 26 hours after surge detection and almost always within 48 hours.[169] However, in clinical practice, both false-negative and false-positive results are relatively common.[171,172] An endometrial biopsy yielding secretory endometrium also implies recent ovulation,[173] but the associated costs and discomfort cannot be justified for that purpose alone.

Serial transvaginal ultrasonography can demonstrate the size and number of developing follicles, track endometrial growth, and provide presumptive evidence of ovulation[174,175] but is difficult to justify when less complicated and costly methods can provide the necessary information. Some advocate monitoring at least the first cycle of treatment to identify those who respond excessively.[176] A study comparing fecundity in clomiphene-induced cycles monitored with BBT, urinary LH excretion, or serial transvaginal ultrasonography found no clear advantage for any one of the three methods.[177]

Traditionally, when the serum progesterone concentration reveals persistent anovulation after clomiphene treatment, a progestin is prescribed (eg, medroxyprogesterone acetate, 5–10 mg daily for 5–7 days) to induce menses before the next cycle begins at a higher dosage. Although effective,

the sequence takes time, and several months may pass before a patient is proven unresponsive to clomiphene or letrozole. A "stair-step" treatment protocol is an alternative that can shorten the time required to achieve ovulation and to identify those who require different treatment. The regimen involves treatment with clomiphene (50 mg) or letrozole (2.5 mg) on cycle days 5 to 9 after a spontaneous or induced menses, ultrasonography on days 11 to 14, immediate treatment at the next higher-dose level (100 mg for clomiphene and 5 mg for letrozole) 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 for clomiphene and 7.5 mg for letrozole), and ultrasonography again 1 week later.[178] Stair-step protocol is associated with a shorter time to ovulation, a higher rate of ovulation, and similar pregnancy rates, albeit with higher incidence of mild side effects.[119,131,179]

Although there are few if any data to demonstrate its value, exogenous human chorionic gonadotropin (hCG) has commonly been used as a surrogate LH surge to trigger ovulation in clomiphene- and letrozole-induced cycles, particularly when IUI is performed, as in couples with unexplained infertility and those with a coexisting male factor. Adjuvant hCG treatment can be useful but has limited indications, distinct disadvantages, and potential consequences.

The question of when to administer hCG presents a dilemma. Although hCG is commonly administered when the lead follicle reaches 18 to 20 mm,[180] clinical studies indicate that the peak preovulatory follicular diameter in successful clomiphene-induced ovulatory cycles ranges between 18 and 30 mm (mean 25 mm).[170,181,182] Considering that the preovulatory follicle grows approximately 2 mm/d as it approaches maturity,[174,175] the corresponding interval may thus span up to 6 days. Normally, the preovulatory follicle triggers its own ovulatory stimulus at the peak of maturity, and the timing of the spontaneous LH surge is therefore always optimal, but that of hCG treatment can never be more than an educated guess.

When combined treatment with IUI is required, insemination is usually best performed on the day after detection of the spontaneous LH surge, using one of the now widely available commercial kits designed for the purpose, because ovulation generally occurs 14 to 26 hours after urinary LH surge detection.[169,183] However, the lower limit of LH detection is usually between 20 and 40 IU/L, and many ovulatory women exhibit peak LH levels below 40 IU/L or surges of brief duration that may escape detection[171]; false-negative results are therefore not uncommon and frustrating. 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. In such circumstances, we believe that hCG is best postponed until the preovulatory follicle reaches or exceeds 20 mm in mean diameter. Ovulation occurs 34 to 46 hours after hCG injection,[184] so IUI is usually performed approximately 36 hours later.

When the LH surge can be detected, adjuvant hCG treatment has no value and only adds unnecessary expense and inconvenience. A 2014 meta-analysis including two randomized controlled trials where anovulatory women undergoing ovulation induction with clomiphene citrate were given an ovulatory dose of hCG or not reported similar live birth, ovulation, pregnancy, and miscarriage rates.[185] Another meta-analysis including seven studies comparing hCG trigger with LH monitorization for timing IUI for women who were treated with clomiphene reported significantly lower pregnancy rates in the hCG group.[186] The idea that hCG may still serve to ensure or improve the quality of luteal function even if it is not required to trigger ovulation is also not supported by existing data. In spontaneous ovulatory cycles, hCG treatment superimposed on the endogenous LH surge has no effect on luteal phase duration or serum estrogen or progesterone concentrations[187]; the same is true in clomiphene or letrozole-induced ovulatory cycles.[188] In sum, adjuvant hCG treatment is best limited to those few women who require IUI and ovulate but cannot reliably detect a midcycle LH surge.

A pelvic ultrasound can be done to exclude residual ovarian cysts before each new treatment cycle began. It is still prudent to postpone further treatment when symptoms lead to discovery of a large cyst or grossly enlarged ovaries, but clinical studies and experience indicate that routine baseline physical examination or ultrasonography is unnecessary.[170] Nevertheless, regular contact should be maintained to review the progress of treatment and to ensure that any additional evaluation needed is accomplished efficiently.

Adjuvant and Combination Treatments

When letrozole or clomiphene fails to induce ovulation as the first-line treatment, some options can be considered before moving to the second-line treatments or IVF. These options include switching from clomiphene to letrozole, if the former was used as the first line. The addition of adjuvants to letrozole or clomiphene can also be considered as discussed later. Failure to respond to these less commonly employed treatment regimens is not a prerequisite prior to adopting second-line treatments. A choice among them is not entirely arbitrary but should consider specific elements of the patient's history, the results of laboratory evaluation, and observations in previous unsuccessful treatment cycles.

Clomiphene resistance describes women who do not ovulate in response to clomiphene treatment, not those who fail to conceive despite successful clomiphene-induced ovulation. In the latter group, additional evaluation is indicated to identify other potential coexisting infertility factors not already excluded. If or when that has been accomplished, persistent infertility is best regarded and treated as unexplained infertility (Chapter 28).

Although most properly selected women will ovulate in response to clomiphene treatment, many do not. As

the other first-line agent, letrozole is the obvious choice in clomiphene-resistant women, if it was not tried before. In an early proof of concept trial involving anovulatory clomiphene-resistant women, 9/12 of patients (75%) ovulated after treatment with letrozole (2.5 mg daily) and hCG (lead follicle >20 mm), three conceived (resulting in two singleton births), and normal endometrial proliferation was observed in all.[39] The 2022 systematic review reported significantly higher live birth rates with letrozole than clomiphene citrate in patients who did not ovulate or achieve a pregnancy in previous clomiphene-induced cycles (OR = 1.70; 1.00–2.93).[38] **Aromatase inhibitors can also be effective in anovulatory women who fail to ovulate in response to clomiphene treatment**.

Aromatase inhibitors might also be considered for women who respond to clomiphene but exhibit grossly poor endometrial proliferation. Indeed, letrozole is associated with a significantly thicker endometrium; however, the mean difference is small, at 1.45 mm (95% CI = 0.98–1.92).[46] **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**.

Metformin

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 are also typically more resistant to clomiphene treatment.

Recognition of the pathophysiologic importance of insulin resistance in PCOS stimulated intense interest in the use of insulin-sensitizing agents for the treatment of the disorder. Metformin is a biguanide oral insulin-sensitizing agent that acts primarily by reducing hepatic gluconeogenesis but that also decreases intestinal absorption of glucose and increases peripheral glucose uptake and utilization. The effects of metformin on insulin levels and sensitivity, androgen concentrations, and other metabolic and clinical measures are considered at length elsewhere in this text (Chapter 11); its adjunctive use as an ovulation-inducing agent is the focus here.

Treatment with metformin alone or with other insulin-sensitizing drugs (thiazolidinediones, D-chiro-inositol) can increase ovulation rates in some women with PCOS,[189–193] but there is no practical method for predicting those who will respond. The literature is populated mostly with small studies that include heterogeneous groups of patients, which vary in their BMI, insulin resistance (which has not been tested at all or tested using different methodologies), and prior treatment status (ie, clomiphene resistant or treatment naïve). Moreover, different treatment regimens with regard to timing and dose have been employed across these studies. Finally, live birth rate, the most important outcome of treatment, has not been reported in many. As can be expected, results from such studies are often heterogeneous, preventing reliable pooling of their data. As such, assessment of the role of metformin and other insulin sensitizers as adjuvants for ovulation induction is difficult, despite years of research.[193]

In the largest randomized trial, 626 women with PCOS from the United States with oligomenorrhea and hyperandrogenism and a mean BMI greater than 34 kg/m^2 were treated with clomiphene, metformin, or both.[146] Ovulation and live birth rates were significantly higher with clomiphene alone compared with metformin (49% vs 29% and 22.5% vs 7.2%, respectively; $P < 0.001$). Addition of metformin did not significantly improve outcomes compared to clomiphene alone.

A 2019 meta-analysis evaluated the effectiveness and safety of metformin in improving reproductive outcomes for women with PCOS undergoing ovulation induction and concluded that metformin is associated with significantly higher rates of ovulation, clinical pregnancy, and live birth rates compared to placebo or no treatment.[194] However, the analysis for live birth rate included four trials with a total of 435 women and demonstrated only a marginal benefit with an odds ratio of 1.59 (CI = 1.0–2.51). When metformin was compared to clomiphene, live birth rates were similar between the groups (OR = 0.70, CI = 0.48–1.01), but data were very low quality and were found to be inconclusive and inconsistent. In subgroup analysis by obesity status, data from the nonobese group showed a possible benefit from metformin for live birth (OR = 1.71, 95% CI = 1.00–2.94) and pregnancy (OR = 1.56, 95% CI = 1.06–2.29) rate and no clear difference in ovulation rates (OR = 0.80, 95% CI = 0.52–1.25). Surprisingly, obese women treated with metformin had a lower ovulation (OR = 0.29, 95% CI = 0.20–0.43), clinical pregnancy (OR = 0.34, 95% CI = 0.21–0.55), and live birth (OR = 0.30, 95% CI = 0.17–0.52) rate, compared to clomiphene. The same meta-analysis also concluded that combined treatment with metformin and clomiphene achieves higher ovulation (OR = 1.65, CI = 1.35–2.03) and pregnancy rates (OR = 1.62, CI = 1.32–1.99), compared to treatment with clomiphene alone.[194] There was no conclusive evidence that combined treatment with metformin and clomiphene can increase live birth rates over those achieved with clomiphene alone (OR = 1.27, CI = 0.98–1.65). The results for combined therapy did not vary across subgroups based on obesity status. The attempt in combining the two medications can be justified for women having few alternatives besides ovarian drilling or treatment with exogenous gonadotropins. Indeed, a sensitivity analysis based on six studies including clomiphene-resistant women showed a more pronounced increase in ovulation rate (OR = 4.97, CI = 2.46–10.03). However, clomiphene resistance was defined differently in all primary trials.

