27 Hormonal Therapy of the Infertile Woman

Shahar Kol, MD

CONTENTS

INTRODUCTION

Fertility requires anatomical and functional integrity of the sexual axis, starting at the level of the hypothalamus, going down to the pituitary, ending at the level of the ovaries, Fallopian tubes, and uterus. From the pharmacological point of view, the current arsenal allows for tight control and flexible manipulation of the sexual endocrine axis, offering a wide range of therapeutic interventions with the goal of achieving pregnancy. This chapter aims at presenting briefly the major therapeutic tools that are currently at our disposal.

ANOVULATION

Anovulation is the single most frequent reason for female infertility, affecting about 10% of the female population of reproductive years. The classification of anovulation into three groups by the World Health Organization (WHO) is used as a practical guideline to diagnosis and treatment.

Group I. Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea): The patients are characterized by low serum gonadotropins and low estradiol. Because the endometrium is not primed with estradiol, progesterone withdrawal does not induce menstrual bleeding. Treatment is usually directed at inducing pituitary response by providing exogenous pulsatile gonadotropin-releasing hormone (GnRH) or by direct

From: *Endocrine Replacement Therapy in Clinical Practice*
Edited by: A. Wayne Meikle © Humana Press Inc., Totowa, NJ

stimulation of the ovaries with gonadotropins. If hyperprolactinemia is diagnosed, specific treatment is required.

Group II. Normogonadotropic normoestrogenic anovulation (hypothalamic–pituitary dysfunction): This is the largest group of anovulatory (or oligo-ovulatory) patients. These women have evidence of endogenous estrogen activity. Physical examination may reveal evidence of excess androgen production. Luteinizing hormone (LH) may be elevated or normal. Follicle-stimulating hormone (FSH) is usually normal. There is withdrawal bleeding in response to progesterone. Ultrasound examination of the ovaries typically shows multiple small follicles (polycystic ovary syndrome [PCOS]). Treatment is based on raising the FSH levels to initiate follicular growth and maturation, leading to ovulation.

Group III. Hypergonadotropic hypoestrogenic anovulation: Patients in this group are characterized by their elevated serum gonadotropins, signifying ovarian failure or premature menopause. Numerous therapeutic maneuvers have been suggested to produce viable pregnancies in this group, all yielding disappointing results. For this group of patients, oocyte donation is the only procedure that offers reasonable chances of achieving pregnancy.

Hyperprolactinemic Anovulation

Hyperprolactinemia is associated with galactorrhea, menstrual disturbances, infertility and osteoporosis. A single, moderately elevated serum prolactin level warrants repeated measurement, as prolactin is secreted episodically. Well-established elevated prolactin levels dictate (after physiologic and pharmacological etiologies have been ruled out) a radiological evaluation (computed tomography [CT] or preferably magnetic resonance imaging [MRI]) of the hypothalamic–pituitary region. Most patients with hyperprolactinemia can be treated medically. Neurosurgical evaluation is indicated in the uncommon cases of large mass or failed medical treatment. Hyperprolactinemia *per se* does not require treatment; however, infertility is clearly an indication for medical treatment. This consists of dopamine agonists, of which bromocriptine (introduced in 1971), has been the standard drug. Bromocriptine is usually begun at a low dose of 1.25 mg daily and increased gradually to 2.5–5.0 mg daily. Occasionally, higher doses are required. Although bromocriptine is effective in 80% of patients (shrinkage of the tumor and substantial reductions of serum prolactin concentrations) its bothersome side effects cause discontinuation of treatment by 5–10% of patients. The most common side effects are nausea, dizziness, and orthostatic hypotension. Efforts to minimize these side effects have led to the development of a number of compounds, of which cabergoline emerged as a leading product. Whereas bromocriptine is given once or twice daily, cabergoline is given once or twice weekly. A 459-patient double-blind study *(1)* of women with hyperprolactinemic amenorrhea compared the safety and efficacy of cabergoline with bromocriptine (the standard therapy). Patients were treated with either cabergoline (0.5–1.0 mg twice weekly) or bromocriptine (2.5–5.0 mg twice daily). Normoprolactinemia was achieved in 186 of the 223 (83%) women treated with cabergoline and 138 of the 236 (59%, $p < 0.001$) women treated with bromocriptine. Ovulation was documented in 72 and 52% of the women treated with cabergoline and bromocriptine, respectively ($p < 0.001$). Adverse effects were recorded in 68% of the women taking cabergoline and 78% of those taking bromocriptine ($p = 0.03$); 3% discontinued taking cabergoline, and 12% stopped taking bromocriptine ($p < 0.001$) because of drug intolerance. Gastrointestinal

symptoms were significantly less frequent, less severe, and shorter-lived in the women treated with cabergoline. Taken together, these results suggest that cabergoline is more effective and better tolerated than bromocriptine.

Another large-scale (455 patients) retrospective, case-series study confirmed the high efficacy and tolerability of cabergoline *(2)*.

Quinagolide is a nonergot dopamine agonist used to treat hyperprolactinemia. This drug is administered once daily. It has similar efficacy to bromocriptine, but is probably less effective than cabergoline. It is better tolerated than twice-daily bromocriptine, but is probably inferior to cabergoline in this regard *(3)*. The superiority of cabergoline is also demonstrated in the treatment of patients with micro- and macroprolactinomas, who are resistant to bromocriptine and quinagolide. These patients respond favorably to cabergoline *(4)*.

Patient monitoring during treatment includes reassurance of compliance and repeat of prolactin levels at 3-mo intervals during the first year and yearly thereafter. If a mass effect is suspected, surgery consultation is warranted. If prolactin levels are stable for more than 2 yr, dosage can be reduced gradually, while monitoring prolactin levels, until complete cessation of medical treatment.

PULSATILE GnRH THERAPY

Indications

The identification and sequencing of GnRH in the early 1970s, opened the opportunity to significantly manipulate the reproductive axis at the hypothalamus–pituitary area. Significant efforts were invested in creating GnRH analog molecules that can induce agonistic or antagonistic effects. Currently, the fruits of these efforts are used routinely in fertility treatments (most notably in the field of in vitro fertilization [IVF]). Soon after its introduction, it became apparent that physiologic activity of GnRH requires pulsatile, or intermittent, administration, because sustained effect (by GnRH agonists) induces pituitary desensitization and gonadotropin suppression.

The ideal candidate for pulsatile GnRH therapy would be the rather rare patient with hypogonadotropic hypogonadism (HH). Exogenous pulsatile administration of the missing primary ingredient (GnRH) results in mimicking the natural ovulatory cycle. Given current significant efforts to minimize fertility-treatment-induced multiple pregnancy, a natural-like, monofollicular stimulation is highly attractive. Indeed, this mode of treatment is highly successful in HH patients.

Other candidates for pulsatile GnRH treatment would be PCOS patients. One of the suggested etiologies for this condition is persistently rapid GnRH pulse frequency, leading to excessive LH secretion and relatively low FSH *(5)*. Although the rational for pulsatile GnRH treatment in these patients is not readily understood, it offers the potential benefit of monofollicular stimulation.

Dosage

Route

Pulsatile GnRH is usually given intravenously. This mode of delivery assures a rapid peak and prompt return to baseline of GnRH and LH that follows. Long-term intravenous administration is cumbersome and not complication–free (iv site infection), although using a sterile technique and proper maintenance seem to reduce the frequency of infec-

tion *(6)*. Pulsatile GnRH can also be given subcutaneously (sc), although this mode of delivery blunts the pulses. This notwithstanding, sc administration leads to ovulation in 75% of cycles in patients with HH and a conception rate of 30% *(7)*. The more physiologic iv administration is advantageous as the ovulation rate is higher (90%), although the conception rate is similar (27.6%) *(8)*.

Frequency

Fixed-pulse frequencies of every 60–120 min have been used successfully *(9)*. An attempt to simulate the normal menstrual cycle *(10)* by changing the pulse frequency from every 60 min to every 4 h did not result in a significant improvement. A frequency of one pulse every 90 min has been advised by pharmaceutical companies, although a 60-min interval may result in further optimization *(11)*.

Dose

A wide range of bolus dose (1–20 μg/bolus) has been used. When the sc route is used, higher dosage is needed. High dosage with the iv route is associated with a greater risk of multiple pregnancy. Most centers start stimulation with a low iv dose (2.5–5 μg/bolus), to be increased (to 10–20 μg/bolus) if needed (i.e., no response after 10–15 d of treatment).

Luteal Support

Once ovulation occurs, luteal support can be given by continuing GnRH pulses, although less expensive and simpler alternatives can be used, like human chorionic gonadotropin (hCG) (two to three injections of 1500–2500 U each in a 3-d interval), or exogenous progesterone.

Monitoring

During the follicular phase, vaginal ultrasound is used to assess follicular development. Appearance of a single growing follicle is taken to reflect a favorable response. Multiple follicular responses, although rare, may lead to cycle cancellation if multiple pregnancy is to be avoided. Estradiol measurements are not needed. Ovulation is detected by urinary LH kits, usually done at home, to allow timed intercourse or intrauterine insemination (IUI).

Outcomes

The best results are achieved with HH patients, as a primary pituitary disorder is rare and treatment often leads to normal gonadotropin secretion. An ovulation rate of 80–90% is usually reported *(12)* and a pregnancy rate of nearly 30% per ovulatory cycle. The multiple pregnancy rate is in the range of 5%, and the abortion rate is 20–25%.