Limited evidence indicates that combined treatment with metformin and roziglitazone,[195] or with clomiphene and

rosiglitazone,[196] is no more effective than metformin alone. Combined with the safety alert issued by the FDA concerning a possible increased risk of ischemic cardiovascular events in patients receiving treatment with thiazolidinediones,[197] these data argue against their adjuvant use for ovulation induction.

In summary, combined treatment with metformin and clomiphene deserves consideration in women who prove to be clomiphene resistant. This recommendation is consistent with the 2023 International Evidence-Based Guideline for the assessment and management of PCOS, which suggested prioritizing clomiphene and metformin combination over clomiphene alone,[10] despite seemingly similar live birth rates with both treatment strategies.

Metformin treatment is commonly associated with gastrointestinal side effects, including nausea, vomiting, abdominal cramps, and diarrhea, that can be severe enough to limit the dose administered or require discontinuation of treatment.[199–202] Because side effects tend to be dose-dependent and diminish with time, it is usually best to begin with a low daily dose (500 mg), increasing gradually at weekly intervals to a daily dose of 1,500 to 2,000 mg, as tolerance allows. Lactic acidosis can be a rare complication of metformin treatment, although recent systematic reviews have questioned whether there is a true causal relationship.[203,204] Women at highest risk are those with chronic hypoxemic conditions related to cardiovascular, renal, hepatic, and pulmonary disease and advanced age.

Although some have advocated metformin treatment to reduce the increased risk of miscarriage in women with PCOS,[205–207] available data suggest otherwise. Miscarriage rates were similar between women treated with metformin compared to no treatment, metformin compared to clomiphene; between combination therapy compared to clomiphene.[194] Metformin treatment during pregnancy has also been advocated to reduce the risk for developing gestational diabetes and other pregnancy complications in women with PCOS.[208,209] In diabetic women, treatment with metformin during pregnancy has been associated with an increased prevalence of preeclampsia and increased perinatal mortality in some studies,[210] but not in others.[211,212] Therefore, although there is no evidence that metformin treatment during pregnancy is associated with any increased risk for major fetal malformations,[213] it is recommended to discontinue metformin by the end of the first trimester when it is used for ovulation induction.[214]

Glucocorticoids

Numerous studies have examined the efficacy of adjuvant treatment with glucocorticoids in clomiphene-resistant anovulatory women, and all have found that combined treatment with clomiphene and a glucocorticoid can successfully induce ovulation in many who fail to respond to clomiphene alone.[128,215–219] 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). Whereas some studies have suggested that combined treatment with clomiphene and glucocorticoids is most effective in women having elevated serum dehydroepiandrosterone sulfate (DHEA-S) concentrations,[215,216] others have found that treatment can also be effective in those with normal DHEA-S levels[217,219] and in unselected populations of clomiphene-resistant women.[128,218,220]

In the largest randomized trial involving more than 200 clomiphene-resistant anovulatory infertile women, over 80% of those receiving combined treatment with clomiphene (200 mg daily, cycle days 5–9) and dexamethasone (2 mg daily, cycle days 5–14) ovulated, compared to 20% of controls treated with clomiphene and placebo; the cumulative pregnancy rate in women receiving dexamethasone (40%) was 10-fold higher than in those who received placebo (4%).[219]

One retrospective study evaluated the effectiveness of glucocorticoids in letrozole-resistant PCOS patients.[221] Twenty-eight patients who did not ovulate with 7.5 mg/d letrozole in a stair-step approach were given an additional 5 days of 7.5 mg/d letrozole with 0.5 mg/d dexamethasone for 7 days. Thirty-five of 48 cycles resulted in ovulation with a 20% pregnancy rate per ovulatory cycle.

The mechanism of glucocorticoid action remains unclear but appears to involve more than simple androgen suppression. Other possibilities include direct effects on the developing oocyte and indirect effects on intrafollicular growth factors and cytokines, which may act synergistically with FSH.[222] Regardless, adjuvant treatment with glucocorticoids may be justified for three to six cycles when it is successful but should be promptly discontinued when it is not. There is no evidence that glucocorticoid treatment has any important side effects or risks when used in the doses and durations described.

Preliminary Suppressive Therapy

Considering that anovulation reflects a dysfunctional hypothalamic–pituitary–ovarian axis, it is reasonable to think that an interval of preliminary suppressive therapy might help restore harmony and ovulatory function, at least temporarily. The idea is consistent with clinical observations of a few normal menstrual cycles immediately following discontinuation of estrogen–progestin contraception in some women who previously exhibited abnormal menstrual patterns. Limited data suggest that a 2-month interval of continuous estrogen–progestin contraception can effectively suppress serum LH and androgen levels and that ovulation rates up to 70% and cumulative pregnancy rates over 50% can be achieved with clomiphene treatment immediately thereafter in women who were previously clomiphene resistant.[223,224]

A long-acting GnRH agonist, alone or in combination with an estrogen–progestin contraceptive, can be used for the same purpose. 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. Spontaneous resumption of ovulatory cycles can follow,[225–227] potentially eliminating even the need for clomiphene or letrozole treatment. GnRH antagonists would likely have a similar effect and allow the use of oral medication.

SECOND-LINE TREATMENTS

Laparoscopic Ovarian Drilling

Surgical treatments aimed at restoring ovulatory function in anovulatory infertile women date back to the classic bilateral ovarian wedge resection described originally by Stein and Leventhal in 1935.[228] The procedure understandably fell out of favor after the introduction of clomiphene citrate and gonadotropins for ovulation induction. Advances in laparoscopic surgery sparked renewed interest in the procedure, with ovarian "drilling" now representing the modern equivalent of the classical wedge resection and another treatment option for anovulatory women who are resistant to oral ovulation induction agents.

Several methods for ovarian drilling have been described, including electrocautery or laser vaporization (three to six sites per ovary, avoiding surfaces near the tubo-ovarian interface to minimize the risk for adhesions that might adversely affect ovum capture).[229–231] All are intended to cause focal destruction of the ovarian stroma in efforts to decrease both intraovarian and systemic androgen concentrations. There is no evidence for the superiority of any one method, but the most common technique involves electrocautery using a unipolar needle electrode insulated above the distal 1 to 2 cm. Unilateral ovarian drilling seems comparable with bilateral drilling for the majority of women, perhaps except for clomiphene-resistant patients.[232–234]

Postoperative serum concentrations of androstenedione and testosterone decrease, at least for a time,[235–238] and inhibin concentrations also decline.[239,240] Both changes likely contribute to an associated increase in FSH levels. As with the classical surgical procedure, the principal risk associated with laparoscopic ovarian drilling is postoperative adnexal adhesion formation that may decrease overall fertility, although the risk and severity of adhesions are lower[241–244]; second-look laparoscopy and adhesiolysis do not appear necessary or useful.[245,246] There is one report of unilateral ovarian atrophy after ovarian drilling with electrocautery[247]; however, the energy levels applied in that case were almost 40 times higher than the currently recommended dose. Whether ovarian drilling might adversely affect ovarian reserve and predispose to early menopause is controversial. Despite a significant decline in serum AMH levels and ovarian volume after drilling, 6 months after the procedure, postoperative levels were still higher than age- and BMI-matched ovulatory fertile women in a retrospective study[248]; other data indicate that reductive ovarian surgery, including ovarian wedge resection, increases risk for early menopause.[249]

In numerous uncontrolled observational studies, 40% to 90% of women have ovulated after laparoscopic ovarian drilling, and approximately half of those have conceived.[229–231,242,250] In truly clomiphene-resistant women, ovarian drilling can improve clomiphene sensitivity or response to exogenous gonadotropins when it does not restore spontaneous ovulatory cycles.[251] When considering laparoscopic ovarian drilling as a treatment option in clomiphene-resistant anovulatory infertile women, the most relevant data derive from randomized controlled trials comparing surgical treatment with ovulation induction using exogenous gonadotropins.[245,252,253] A 2022 systematic review and meta-analysis including 38 trials found no evidence of a difference in live birth (OR = 0.87, CI = 0.56–1.36); however, this was based on a subgroup analysis of four trials. Overall, when compared with all other alternatives tested— that is, clomiphene and metformin, clomiphene and tamoxifen, or letrozole, laparoscopic ovarian drilling was associated with a slight decline in live birth rates (OR = 0.71, 95% CI = 0.54–0.92).[234] Yet a pooled analysis of nine trials comparing laparoscopic ovarian drilling and gonadotropins showed similar clinical pregnancy rates (OR = 1.01, 95% CI = 0.74–1.36). However, as might be expected, laparoscopic ovarian drilling yields far fewer multiple pregnancies than gonadotropin treatment (1.1% vs 9.5%; OR = 0.22, CI = 0.1–0.46); the miscarriage rates associated with surgical and medical treatment are comparable.[234]

The ideal candidates for ovarian drilling are women who are not obese and who have no other infertility factors. The procedure is often unsuccessful in obese women (BMI >30 kg/m^2),[254,255] and whereas over 80% of women can be expected to conceive after surgery when clomiphene-resistant anovulation is the sole cause of infertility,[254,256] only 15% to 30% achieve pregnancy when there is a coexisting tubal, male, or other infertility factors.[237,256]

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 and/or assisted reproduction.

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 decades. 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.[257,258]

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. Originally, the urinary source was a single convent in Italy, but later, collections were expanded to a number of centers in other countries.[259] Urinary menotropins also contain small but measurable and varying amounts of hCG, most of it added intentionally during the manufacturing process to provide the appropriate amount of LH activity.[260] Clinical use of hMG began in 1950, but the clinical trials did not begin until after 1960.[261,262] Relatively crude gonadotropin extracts like traditional hMG also contained significant amounts of uncharacterized urinary protein that may be antigenic.[263] Contemporary hMG preparations are more highly purified than in the past and can be administered subcutaneously.[264]

More purified urinary FSH preparations (urofollitropin) were developed by removing LH from urinary extracts using immunoaffinity columns containing polyclonal anti-hCG antibodies.[265] Early preparations of purified urinary FSH (75 IU) contained less than 1 IU LH, but a considerable amount of other urinary protein still required intramuscular administration. Further purification using monoclonal antibodies specific for FSH yielded a preparation containing less than 0.1 IU LH and less than 5% unidentified protein. The even more highly purified products now in use contain less than 0.001 IU LH and very low levels of urinary protein and can be administered subcutaneously.

The in vitro production of recombinant human FSH was achieved through genetic engineering. Briefly summarized, the process involves introduction of the genes encoding the α and β-FSH subunits into the genome of a Chinese hamster ovary cell line, which then synthesizes and secretes a glycosylated bioactive dimeric FSH that is purified by immunochromatography using a specific anti-FSH monoclonal antibody. Recombinant FSH preparations contain less acidic FSH isoforms that have a shorter half-life than those derived from human urine but that stimulate estrogen secretion as or even more efficiently.[266] The advantages of recombinant FSH preparations include the absence of urinary protein, more consistent supply, and less batch-to-batch variation in biologic activity. The two original recombinant FSH preparations are marketed as follitropin α and follitropin β. They are both structurally identical to native FSH and contain one α and one β glycoprotein chain, but the posttranslational glycosylation process and purification procedures for the two are different.[267] Despite the subtle differences in structure, they are functionally the same.

Recombinant technology has also been used to create a new chimeric gene containing the coding sequences of the FSH β-subunit and the C-terminal peptide of the hCG β-subunit (containing additional glycosylation sites). Coexpression of the α-subunit and the chimeric FSH β-subunit produces a new molecule called corifollitropin α, which has a prolonged half-life and enhanced in vivo bioactivity compared with wild-type FSH. Early studies in women suppressed by treatment with a long-acting GnRH agonist have confirmed the extended half-life of the compound, and clinical trials have demonstrated that corifollitropin α can induce and sustain multifollicular growth for a week in women receiving ovarian stimulation for IVF. Corifollitropin α provides the means for simpler and more convenient treatment compared with conventional treatment regimens involving daily injections with FSH and GnRH agonist. However, this recombinant gonadotropin with extended half-life is designed to induce multifollicular development, and it is not well suited for ovulation induction where unifollicular development is the objective.[268,269] This product is widely available outside of the United States.

Subsequently, follitropin Δ, the first recombinant FSH protein that is expressed in a human cell line (PER.C6), has become available for use in ART. Follitropin Δ has the same amino acid FSH sequence as follitropin α, but the glycosylation patterns of the two molecules are different. Follitropin Δ has distinct pharmacokinetics and pharmacodynamics, with higher exposure and lower serum clearance than follitropin α.[270] In patients undergoing ovarian stimulation for ART, a recent meta-analysis showed **that follitropin Δ results in no difference in live birth rates or in the incidence of moderate or severe OHSS compared with follitropin α/β.**[271] **Similarly to corifollitropin α, follitropin Δ is also licensed for use in ART cycles aiming at multifollicular development and is currently not suitable for induction of monofollicular development.**

Recently, biosimilar recombinant FSH preparations became available. While the primary structures of these molecules are identical, differences between glycosylation

occupancy, antennarity, and sialylation can differ between them.[272] Whether these differences have implications for effectiveness needs to be determined.

A recombinant form of human LH having physicochemical, immunologic, and biologic activities comparable to those of human pituitary LH is also available, supplied in vials with syringes designed to deliver 75 IU.[273–275] Combined use of recombinant LH and FSH (or hMG) helps promote follicular development in women with hypogonadotropic hypogonadism who have a profound LH deficiency[276] but otherwise does not appear necessary.[277,278]

Traditionally, and still today, by virtue of its structural and biologic similarity to LH, hCG is used to simulate the LH surge and induce ovulation in gonadotropin-stimulated cycles once follicle development reaches maturity. LH/hCG promotes the final stages of follicular and oocyte maturation (from prophase I, the germinal vesicle stage, through meiotic maturation and metaphase II), which requires approximately 36 hours to complete, and ovulation generally occurs approximately 4 hours later. A recombinant form of hCG, produced using techniques similar to those described earlier for recombinant FSH,[279] has widely replaced hCG extracted from human pregnancy urine and placental tissue. Studies indicate that 250 μg of the recombinant product yields results comparable to those achieved with 5,000 to 10,000 IU of urinary hCG.[279–284]

The availability of recombinant FSH, LH, and hCG has done much to further our understanding of the specific actions of individual gonadotropins in follicular development and oocyte maturation.[285–287] Recombinant gonadotropins provide the capability to tailor ovarian stimulation regimens to the needs of the individual woman in an effort to optimize oocyte quality and cycle fecundity. Unfortunately, we still do not yet have the ability to accurately define what those specific needs are. It may someday be possible to design combinations of recombinant gonadotropins that will vary with the hormonal milieu of the individual, perhaps even within a cycle of stimulation, but for the present, our existing more generic treatment regimens must suffice.

Indications for Gonadotropin Treatment

Any discussion of ovulation induction with exogenous gonadotropins must first define the different clinical situations in which they may be used because the choice of gonadotropin preparation and treatment regimen vary with the type of ovulatory disturbance.

Hypogonadotropic Hypogonadism

Women with hypogonadotropic hypogonadism (hypothalamic amenorrhea, WHO Group I) are the most obvious candidates for ovulation induction with exogenous gonadotropins. Oral antiestrogens are typically ineffective because their actions require an intact and functional hypothalamic–pituitary–ovarian axis. In a sense, gonadotropin therapy in women with hypogonadotropic hypogonadism may be viewed as hormone therapy intended to stimulate normal folliculogenesis and ovulation once fertility becomes a priority.

In women with hypogonadotropic hypogonadism, ovulation induction regimen must contain both FSH and LH activity. Although follicular growth and oocyte maturation can be successfully stimulated with FSH alone,[288] LH is also required for normal steroidogenesis, luteinization, and ovulation[276,289–292]; endogenous LH levels are typically inadequate. Traditionally, menotropins are the drug of choice. One small randomized controlled trial including 35 women with hypogonadotropic hypogonadism compared 150 IU/d of menotropin with a combination of 150 IU/d of rFSH and 75 IU/d of rLH.[293] Following three cycles, ovulation rates were similar with hMG and rFSH/rLH combination (88% vs 70%), but women receiving rFSH/rLH combination had higher pregnancy rates (23.3% vs 55.6%). The study has multiple limitations, that is, lack of sample size calculation, blinding, unclear allocation concealment, and inclusion of each woman with more than one cycle, and as such should be regarded as providing low-quality evidence. The multiple pregnancy rate was 5/25 (20%) in this study, using a starting dosage of 150 IU/d. **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. The objective, unifollicular ovulation, must be kept clearly in mind because hypogonadal women are otherwise normally fertile and at high risk for multiple pregnancy.**

The quality of luteal function after exogenous gonadotropin-induced ovulation in women with hypogonadotropic hypogonadism merits specific consideration. **Although not always required,[294] luteal phase support with supplemental hCG (2,000–2,500 IU every 3–4 days)[295] or progesterone[296] generally is needed to compensate for low levels of endogenous LH secretion that can prove insufficient to support normal luteal function**. Premenstrual spotting or a grossly short luteal phase suggests the possibility. Some have observed that supplemental hCG treatment can improve cycle fecundity,[295,297] but its value has not been conclusively demonstrated, probably because endogenous LH levels vary in women with hypogonadotropic hypogonadism and only those with profoundly low LH concentrations (approximately <3 IU/L) may benefit from luteal phase support.[276,298] Because supplemental hCG also increases the risk for OHSS, treatment with hCG is best reserved for women who exhibit evidence of poor luteal function after ovulation induction; empiric treatment with progesterone is the obvious alternative.

Some women with secondary hypogonadotropic hypogonadism related to hyperprolactinemia become candidates for

treatment with exogenous gonadotropins because they cannot tolerate dopamine agonist therapy. Consequently, it is important to know that hyperprolactinemia has no apparent adverse effect on the response to exogenous gonadotropins.[299]

Oral Antiestrogen–Resistant Anovulation

When oral antiestrogen treatments such as clomiphene or aromatase inhibitors fail to achieve ovulation, exogenous gonadotropins are an obvious option. Any of the alternative and adjuvant therapies discussed previously might also be chosen in efforts to avoid the costs, logistical demands, and risks of gonadotropin treatment, but failure with other such strategies is not a prerequisite for the use of gonadotropins.

In women with hypogonadotropic hypogonadism, endogenous gonadotropin secretion is extremely low, and menotropin (hMG) therapy provides the necessary gonadotropin stimulation. In contrast, serum gonadotropin concentrations in oral antiestrogen–resistant anovulatory women with PCOS (WHO Group II) are generally normal and, in many, LH levels are relatively high. In this population of women, treatment with exogenous gonadotropins is superimposed on a background of erratic endogenous FSH and LH secretion. Purified or recombinant FSH preparations offer a theoretical advantage over conventional menotropins because they avoid the risk of amplifying endogenous LH hypersecretion. However, in practice, there is no evidence that purified or recombinant FSH has greater efficacy than hMG, and either may be used. Numerous randomized controlled trials have compared urinary FSH, recombinant FSH, and hMG for ovulation induction in clomiphene-resistant anovulatory women with PCOS. A meta-analysis including 15 such trials found no differences in the ovulation rate, pregnancy rate, miscarriage rate, multiple pregnancy rate, or incidence of OHSS.[300]

Like women with hypogonadotropic hypogonadism, clomiphene-resistant anovulatory women with PCOS generally respond to relatively low doses of gonadotropin stimulation. **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**. Treatment again must be carefully monitored and frequently requires small adjustments. Unifollicular ovulation remains the objective but can often be difficult to achieve. The risk for multiple pregnancy is high and the risk of ovarian hyperstimulation is greater than in hypogonadal women.

Luteal phase support is seldom necessary after gonadotropin-induced ovulation in women with PCOS because endogenous LH levels are typically more than sufficient to support normal luteal function. However, in women also receiving treatment with a GnRH agonist to suppress endogenous gonadotropin secretion (discussed later)[301] and in others who may exhibit evidence of poor luteal function after otherwise successful ovulation induction, luteal phase support should generally be provided; considering the higher risk of OHSS associated with hCG, progesterone therapy is preferable.[259,302]

Unexplained Infertility

Exogenous gonadotropins can be used intentionally to stimulate the development and ovulation of more than one mature ovum in efforts to increase cycle fecundity in older subfertile women and those with otherwise unexplained infertility; superovulation is most effective when combined with timely IUI (Chapter 28). In this context, higher initial daily doses of exogenous gonadotropins are typically employed,[301] and because such women already ovulate normally and have no endocrinopathy, any of the available gonadotropin preparations can be used. Although superovulation is intended, careful monitoring is still required to avoid obviously excessive stimulation. The risk of multiple pregnancy is even greater than with ovulation induction in clomiphene-resistant anovulatory women, not surprising considering that superovulation is specifically intended. A 2017 meta-analysis including 11 trials found that luteal support with vaginal progesterone increased clinical pregnancy (RR = 1.56, 95% CI = 1.21–2.02) and live birth rates (RR = 1.77; 95% CI = 1.30–2.42) significantly.[303]

Gonadotropin Treatment Regimens

Careful counseling and instruction are essential to the success of gonadotropin treatment. Couples must be thoroughly familiar with the medications prescribed; the methods for their preparation and injection; the need for frequent office visits to monitor response and reliable lines of communication; and the costs, prognosis, and risks associated with exogenous gonadotropin therapy.