Patients with PCOS do not respond as well as HH patients. The ovulation rate in these patients is 40–50%, with pregnancy in only 16% of the cycles *(11)*. Better results may be obtained by pretreatment with a GnRH analog for 6–8 wk to induce pituitary suppression.

Complications

A multiple pregnancy rate of 5–8%, which is significantly higher than the 1% rate observed in spontaneous pregnancies, should be regarded as a significant complication. A low starting pulse dose and accurate assessment of the number of growing follicles may lower this rate. Furthermore, if multiple pregnancy is likely, based on ovarian

response, the patient should be informed in detail regarding possible consequences. A prudent professional advice in these cases would be to abort the cycle. A severe ovarian hyperstimulation syndrome (OHSS) has not been described with pulsatile GnRH treatment. The risk of iv catheter-related infections seems to be low *(13)*, as 2% of the patients had positive blood cultures at the time of catheter removal.

ANTIESTROGENS

Clomiphene

Clomiphene citrate (CC) was synthesized in 1956 and was first used in clinical trials 4 yr later. By now, it is the most widely used (and abused) ovulation promoter. The primary indication for CC is infertility associated with normoprolactinemic normogonadotropic normoestrogenic anovulation (WHO group II). Over the years, other indications were added, most notably controlled ovarian stimulation in unexplained infertility, and "mild male" factor in association with IUI. These indications have broadened the patient pool for CC considerably. Given its cost, route of administration (oral), and safety, CC has become a universal first-stage fertility drug. All too often we see patients who are given CC, before any fertility workup is done.

Monitoring During CC Therapy

In the typical anovulatory patient, CC may be initiated at any time. A starting point timed from uterine bleeding is hormonally meaningless in these patients. However, if bleeding occurs spontaneously or is induced (usually with a progestin), CC treatment is started on d 3–5 of the "cycle." The recommended starting dose is 50 mg daily for 5 d. If ovulation does not occur, the daily dose is increased by 50-mg increments. The maximal CC dose is 250 mg for 5 d. Lack of ovarian response to this dose is considered a CC failure. Treatment variations by extending CC intake duration to more than 7 d or more have been suggested. Theoretically, luteal support is not indicated, although one cannot rule out a compromised luteal function as a result of CC treatment.

Some practitioners believe that CC treatment monitoring can be limited to daily basal body temperature (BBT) measurement in order to document ovulation. This clearly represents a simple, low-cost monitoring plan. Indeed, a small randomized study concluded that "high-tech" monitoring (vaginal ultrasound and LH monitoring) offered no advantage over BBT alone *(14)*. However, detailed monitoring may be desirable if timed intercourse or IUI is planned, or for the purpose of documenting the number of responding follicles, or for the typical progesterone rise after ovulation. Objective monitoring is based on hormonal measurements and ultrasound. Because ovulation usually occurs 5–10 d after the last dose of CC, serum E_2 can be taken during this window of time followed by progesterone measurement in the projected mid-luteal phase to document ovulation. High-frequency transvaginal sonography (TVS) can be used as the only tool for follicular phase monitoring. Monitoring follicular response from the fifth day after the last CC dose onward by TVS is used to document the number of growing follicles. The purpose of the treatment is to achieve a single responding follicle that hopefully harbors a single fertilizable oocyte. Once the follicle reaches >20 mm in diameter, hCG (a single dose of 5000 IU) can be given if timed IUI is planned. If natural intercourse is preferred, hCG can also be given, although spontaneous ovulation may occur without any further intervention. However, in the case of a multi-follicular response, serious

consideration should be given to aborting the cycle, if multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) are to be avoided. In fact, these situations present a major contribution of TVS to treatment monitoring (i.e., allowing accurate estimation of the responding follicles). The risk of multiple pregnancy and OHSS is directly correlated with the number of responding follicles.

Other antiestrogens have been introduced as alternatives to CC, most notably tamoxifen, which presumably offers comparable ovulation and pregnancy rates *(15)*.

Another seemingly promising alternative is the use of an aromatase inhibitor for induction of ovulation. The preliminary reported experience with such a compound (letrozole) is favorable *(16)*. Not only was a high ovulation rate achieved but this approach also avoids the unfavorable effect on the endometrium that is associated with CC.

Outcomes

Of the anovulatory patient pool, about 80% can be expected to ovulate and consequently become pregnant unless other infertility factors exist. Once ovulation occurs conception becomes a matter of chance with somewhat lower pregnancy rates compared to those reported in the general population. Because CC is not given exclusively to the classical anovulatory patients, the conception rate for other groups of patients may be lower, although the ovulation rate is higher.