Early retrospective studies established that daily treatment, frequently adjusted according to the clinical response, is the most effective treatment regimen.[304,305] The dose and duration of gonadotropin treatment required to induce ovulation successfully vary among women, sometimes even among cycles within women, and must be determined empirically. Whereas many women are extremely sensitive to relatively low doses of gonadotropins (75 IU daily), others require substantially greater stimulation (300–450 IU daily). Although there is a direct relationship between body weight and dose requirement, the response threshold for a specific individual cannot be predicted reliably, even in the obese.[306] The treatment plan must also consider the intended goal, unifollicular ovulation, or purposeful superovulation. **Safe and effective ovulation induction with exogenous gonadotropins depends heavily on the experience and clinical judgment of the treating clinician**.

In both women with hypogonadotropic hypogonadism (WHO Group I) and those with oral antiestrogen–resistant anovulation (WHO Group II), initial attempts to induce ovulation generally should begin with a low daily dose

(75 IU daily) in a **"step-up" treatment regimen** designed to define the effective threshold of response. After 4 to 7 days of stimulation, transvaginal ultrasonography, with or without a serum estradiol level, provides the first measure of response. Thereafter, the dose of gonadotropins may be maintained or increased, as indicated. Once there is a dominant follicle and/or serum estradiol level begins to rise the frequency of evaluation increases to every 1 to 2 days. When the mean diameter of the lead follicle reaches 16 to 18 mm, hCG is administered to trigger ovum release; ovulation may generally be expected to occur approximately 36 to 48 hours later. In subsequent stimulation cycles, the initial dose of gonadotropins should consider the response threshold and pattern of follicular development observed in previous cycles.

Because women with PCOS are often exquisitely sensitive to low doses of gonadotropin stimulation, early and frequent monitoring is generally wise. Such women typically have a larger number of small antral follicles (recruitable follicles) poised to respond to FSH stimulation.[307] Ovarian hyperstimulation, higher risks of multiple pregnancy, and the expense and frustration associated with canceled cycles can usually be avoided by using a **"low-slow" treatment regimen** involving low doses (37.5–75 IU daily), small increments, and a longer duration of stimulation.[308–312] Although most gonadotropin stimulations span an interval of 7 to 12 days, low-dose stimulations in women with PCOS can take longer. Insulin-resistant women may be less sensitive to gonadotropin stimulation than those who have normal insulin response.[313] In some such women, metformin treatment before and during gonadotropin stimulation can help to improve response, limit the number of smaller developing ovarian follicles,[314] and reduce the likelihood of cycle cancellation for excessive stimulation.[202]

The alternative **"step-down" treatment regimen** is designed to more closely approximate the pattern of serum FSH concentrations observed in spontaneous ovulatory cycles. Treatment begins with a higher dose (150–225 IU daily) and decreases gradually thereafter in an effort to promote continued development of only the more sensitive dominant follicle while withdrawing support from the less sensitive smaller follicles in the cohort. Considering that many anovulatory women are quite sensitive to low doses of exogenous gonadotropin stimulation, the step-down method is generally best applied only after the response threshold has been established in one or more previous stimulation cycles. However, the 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.

Recognition of the role that LH plays in the latter stages of follicular development, when FSH levels decline steadily, has suggested other approaches to ovulation induction with gonadotropins that may have particular value for women with PCOS, in whom standard treatment regimens too often result in multifollicular development and ovarian hyperstimulation. Although the selected dominant follicle is more sensitive to FSH than smaller follicles in the cohort, by virtue of its greater granulosa cell mass, FSH receptor content, and advanced microvascular development, the final stages of maturation are equally, if not more, dependent on low levels of LH.[286,287,315,316] Whereas LH stimulates the theca (to produce androgens as substrate for estrogen synthesis) in all follicles, it also stimulates granulosa cells in larger follicles, via LH receptors induced by FSH and estrogen.[317–320] LH thus becomes the principal stimulus for the final stages of follicular maturation, while declining concentrations of FSH starve the smaller, more FSH-dependent follicles into atresia.

Low doses of hCG[321] or recombinant LH[276] can selectively promote larger follicle growth while also hastening the regression of smaller follicles. To a limited extent, step-down gonadotropin treatment regimens, in which the amounts of FSH stimulation are gradually reduced, have exploited this phenomenon. The practice of "coasting," wherein FSH stimulation is withdrawn altogether during the latter stages of follicle development, does so even more. In the latter instance, the largest follicles generally continue to function, most likely because their LH receptor expression renders them receptive to prevailing low concentrations of endogenous LH,[322] whereas estrogen levels plateau or decline, and smaller follicles arrest or begin to regress.[323,324] Continuing stimulation with low doses of hCG or recombinant LH after decreasing or discontinuing FSH treatment takes fullest advantage of the differential actions of LH in larger and smaller follicles by supporting continued development of the former[286,316] and selectively excluding the latter,[315,325] both by withdrawing FSH and by directly stimulating increased intrafollicular androgen concentrations.[326]

In women with hypogonadotropic hypogonadism or PCOS, recombinant LH treatment (225–450 IU daily) during the latter stages of follicular development can decrease the number of developing follicles.[325] In GnRH agonist–suppressed normal ovulatory women treated with 150 IU FSH daily for 7 days, a variety of treatment regimens involving combinations of decreasing FSH (50, 25, 0 IU) and increasing hCG (50, 100, 200 IU) have been observed to support the development of larger follicles and to speed the regression of smaller follicles.[327] Whereas either hCG or recombinant LH might be used, the longer half-life of hCG may help to provide a more stable level of LH activity between daily injections.[327] Interestingly, low-dose hCG treatment during the late stages of follicular development appears to have little effect on circulating progesterone or testosterone concentrations, at least in normal women, suggesting that the risk of causing premature luteinization or other adverse effects is low. By inducing the regression of smaller follicles, such treatment may also help to reduce the risk of ovarian hyperstimulation associated with exogenous gonadotropin therapy. The optimum sequence and relative amounts of FSH and LH/hCG to administer have not been defined and likely

vary with the goals of treatment and the endocrinology of individual women.[325,328,329]

Some clomiphene-resistant anovulatory women can benefit from **sequential treatment with clomiphene and gonadotropins**. The typical cycle involves a standard course of clomiphene treatment (50–100 mg daily), followed by low-dose FSH or hMG (75 IU daily) beginning on the last day of clomiphene therapy or the next day; treatment is monitored and individualized thereafter as in standard gonadotropin-stimulated cycles. In most,[330–332] but not all studies,[333] cycle fecundity in sequential treatment cycles has approached or equaled that achieved with gonadotropins alone. In all, the dose and duration of gonadotropin therapy and the associated costs of monitoring were decreased significantly by 50% or more. Logically, sequential therapy is generally useful only in women who respond to clomiphene, at least to some extent. Otherwise, treatment does not effectively begin until gonadotropin therapy starts.

The elevated endogenous LH levels in many clomiphene-resistant anovulatory women with PCOS predispose to premature follicular luteinization during exogenous gonadotropin stimulation[301,334,335] and have been implicated as a contributing factor in the higher incidence of spontaneous miscarriage observed in those who conceive.[336–339] **Adjuvant treatment with a long-acting GnRH agonist** before exogenous gonadotropin stimulation suppresses endogenous LH levels and continued GnRH agonist treatment during gonadotropin stimulation can prevent premature luteinization.[301,335,340] The risk that residual GnRH agonist–induced LH suppression might result in poor luteal function after ovulation induction appears more theoretical than real.[341]

Nonrandomized clinical trials have suggested that combined treatment with a GnRH agonist and exogenous gonadotropins can improve cycle fecundity in clomiphene-resistant anovulatory women.[335,340,342] However, randomized controlled trials comparing combined treatment with a GnRH agonist and exogenous gonadotropins to stimulation with gonadotropins alone have failed to demonstrate any differences in cycle fecundity or the incidence of ovarian hyperstimulation.[301,341,343,344] Adjuvant GnRH agonist therapy also has no proven benefits for unselected subfertile women receiving gonadotropins to induce superovulation[345] and may even increase the amount and duration of gonadotropin stimulation required, at least in some.[301,343] **Although combined treatment with a GnRH agonist/antagonist and exogenous gonadotropins is the established standard for ovarian stimulation in IVF cycles, it has no proven advantage over gonadotropin stimulation alone for ovulation induction**.

Monitoring Gonadotropin Therapy

To achieve ovulation but also avoid ovarian hyperstimulation and minimize the risk for multiple pregnancy, gonadotropin therapy must be carefully monitored with serial serum estradiol measurements and transvaginal ultrasonography. In effect, the clinician replaces the hypothalamus and pituitary in the feedback loop during treatment with exogenous gonadotropins. The chosen dose is administered; the ovarian response is measured and judged according to needs and expectations; and the gonadotropin dose is maintained or adjusted, reevaluated, and readjusted as needed. Under normal circumstances, the hypothalamic–pituitary–ovarian axis performs the same task, constantly and repeatedly refining and coordinating the level of gonadotropin stimulation with the ovarian response. By contrast, the clinician can make no more than one such assessment daily, at most. Not surprisingly, the results achieved are relatively crude by comparison.

Serum Estradiol Levels

To best reflect the ovarian response to stimulation and provide for an efficient flow of information, gonadotropins are generally administered in the evening, typically between 5:00 and 8:00 PM, and serum estradiol measurements are obtained early in the morning. Results are usually available for review by midday, and new instructions regarding the dose and duration of treatment and the next scheduled evaluation are communicated before the evening dose of that day is due. In general, follicles less than approximately 10 mm in mean diameter produce relatively little measurable estrogen, and larger follicles secrete progressively more as they grow and approach maturity. Usually, estradiol levels rise at a constant exponential pace, doubling approximately every 2 to 3 days over the days before peak follicular development is achieved. A shallower or steeper slope of increase suggests the need to increase or decrease the level of stimulation.

In the natural ovulatory cycle, estradiol levels peak between 200 and 400 pg/mL just before the LH surge. Comparable levels of estradiol should be expected in gonadotropin-stimulated cycles, for each mature follicle observed. Clinical judgments must also consider the number and size of smaller follicles and their lesser but collective contributions to the serum estradiol concentration. **Not surprisingly, cycle fecundability increases with serum estradiol levels; unfortunately, so do the risks of multiple pregnancy and ovarian hyperstimulation. With existing gonadotropin stimulation regimens, pregnancies are uncommon at levels below 200 pg/mL.**[346–350]

Ultrasonography

Ovarian ultrasonography defines the size and number of follicles contributing to the measured estradiol level. In the normal ovulatory cycle, the recruited cohort of antral follicles can be identified by cycle days 5 to 7, and the dominant follicle emerges by days 8 to 12, grows approximately 1 to

3 mm/d thereafter (most rapidly over the 1–2 days immediately preceding ovulation), and measures approximately 20 to 24 mm in mean diameter when the LH surge occurs; lesser follicles rarely exceed approximately 14 mm in diameter.[174,175] In 5% to 10% of spontaneous cycles, two preovulatory follicles may develop.

In exogenous gonadotropin-stimulated cycles, dominant follicles exhibit a similar linear growth pattern but reach maturity at a smaller mean diameter and over a wider range of sizes. **The likelihood of ovulation increases with follicular diameter.** As judged by serial ultrasonography after hCG administration, follicles 14 mm and smaller occasionally ovulate, but about 40% of those measuring 15 to 16 mm, 70% measuring 17 to 18 mm, 80% measuring 19 to 20 mm in size, and virtually all larger follicles will ovulate.[351] The larger range of follicle size at maturity complicates clinical judgments. **The risk of multiple gestation rises with the number of follicles likely to ovulate. Consequently, hCG should generally not be administered when the risk of multiple ovulation is high and the goal of treatment is monofollicular ovulation.** A large number of intermediate and small follicles also increase the risk for OHSS.[352]

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. Higher cycle fecundability and cumulative pregnancy rates have been observed in consecutive treatment cycles than with alternating cycles of stimulation and no treatment.[353,354] When baseline ultrasonography reveals one or more residual ovarian cysts, it is usually best to briefly postpone further treatment. Stimulation cycles in the presence of ovarian cysts are less often successful,[355] possibly because newly emerging follicles can be difficult to distinguish from regressing cystic follicles, leading to errors in interpretation. Although many believe that suppressive therapy with a cycle of oral contraceptives helps to speed the regression of residual ovarian cysts, there is no evidence that such treatment is more successful than observation alone.

Studies of endometrial growth in exogenous gonadotropin-induced ovulatory cycles suggest that ultrasonographic measurements of endometrial thickness may also have some value, but this is questionable.[356] A 2017 systematic review and meta-analysis, including 23 studies and 3,846 women undergoing ovarian stimulation and IUI, report similar endometrial thickness between women who achieved a pregnancy and who did not.[357]

Results of Gonadotropin Treatment

Although exogenous gonadotropin therapy can successfully induce ovulation in over 90% of women with either hypogonadotropic hypogonadism (WHO Group I) or clomiphene-resistant anovulation (WHO Group II), the pregnancy rates achieved in the two populations differ significantly.[252,358–360] **In women with hypogonadotropic hypogonadism, cycle fecundity is approximately 25%, equal to or even greater than that observed in normal fertile women; cumulative pregnancy rates after up to six cycles of gonadotropin stimulation approach 90%. By comparison, cycle fecundity is significantly lower in clomiphene-resistant anovulatory women. Overall, cycle fecundity ranges between 5% and 15%, and cumulative conception rates range between 30% and 60%; within the group, those with hyperandrogenic chronic anovulation have the poorest prognosis**.[252,358–361] Although results generally do not vary with the duration of infertility or parity, pregnancy rates are significantly lower in women 35 years or older than in younger women.[360,361]

The incidence of multifetal gestation is greatly increased in pregnancies resulting from exogenous gonadotropin-induced ovulation, even in anovulatory women where the goal of treatment is unifollicular ovulation. Whereas approximately 1 in 80 (1.25%) spontaneous pregnancies and 5% to 8% of those following clomiphene treatment are multiples,[135–137,362] in anovulatory women undergoing gonadotropin-induced ovulation, the rate of multiple pregnancy is reported to be approximately 15%.[358,360] Not surprisingly, the incidence of multiple gestation among subfertile women receiving gonadotropin stimulation for intentional superovulation is even higher and may approach 30%, with nearly one-third being high-order multiple pregnancies (approximately 10% overall).[363] The higher frequency of multiple pregnancy after gonadotropin treatment obviously results from inadvertent or intentional multiple ovulation. However, when the cycle is canceled by withholding the hCG injection and abstinence from intercourse, or selective follicular aspiration is undertaken in the presence of multifollicular growth (ie, ≥3 follicles ≥14–16 mm), multiple pregnancy rates are decreased to 4.4% and 6.5%, while pregnancy rates are maintained between 10% and 14% per stimulation cycle.[364,365] **It is prudent to take necessary measures, including cycle cancellation, to prevent multiple pregnancy in women undergoing ovarian stimulation since they are usually young and have good ovarian reserve, both of which are assuring for a better adjusted response in a subsequent cycle. The complications and costs of high-order multiple pregnancies would be significantly more than the cost and inconvenience associated with forfeited gonadotropin injections**. Interestingly, however, there is some evidence to suggest that the normal frequency of monozygotic twinning (0.3–0.4%)[362] may be increased as much as 3-fold in pregnancy resulting from ovulation induction with exogenous gonadotropins.[366]

The overall incidence of spontaneous miscarriage in gonadotropin-induced conception cycles is approximately 20% to 25%,[242,358–360] moderately higher than is generally observed (15%). A higher prevalence of advanced maternal age and obesity among women who receive gonadotropin therapy appear to contribute to the higher incidence,[367] but

miscarriage rates also differ with the indication for treatment. In general, miscarriage rates are low in those with hypogonadotropic hypogonadism and significantly higher in clomiphene-resistant anovulatory women,[358–360] but not in all studies.[252] **As with clomiphene, there is no evidence that gonadotropin therapy is associated with any increased prevalence of congenital anomalies**.[368]

Risks of Gonadotropin Treatment

In addition to the obviously greater costs and logistical demands involved, exogenous gonadotropin treatment also poses significant risks. Chief among these are the risks of multiple pregnancy and OHSS. Neither can be avoided altogether, even by the most experienced clinician, but both risks can be reduced with careful management. As with any complicated form of treatment having significant intrinsic risks, thorough pretreatment counseling is essential.

Multiple Pregnancy

Twin births rose by 76% between 1980 and 2009 (from 18.9 to 33.2 per 1,000 births), plateaued between 2009 and 2012, rose to a record high of 33.9 per 1,000 births in 2014, and have been declining since, reaching 31.22 per 1,000 births in 2022.[369] Births of triplet and higher-order multiple pregnancies more than quadrupled between 1980 and 1998 but declined to 78.9 per 100,000 total births in 2022, reaching the lowest level in more than two decades.[369] About 20% of the increase in multiple births, overwhelmingly twins, can be attributed to advanced maternal age and the societal trend toward older age at childbearing (older women are more likely to conceive a multiple pregnancy). The remainder, including almost all high-order multifetal gestations, result directly from the use of exogenous gonadotropins for ovulation induction, superovulation, and ART.[370] The number of multiple pregnancies *conceived* is even greater because spontaneous and intentional multifetal pregnancy reductions do not appear in birth statistics.

Multiple pregnancies are high-risk pregnancies at any age because they are frequently complicated by preterm delivery, low birth weight, gestational diabetes, and preeclampsia and associated with high infant morbidity and mortality.[371–374] Their clinical management often requires extended hospitalization, cesarean delivery, and neonatal intensive care; the associated health care costs are enormous, for both individual couples and society. **In fact, evidence indicates that the combined costs associated with multifetal pregnancies and their complications exceed those of all the treatments from which they derive**.[375,376] The less obvious social "costs" associated with multiple births are also high and include increased levels of parental stress, a higher incidence of maternal depression and child neglect or abuse, and a greater likelihood of behavioral problems among siblings.[377] Several factors contribute to the risks of multiple pregnancy associated with exogenous gonadotropin therapy. Although much of the attention in recent years has focused on embryo transfer practices in ART centers, less than half of all treatment-related multiple pregnancies results from IVF.[378,379] The majority of multiple pregnancies, and the focus here, result from exogenous gonadotropin therapy for ovulation induction and superovulation.

Exogenous gonadotropins are an essential part of the therapeutic armamentarium with specific indications, and very real risks, including multiple pregnancy. **Gonadotropins should be reserved for ovulation induction in infertile women with hypogonadotropic hypogonadism and oral antiestrogen–resistant anovulation and for intentional superovulation in subfertile women and those with otherwise unexplained infertility, including women who ovulate in response to treatment but ultimately fail to conceive**. If unnecessary risk is to be avoided, the objective (unifollicular ovulation vs intentional superovulation) must be kept clearly in mind; there is seldom an indication for superovulation in anovulatory but presumably otherwise fertile women.

Many infertile women seek the most aggressive forms of treatment simply because they offer the greatest chance of success, finding it hard to believe that any treatment could be *too* successful. Even those committed to avoiding excessive risks can find it very difficult to accept recommendations to cancel a treatment cycle, thereby forfeiting their investment of time and resources.[380] Financial pressures weigh heavily on the minds of even the most risk-averse patients and physicians. Cost considerations color perspectives and influence treatment decisions, tempting all involved to accept risks they would otherwise choose to avoid and may later regret. Some childless couples may actually hope for twins, but most are more circumspect when thoroughly counseled,[381] and none should want triplets or more.

Multiple pregnancy is an intrinsic risk of intentional superovulation. In IVF cycles, the risk of multiple pregnancy relates to the number of embryos transferred, which the physician and patient control. However, the number of embryos that may implant is difficult to predict or control in superovulation cycles. Logically, risk might be reduced if ovulation was simply not triggered when the estradiol level or number of maturing follicles was excessive. Unfortunately, the response parameters that offer the best balance between increased cycle fecundity and the risks of multiple pregnancy and ovarian hyperstimulation have not been clearly defined and remain controversial.[382,383] **The risk of multiple pregnancy increases with serum estradiol concentrations, with the total number of developing ovarian follicles, and with decreasing maternal age but does not correlate well with the number of larger preovulatory follicles**.[87,363,384–387] Some have suggested varying cycle cancellation criteria that might be used to guide treatment and limit risks of multiple pregnancies.[363,384,385] Whereas there is little doubt that withholding hCG when serum estradiol levels rise above approximately 900 to 1,400 pg/mL

or ultrasonography reveals more than four to six follicles larger than 10 to 14 mm, or more than three follicles of 15 mm or more, application of such criteria would also dictate cancellation up to one-third of all exogenous gonadotropin-stimulated cycles.[133,387]

With relatively few exceptions among anovulatory women, exogenous gonadotropin therapy can be refined to achieve unifollicular ovulation with limited risk of multiple pregnancy and minimal risk of high-order multiple pregnancy. Conservative superovulation strategies can likely reduce the risk of multiple pregnancy associated with gonadotropin treatment, but any therapy wherein the specific objective is multifollicular ovulation cannot logically avoid the consequence. It is important to acknowledge that superovulation treatment exists primarily because practical considerations effectively prevent so many from pursuing the obvious alternative of IVF. In all likelihood, superovulation would fade into obsolescence if IVF was available to all those who need it, and few physicians or patients would lament its passing.

When ovarian stimulation exceeds its targeted goals, management options other than cycle cancellation include conversion to IVF and transvaginal aspiration of "excess" follicles. Unfortunately, the first of these is available only in centers where IVF is also offered. While, based on limited evidence, "rescue" IVF can provide equally good clinical outcome with "regular" IVF,[388–390] most couples are unprepared for the change in plan and the substantial additional costs involved. Limited experience with the second option of aspirating excess follicles before hCG is administered to prevent ovulation of more than three ova suggests the strategy can effectively reduce the risk of multiple pregnancy and may be a legitimate alternative to cycle cancellation.[391,392]

Multifetal Pregnancy Reduction

Women who conceive a high-order multiple pregnancy despite all efforts to avoid the complication must choose from among three difficult options. Termination of the entire pregnancy is generally unacceptable, particularly for those who have overcome infertility. Continuing the pregnancy carries the inherent risks of preterm birth and associated complications of increased neonatal morbidity and mortality and longer-term disability. Multifetal pregnancy reduction sacrifices a portion of the pregnancy in efforts to save the whole, but for many, it is no option at all, for a variety of personal, moral, ethical, or religious reasons. For most, a choice between the risks of carrying a high-order multiple pregnancy and those associated with pregnancy reduction presents a most difficult dilemma. Couples that ultimately choose pregnancy reduction experience a rapidly shifting tide of strong emotions. Anxiety falls with the diagnosis of pregnancy, rises to very high levels with recognition of a multiple pregnancy, decreases to some extent after consultation before reduction, increases sharply during the procedure, and falls to lower levels after its completion.[393] In retrospect, two-thirds of couples recall acute emotional pain, stress, and fear, and almost 20% report feelings of guilt and anger.[394]

In most cases, multifetal pregnancy reduction is performed under transabdominal ultrasound guidance between 10 and 14 weeks of gestation. By then, the possibility of spontaneous reduction has passed,[395] and a limited screen for gross structural anomalies and features of aneuploidy can be performed to guide selection of fetuses for reduction.[396] There have been no randomized controlled trials comparing maternal and neonatal outcomes in high-order multiple pregnancies managed expectantly with those in which a multifetal reduction was performed, and it is unlikely that there will be.[397] A 2001 report from an international registry including over 3,500 reductions performed at 11 centers indicated that multifetal pregnancy reduction had an overall pregnancy loss rate of nearly 10% with approximately 4% of subsequent deliveries occurring between 25 and 28 weeks of gestation (severe prematurity).[398] Both results compare favorably with published outcomes for series of unreduced high-order multiple pregnancies.[399–402] Outcomes correlated with the number of fetuses both before and after reduction and improve with the experience of the operator.[403,404] Outcomes were better for triplet pregnancies (6% pregnancy loss rate, 3% severe prematurity) than for quadruplet and higher-order pregnancies (12–22% and 4–11%) and improved as the number of fetuses remaining after reduction decreased from three (20% and 6.5%) to two (9% and 4%) to one (9% and 1.6%).[398] A 2017 systematic review and meta-analysis showed that, when compared with unreduced triplets, reduction from triplets to twins was associated with a significantly lower risk of preterm birth (RR = 0.36, 95% CI = 0.28–0.48) and similar risk of miscarriage (RR = 1.08, 95% CI = 0.58–1.98).[405] Another systematic review of prospective studies comparing outcomes from multifetal pregnancy reduction with those from twin pregnancies (conceived spontaneously or after ART) found no differences between women having a multifetal reduction and women with a twin pregnancy for pregnancy loss (RR = 1.32, CI = 0.42−4.16), preterm birth (before 34 weeks; RR = 0.20, CI = 0.01−3.18), stillbirth (RR = 0.86, CI = 0.05−13.48), or neonatal death (RR = 0.86, CI = 0.05−13.45).[406] Limited available information suggests that reduction to a singleton is associated with fewer pregnancy losses and preterm deliveries than reduction to twins.[407,408] **Multifetal pregnancy reduction is an effective management tool for the complication of high-order multiple pregnancy, but one that all would prefer to avoid**.

There is very limited information on the outcome of elective reduction from twins to a singleton between 10 and 14 weeks of gestation. Available data suggest that elective reduction to a singleton can be associated with lower rates of preterm delivery less than 37 weeks and low birth weight, however, with similar rates of serious neonatal

morbidity or perinatal death, very preterm birth, and small-for-gestational-age live birth, at the cost of an overall increased risk of loss of the entire pregnancy.[409,410]

Ovarian Hyperstimulation Syndrome

OHSS is an iatrogenic complication of ovulation induction with exogenous gonadotropins. The disorder can also be observed occasionally in clomiphene-induced cycles. However, to date, OHSS is not reported following ovulation induction with letrozole alone. To the contrary, a 2024 meta-analysis including eight RCTs suggests that combination of letrozole with gonadotropins or letrozole administration in the luteal phase significantly decreases the risk of OHSS.[411] However, given the fact that estradiol per se does not affect vascular permeability and heterogeneity between study results, whether letrozole prevents OHSS is controversial. Yet the data is reassuring about its safety.

Rare cases of OHSS in spontaneous pregnancies have generally been associated with conditions characterized by supraphysiologic concentrations of hCG (multiple gestations, molar pregnancy). Cases of recurrent OHSS in spontaneous singleton pregnancies in individuals and families have been described and linked to germline mutations in the FSH receptor resulting in the loss of ligand specificity that permits activation by hCG.[412–414]

OHSS has a broad pathophysiologic spectrum ranging from mild illness to severe disease. The syndrome is normally self-limited and resolves spontaneously within several days but may persist for longer durations in conception cycles. The hallmark of OHSS is an increase in capillary permeability, resulting in a fluid shift from the intravascular to extravascular spaces,[302,415,416] mediated by increased secretion of vasoactive substances, including vascular endothelial growth factor (VEGF), elements of the renin–angiotensin system, and other cytokines.[417–421] Resultant hypovolemia leads to hemoconcentration and increased risk of thrombosis.

Risk factors for OHSS include young age, low body weight, high ovarian reserve as indicated by high serum AMH levels or antral follicle count, PCOS, higher doses of gonadotropins, and previous episodes of hyperstimulation.[352,422–429] **Risk increases with serum estradiol levels and the number of developing ovarian follicles and when supplemental doses of hCG are administered after ovulation for luteal phase support**.[430–432] OHSS has been classified as mild, moderate, severe, or critical but is perhaps best viewed as a continuum with a widely varying number and severity of symptoms.[433]

Mild illness is characterized by ovarian enlargement, lower abdominal discomfort, and mild nausea and vomiting, diarrhea, and abdominal distention and occurs in up to one-third of superovulation cycles.[423] In general, only oral analgesics and counseling to alert affected women to the signs and symptoms of progressive illness are required; intercourse may be painful and is best avoided to limit the risk of ovarian rupture.

Persistent or worsening symptoms or ascites signal progressing illness and require treatment with antiemetics and more potent oral analgesics. Outpatient management is usually still feasible but must include careful monitoring of daily weights and urinary frequency; serial clinical examinations to detect increasing ascites; and laboratory evaluation of hematocrit, electrolytes, and serum creatinine.[434] Oral fluid intake should be maintained at no less than 1 L/d; electrolyte-supplemented commercial drinks are generally well tolerated and can help to maintain electrolyte balance. Strenuous physical activity is best avoided to reduce the risk of ovarian torsion,[435] but light physical activity is preferable to bed rest, which can increase the risk for thromboembolism. Weight gain greater than approximately 2 lb daily and decreasing urinary frequency are indications for prompt clinical and laboratory reevaluation. **Pregnant women with OHSS merit particularly close monitoring because rapidly rising hCG levels increase the risk for progression to severe illness**. The severity of symptoms, inadequate pain relief, or social considerations may require hospitalization.

Serious illness is uncommon but not rare, having an incidence of approximately 1%. Characteristic features include severe pain, rapid weight gain, tense ascites, hemodynamic instability, respiratory difficulty, progressive oliguria, and laboratory abnormalities. Hypotension can result from vascular volume depletion, oliguria from reduced renal perfusion due to low vascular volume or tense ascites, and dyspnea from ascites or hydrothorax. Hemoconcentration, reduced peripheral perfusion, and inactivity increase the risk of thromboembolism. Renal failure, adult respiratory distress syndrome, hemorrhage from ovarian rupture, and thromboembolic phenomena are potential life-threatening complications of OHSS.[436–439]

Hospitalization for more careful monitoring and aggressive treatment warrants serious consideration in women with severe abdominal pain or peritoneal signs, intractable nausea and vomiting, severe oliguria, tense ascites, dyspnea or tachypnea, dizziness or syncope, severe hyponatremia (sodium <135 mEq/L) or hyperkalemia (potassium >5 mEq/L), hemoconcentration (hematocrit >55%), or abnormal renal functions (serum creatinine >1.2 mg/dL; creatinine clearance <50 mL/min), or abnormal liver functions (elevated transaminases).[302,433,434,437,438]

Recommended inpatient care for hospitalized women includes frequent evaluation of vital signs, daily weights, measurements of abdominal circumference and fluid intake and output, chest x-ray and echocardiogram when pleural or pericardial effusion is suspected, pulse oximetry for those with pulmonary symptoms, and serial hematocrits, electrolytes, and renal and liver function studies.[434] Intravenous fluid management must restore an effective plasma volume but not contribute unnecessarily to the accumulation of extravascular fluid. After initial rehydration, fluids should be administered judiciously in the lowest volumes necessary to maintain adequate urine output and relieve

hemoconcentration; because of the tendency to develop hyponatremia, saline is preferable to lactated Ringer solution. When saline fails, slow infusions (over 4 hours) of albumin (25%; 50–100 g at 4–12 hours intervals) can effectively expand plasma volume.[440] However, as albumin also escapes to the third space through fenestrated endothelial barriers, volume expanders such as 6% hydroxy ethyl starch with larger molecular size can be preferred over albumin when it is available.[441] Premature or excessive use of diuretics is counterproductive and should be avoided as they cause further volume depletion. Intravenous fluid support can be reduced substantially after diuresis begins and oral intake is reestablished. Hyperkalemia may require specific treatment to move potassium into the intracellular space (insulin/glucose, sodium bicarbonate) or to prevent cardiac dysrhythmias (calcium gluconate).

Ultrasound-guided transabdominal or transvaginal paracentesis can be helpful in women with painful ascites, pulmonary symptoms, or oliguria that does not respond to fluid management.[439,442–445] In rare women with persistent bilateral or severe pleural effusions, thoracentesis may also be required to relieve pulmonary symptoms.[446] Full-length venous support stockings are recommended, and prophylactic anticoagulation is warranted in cases of moderate to severe OHSS and should be continued at least until the end of the first trimester in case of pregnancy.[447,448] When symptoms prevent ambulation, the use of an intermittent pneumatic compression device can help to reduce the risk of thrombosis. Clinical signs and symptoms suggesting thromboembolism demand prompt additional diagnostic measures and therapeutic anticoagulation when the diagnosis is confirmed or strongly suspected.

In critical cases of OHSS, intensive care may be required for management of thromboembolism, renal failure, or deteriorating pulmonary function. Women with severe hyperstimulation and ovarian torsion or a ruptured ovarian cyst with hemorrhage who require surgical management present a challenge to anesthesiologists who are understandably seldom familiar with the pathophysiology of OHSS.[449]

Knowledge and prompt recognition of the risk factors for ovarian hyperstimulation are essential for its prevention. Rapidly rising serum estradiol levels, concentrations over 2,500 pg/mL, and observations of a large number of small- and intermediate-sized ovarian follicles are high-risk indicators and signal to cancel or proceed with great caution. Cycle cancellation and less aggressive stimulation in a subsequent cycle warrant strong consideration. Coasting without further gonadotropin stimulation and delaying administration of hCG for 1 to 3 days until estradiol levels plateau or decline can reduce the risk of hyperstimulation.[450–454] A lower dose of hCG (2,500–5,000 IU) may also help reduce risk.[302] Alternatively, a GnRH agonist (leuprolide 0.5–1.0 mg) to trigger an endogenous LH surge can be administered,[455] thereby avoiding the longer duration of action and further stimulation of hCG.[456] However, GnRH agonist trigger without any hCG is associated with decreased pregnancy and increased miscarriage risk and does not ensure complete prevention of OHSS.[457] Evidence from a trial involving 69 oocyte donors at high risk for developing OHSS suggests that treatment with a dopamine agonist (cabergoline 0.5 mg) may decrease vascular permeability (mediated via VEGF) and decrease the risk for OHSS.[458] When luteal support is judged necessary, exogenous progesterone administered by injection (50 mg daily) or vaginally (suppositories 100 mg or 8% gel, daily) are preferable to supplemental doses of hCG.[430]

Breast and Ovarian Cancer

The evidence suggesting that ovulation-inducing drugs might be associated with an increased risk of breast or ovarian cancer was reviewed when discussing the potential risks associated with clomiphene treatment earlier in this chapter. In brief summary, although most studies have found no evidence that fertility drug use increases overall breast cancer risk, some studies suggest that prolonged or repeated use of exogenous gonadotropins (six cycles or more) may increase risk.[459–461] Overall, the available data are quite reassuring. **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 GONADOTROPIN-RELEASING HORMONE

Exogenous pulsatile GnRH therapy has been used successfully to induce ovulation since 1980.[462,463] Compared to gonadotropin therapy, GnRH treatment has both advantages and disadvantages. 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 to 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.

Where it is available, synthetic GnRH comes in a crystalline form that remains stable for at least 3 weeks at room temperature after reconstitution in aqueous diluent. GnRH is administered in a continuous pulsatile fashion using a portable, programmable mini-pump that must be worn constantly, around the clock, requiring some logistical ingenuity during bathing and sleep. Although the drug may be administered intravenously or subcutaneously, the intravenous

route requires lower doses involving less cost (2.5–5.0 vs 15–20 μg/pulse, depending on body weight) and is more physiologic and more effective. The drug is metabolized rapidly and has a terminal half-life of 10to 40 minutes after intravenous administration. Compared to the brief spikes in serum levels that result from intravenous administration and effectively mimic the normal pattern of pulsatile hypothalamic GnRH secretion, subcutaneous treatment creates a more continuous low level of GnRH stimulation without definite peaks.

In effect, pulsatile intravenous exogenous GnRH therapy represents an artificial hypothalamus. In women with hypogonadotropic hypogonadism who have absent or low levels of endogenous pulsatile GnRH secretion, treatment restores a normal pulsatile GnRH rhythm. In those with other forms of ovulatory dysfunction, treatment superimposes a normal rhythm on an existing but disorganized pattern of endogenous GnRH secretion. **Importantly, exogenous pulsatile GnRH treatment generally stimulates only normal physiologic levels of pituitary gonadotropin secretion and allows normal feedback modulation of the pituitary response by ovarian steroids and peptides to operate. Consequently, follicular recruitment, selection, growth, and development in women using the GnRH pump progress as they do in the normal menstrual cycle**.[464–466]

Indications for Pulsatile GnRH Treatment

Anovulatory infertile women with hypogonadotropic hypogonadism are the best candidates for ovulation induction with exogenous GnRH because treatment is specific, physiologic, and highly effective; the GnRH pump provides the only instructional signals the pituitary gonadotropes are likely to receive. Although the drug can also be used in women with other ovulatory disorders, it is much less often effective, probably because the pituitary has more difficulty interpreting the mixed signals of endogenous and exogenous GnRH stimuli. As may often be observed in women with PCOS, an increased BMI (>24), serum LH (>15 IU/L), serum testosterone (approximately >100 ng/dL), and fasting serum insulin (approximately >15 units/mL) are associated with lower ovulation rates in response to exogenous GnRH and lower pregnancy rates per ovulatory cycle.[467,468] The GnRH pump can also be effective in women with hyperprolactinemia and offers an alternative to exogenous gonadotropins when dopamine agonist treatment fails or cannot be tolerated.

Exogenous GnRH Treatment Regimens

Exogenous GnRH is most effective when administered intravenously in low doses (2.5–5.0 μg/pulse) at a constant interval (every 60–90 minutes).[467] Those who fail to ovulate may respond to a higher dose (10–20 μg).[469,470] As with oral antiestrogens and exogenous gonadotropins, treatment should begin with a low dose and gradually increase to meet the needs of the individual because the risk of multiple pregnancy increases with the pulse dose.[471] To a large extent, the dose and duration of exogenous GnRH treatment required to induce ovulation depend on the underlying endocrine milieu.[467,472,473]

In women with primary hypogonadotropic hypogonadism, a low dose (2.5 μg/pulse) can induce ovulation effectively, but follicular phase LH concentrations may remain lower than normal, and luteal phase progesterone concentrations are often reduced; both are typically normal when a higher dose of GnRH (5.0 μg/pulse) is used. Longer durations of treatment are typically required because available stores of pituitary gonadotropins are markedly reduced due to the historically low levels of endogenous GnRH secretion. In women with secondary idiopathic hypogonadotropic hypogonadism, treatment should begin with a low dose of GnRH (2.5 μg/pulse); the higher dose (5.0 μg/pulse) is associated with higher follicular and luteal phase LH and estradiol levels, a short follicular phase, multiple folliculogenesis, and a higher risk of multiple pregnancy, possibly because previous pituitary or ovarian priming confers a greater sensitivity to GnRH therapy.[467,474]

The endocrine response of women with PCOS to pulsatile exogenous GnRH (5.0 μg/pulse) is markedly abnormal but can be normalized by pretreatment with a long-acting GnRH agonist (daily subcutaneous administration) for 6 to 8 weeks immediately before starting pulsatile exogenous GnRH treatment.[465,467,475] Without GnRH agonist pretreatment, follicular phase FSH, LH, and estradiol levels and luteal phase estradiol concentrations are all abnormally elevated. After preliminary down-regulation with a GnRH agonist, the endocrine characteristics of induced cycles are much improved and closer to those observed in spontaneous ovulatory cycles in normal women. Unless similar down-regulation with a GnRH agonist also precedes subsequent cycles, the response to exogenous GnRH therapy again becomes abnormal. The benefits of GnRH agonist pretreatment probably result from suppression of intraovarian androgen levels[476] and improved (higher) FSH/LH ratios before GnRH therapy begins.[477]

After ovulation has been achieved, GnRH therapy can continue at the same or a slower pulse frequency (every 120–240 minutes).[467,469] Whereas either can stimulate sufficient endogenous LH secretion to support normal corpus luteum function, a slower frequency more closely approximates the reduced endogenous pulse frequency observed in normal cycles during the luteal phase and may help to reduce the cost of treatment. However, it is simpler, much less costly, and just as effective to discontinue the pump after ovulation has occurred and to support the luteal phase with small doses of hCG (2,000 IU every 3 days)[467] or exogenous progesterone.

One of the advantages that GnRH pump therapy has over exogenous gonadotropin treatment is that monitoring is not required once an effective treatment regimen has been established. Serial estradiol measurements and ovarian ultrasonography can certainly be used to monitor ongoing treatment but are not necessary. Objective evidence of

ovulation can be obtained by periodic progesterone measurements. If needed, the time of ovulation can be estimated more accurately by monitoring urinary LH excretion as in spontaneous or clomiphene-induced ovulatory cycles.

Results of Exogenous GnRH Treatment

A 2018 systematic review and meta-analysis, including 35 studies and 1,002 women with hypothalamic amenorrhea, reported ovulation rates of 75% (95% CI = 64.91–84.44%, based on 3 RCTs) and 85% (95% CI = 81.35–88.68%, based on 32 observational studies).[478] Pooled estimates of pregnancy rate per ovulatory cycle were 38% (95% CI = 14.54–65.85%, 3 RCTs) and 31% (95% CI = 27.77–35.63%, 27 observational studies). Pooled estimates of live birth rates per ovulatory cycle were 35% (95% CI = 15.61–58.12%, 3 RCTs) and 25% (95% CI = 22.27–29.58%, 27 observational studies).[478] **Overall, results are best in women with hypogonadotropic hypogonadism and worse in those with PCOS.**[467,470,479,480] In the former, cycle fecundity equals that observed in normal fertile women, and cumulative pregnancy rates can reach 80% or higher after 6 to 12 cycles of treatment.[467,469,479,481] In the latter, cycle fecundability and cumulative pregnancy rates are moderately lower, when ovulation can be successfully induced, and pretreatment with a GnRH agonist improves ovulation rates.[467,469,479]

Overall, pulsatile GnRH therapy can achieve ovulation and pregnancy rates that compare with or even exceed those observed with exogenous gonadotropin treatment in women with PCOS,[480] but how the two treatments might compare in eugonadotropic oral antiestrogen–resistant anovulatory women, arguably the more clinically relevant question, is much less clear because no studies have examined their relative efficacy in such a selected population. One small randomized controlled trial in which pulsatile GnRH therapy (10–20 μg/90 min) after GnRH agonist suppression (nafarelin 400 mg daily for 3 weeks or longer) was compared directly with clomiphene citrate treatment (50–150 mg daily, cycle days 3–7) as first-line ovulation induction strategy over two to three cycles observed similar ovulation and pregnancy rates in the two groups.[470] These data serve to reaffirm that more complicated and costly ovulation induction regimens involving GnRH pump therapy or exogenous gonadotropin treatment are best reserved for those who fail to ovulate in response to oral antiestrogens.

In addition to requiring less or no monitoring after an effective treatment regimen has been established, another advantage that pulsatile GnRH therapy has over exogenous gonadotropin treatment is that it rarely results in multiple follicular development and ovulation; the risk for multiple gestation is therefore substantially lower, and that for serious ovarian hyperstimulation is eliminated almost entirely. The aforementioned 2017 systematic review reported a pooled incidence of multiple pregnancy to be 3.35% (95% CI = 0.03–20.44%, 3 RCTs) and 5.67% (95% CI = 3.96–7.8%, 29 observational studies).[478] In the largest single collected series, including over 100 pregnancies in 600 GnRH-stimulated cycles in nearly 300 women with a variety of ovulatory disorders, only four multiple pregnancies (4% incidence, one triplet and three twin pregnancies) and no cases of moderate or severe ovarian hyperstimulation were observed.[467] Overall, the risk of multiple pregnancy in GnRH-induced conception cycles is comparable to that associated with clomiphene treatment (5–8%) and 40% to 75% lower than that associated with exogenous gonadotropin therapy in anovulatory women (~15%). Based on a meta-analysis of 29 studies including 2,029 cycles, the pooled estimate of incidence of OHSS is 1.86% (95% CI = 0.79–3.37%).[478]

The overall incidence of spontaneous miscarriage in exogenous GnRH-induced conception cycles is approximately 30%.[467,479] As has been observed in most studies of pregnancies resulting from exogenous gonadotropin treatment,[358–360] miscarriage rates are lowest in women with hypogonadotropic hypogonadism (<20%) and highest in those with PCOS (over 40%).[465,467,479]

Taken together, the results achieved with pulsatile exogenous GnRH therapy support its use as the drug of choice for treatment of anovulatory infertile women with hypogonadotropic hypogonadism.[467,479] **Unfortunately, few clinicians have experience with the method, and relatively few women judge it as an attractive choice after considering the available alternatives**.

DOPAMINE AGONISTS

Hyperprolactinemia and its treatment with dopamine agonists are considered at length elsewhere in this text in the context of their association with amenorrhea (Chapter 10). Relevant details from that discussion are summarized briefly again here in an expanded discussion focused on the use of dopamine agonists for ovulation induction.

The two most common dopamine agonists in clinical use are bromocriptine and cabergoline. Both are ergot alkaloids that mimic the actions of dopamine via their binding to dopamine receptors. Serum concentrations peak 1 to 3 hours after an oral dose of bromocriptine, and very little remains in the circulation 14 hours after administration; an oral dose of 2.5 mg generally lowers prolactin concentrations for up to 12 hours.[482] When administered vaginally, the same dose of bromocriptine has peak effects approximately 10 to 12 hours later that are sustained for up to an additional 12 hours.[483] Cabergoline is a longer-acting dopamine agonist with a high affinity for the dopamine receptor. A single dose of cabergoline effectively inhibits prolactin secretion for 7 days or longer.[484]

Like endogenous hypothalamic dopamine, the agonists inhibit pituitary lactotrope prolactin secretion directly. By lowering serum prolactin levels into the normal range, dopamine agonist treatment allows the hypothalamic–pituitary–ovarian

axis to escape from the suppressive influence that hyperprolactinemia has on pulsatile GnRH secretion and to resume normal operation, thereby restoring ovulatory function. Because even prolactin-secreting pituitary adenomas remain sensitive to the actions of dopamine, the agonists are effective in hyperprolactinemic women with and without a pituitary adenoma.[485]

Indications for Dopamine Agonist Treatment

Dopamine agonists are the treatment of choice for hyperprolactinemic infertile women with ovulatory dysfunction who wish to conceive. Although some hyperprolactinemic women will respond to oral antiestrogen treatment, most do not, because the neuroendocrine consequences of hyperprolactinemia generally disrupt the mechanism by which clomiphene exerts its therapeutic action.

Dopamine agonist treatment can be highly effective in women who have galactorrhea but normal serum prolactin levels.[486] With few exceptions, the presence of galactorrhea can be regarded as a reliable indicator of excess prolactin secretion. Possible explanations for occult hyperprolactinemia include excess production of biologically active forms of prolactin not detected in all immunoassay systems and transient but exaggerated nocturnal prolactin secretion that goes unrecognized in randomly drawn blood samples.[486–490]

Up to 30% of women with PCOS can exhibit mild hyperprolactinemia.[491,492] Reduced levels of dopaminergic inhibition have also been implicated as a contributing cause of the elevated serum LH concentrations observed in women with the disorder.[491,493] Consequently, dopamine agonists have also been advocated as adjuvant therapy for hyperprolactinemic anovulatory women with PCOS who require exogenous gonadotropin treatment. Limited evidence suggests that pretreatment with a dopamine agonist can temper the ovarian response to exogenous gonadotropins and may thereby help to decrease the risks of multiple pregnancy and ovarian hyperstimulation associated with such treatment.[492]

Dopamine Agonist Treatment Regimens

Because many hyperprolactinemic women are very sensitive to low doses of dopamine agonists, treatment should generally begin with a low dose and increase gradually until the dose required to restore and to maintain euprolactinemia has been established. Although the dose ultimately required roughly correlates with the degree of hyperprolactinemia, many women with very high prolactin levels respond to relatively low doses of dopamine agonists. The dose of dopamine agonist required to maintain euprolactinemia is very often lower than that needed to achieve it initially.[494]

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. Treatment with cabergoline usually begins with a dose of 0.25 mg twice weekly, increasing gradually thereafter about every 4 weeks until the effective dose is established. Most women achieve normal prolactin levels with 0.5 to 1.0 mg weekly, and doses greater than 2.0 mg weekly are rarely required.[12,494]

With bromocriptine, treatment usually begins with a dose of 1.25 to 2.5 mg, administered at bedtime to more effectively suppress the normal nocturnal increase in prolactin secretion. A low initial dose also helps to minimize the frequency and severity of gastrointestinal and cardiovascular side effects related to dopamine receptor stimulation.[495] **Prolactin levels decrease and stabilize shortly after treatment begins, and a repeated serum prolactin measurement will demonstrate the effectiveness of any given dose in as little as a week**. If needed, a second dose can be added, administered with breakfast or lunch. Although most women respond to 2.5 to 5.0 mg bromocriptine daily, some may require as much as 10 mg daily.[12]

Exogenous gonadotropins are an effective alternative for the few who do not respond to a dopamine agonist, either alone or in combination with clomiphene.

Results of Dopamine Agonist Treatment

Overall, dopamine agonist treatment normalizes and maintains normal prolactin levels in approximately 60% to 85% of hyperprolactinemic women. Cyclic menses are restored in 70% to 90%, usually within 6 to 8 weeks after treatment begins, and ovulatory cycles return in 50% to 75% of treated women with or without tumors.[12,13,494] The probability of successful treatment is modestly lower in women with markedly elevated prolactin levels (>100 ng/mL) than in those with lesser degrees of hyperprolactinemia. Breast secretions typically diminish noticeably within approximately 6 weeks, and complete cessation of galactorrhea generally takes about twice as long to achieve. After discontinuation of dopamine agonist therapy, hyperprolactinemia and associated menstrual dysfunction return in 75% to 80% of women.

A 2012 systematic review and meta-analysis including nine studies found that cabergoline was more effective than bromocriptine in reducing the risk of persistent hyperprolactinemia (RR = 2.88; 95% CI = 2.20–3.74), amenorrhea/oligomenorrhea (RR = 3.41, 95% CI = 1.40–2.36), and galactorrhea (RR = 3.41, 95% CI = 1.9–5.84).[496] Moreover, cabergoline has proven effective in 70% to 85% of hyperprolactinemic women who are resistant to or cannot tolerate bromocriptine treatment.[12,494,497] Compliance with a twice weekly treatment (cabergoline) is also better than with a twice-daily regimen (bromocriptine).[12]

Side Effects of Dopamine Agonists

Overall, side effects of dopamine agonist treatment are common and are most severe during the first 2 weeks of therapy but generally well tolerated. Because bromocriptine

stimulates both D1 and D2 dopamine receptors, most women will experience mild adrenergic side effects[495]; dizziness, nausea, vomiting, nasal stuffiness, and orthostatic hypotension are the most common. Although cabergoline has similar side effects, they are generally less frequent and severe because of the drug's higher affinity to D2 dopamine receptors. Side effects are severe enough to require discontinuation of treatment in approximately 12% of women treated with bromocriptine and in 3% of those treated with cabergoline.[12,496]

Side effects can be minimized by starting with a low dose, increasing gradually thereafter as needed and tolerated. Taking the medications with a snack or meal also improves tolerance. When necessary, vaginal administration of bromocriptine or cabergoline can help to reduce side effects and improve compliance.[498–500] Whereas much of an orally administered dose is not absorbed or rapidly metabolized in the first pass through the liver, vaginal absorption is more complete and avoids immediate hepatic metabolism. Consequently, therapeutic results can often be achieved with lower doses when the drugs are administered vaginally.

Risks of Dopamine Agonist Treatment

There is no evidence that dopamine agonists pose any increased risk for spontaneous miscarriage or birth defects. Numerous studies of women who have conceived during treatment have found no increase in the incidence of spontaneous miscarriage or congenital anomalies in pregnancies resulting from treatment with bromocriptine[12,501–504] or cabergoline.[12,483,494,497]

Treatment for Parkinson disease with cabergoline or another dopamine agonist, pergolide, has been associated with a 4- to 7-fold increased risk for valvular heart disease (mitral, aortic, or tricuspid regurgitation).[505,506] The risk appears to result from mitogenic stimulation of normally quiescent valve cells via activation of serotonin (5-hydroxytryptamine, 5-HT) receptors (specifically, the 5-HT_{2B} receptor).[507] Bromocriptine, which has no 5-HT_{2B} agonist activity, has not been associated with any increased risk of valvular heart disease. Although the doses of cabergoline used for the treatment of hyperprolactinemia are less than 10% of those used for the treatment of Parkinson disease and have not been associated with the development of heart disease, it seems prudent to use the lowest effective dose of cabergoline for the shortest time required to achieve the goals of treatment. Current evidence does not support a recommendation for echocardiography before or during treatment with low doses of cabergoline in asymptomatic women.

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