Complications

Hot flashes, probably secondary to antiestrogenic effect, are reported by 11% of patients. Visual symptoms (blurring, spots, and flashes) occur in 2% of patients and are reversible. More important is the antiestrogenic effect of CC at the level of the endometrium and cervical mucus. Although the direct effect on cervical glands is difficult to document and easy to bypass (by IUI), adverse changes in endometrial morphology were reported using TVS *(17)*. It appears that, in a subset of patients, endometrial growth during the proliferative phase is hampered by CC. This effect is documented by as a thin, poor endometrial lining, in spite of high estradiol levels. These effects prompted researchers to add estrogen to the treatment protocol, with apparent success *(18)*.

Use of Metformin and Insulin Sensitizers for Ovulation Induction

Polycystic ovary syndrome is commonly associated with obesity and insulin-resistance, leading to hyperinsulinemia. High insulin contributes to anovulation and hyperandrogenism, suggesting that an insulin sensitizer may decrease insulin secretion, followed by ovulation. Indeed, several studies have documented that agents like metformin *(19)* or troglitazone (this compound has been recalled by the manufacturer because of safety concerns) *(20)* increase the rate of ovulation with or without concomitant treatment with CC. A randomized, double-blind, placebo-controlled study of CC-resistant PCOS patients showed that treatment with metformin (1500 mg daily) significantly increased ovulation and pregnancy rates *(21)*. A similar study, with rather lean, Chinese PCOS patients, failed to show any improvement with metformin *(22)*, indicating that treatment individualization is always important and that body mass index (BMI) may correlate with the degree of response to metformin.

OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome still remains the most important complication of controlled ovarian stimulation. In fact, it can be looked at as a situation in which the ovaries run "out of control," producing a typical syndrome during the luteal phase of the stimulated cycle. Being an iatrogenic complication associated with a purely elective medical procedure, all efforts must be made to prevent its occurrence. Mild stimulation, individualization of treatment protocol to suit each patient's needs and regarding patient safety as first priority may minimize OHSS occurrence.

Strategies for OHSS prevention include the following:

1. Cycle cancellation in a high-risk situation is a prudent approach. Ovarian stimulation is stopped and hCG is not given. It should be noted that spontaneous ovulation by an endogenous LH surge may still occur followed by OHSS. If pregnancy is achieved, the severity of OHSS often increases. Therefore, in addition to cycle abortion, the patient should be counseled about abstinence until menses. A spontaneous LH surge will not occur in GnRH-agonist-induced pituitary downregulated patients or if a GnRH antagonist is given to ascertain that ovulation is prevented.
2. Reducing the dose of hCG given for ovulation triggering is a popular approach, although it cannot guarantee total OHSS prevention.
3. Other modalities taken to lower the risk of OHSS include luteal phase support with a progesterone (instead of hCG), withholding fresh embryo transfer (and in that context averting "in vivo" ovarian stimulation to IVF), and use of a recombinant LH to trigger ovulation.
4. The single approach that combines efficient ovulation triggering and total OHSS prevention is the use of a singe bolus of a GnRH agonist *(23)*. This approach has been successfully used in both ovulation induction and IVF patients. The recent introduction of GnRH antagonists makes this protocol more applicable, especially in the IVF setting. A single dose (0.2 mg) of GnRH agonist reliably and effectively triggers ovulation. Oocyte retrieval (for IVF) or IUI is timed as if hCG were given. Luteal support with a progesterone is mandatory (estradiol may also be supplemented) because endogenous biosynthesis of sex steroids by the corpora lutea decreases sharply. In fact, a situation of complete luteolysis is attained, which is the key to OHSS prevention. Early luteolysis also assures that if pregnancy is achieved, the associated endogenous hCG will not "revive" the corpora lutea. If stimulation is performed for IUI (or natural intercourse, not for IVF) the subject of multiple pregnancy should be discussed with the patient. Although OHSS is completely prevented, there is no control over the number of embryos that may develop. Therefore, it is recommended to switch to IVF for the purpose of controlling the number of transferred embryos.
5. Numerous researchers have suggested that intravenous albumin at the time of oocyte retrieval in IVF may prevent or alleviate OHSS. There is no evidence to support this approach; therefore this treatment is not recommended *(24)*.

Treatment of OHSS is supportive in nature. In mild cases, bed rest and periodic observation is sufficient. Patients with severe OHSS should be hospitalized. Hemoconcentration and electrolyte imbalances are treated with intravenous fluid. Other therapeutic measures include plasma expanders, diuretics, paracentesis for tense ascites and finally, therapeutic abortion if all measures fail.

GONADOTROPIN THERAPY

In the late 1950s and early 1960s, exogenous gonadotropins were introduced as a novel therapeutic tool in infertility. In their early days, gonadotropins were produced

from human pituitaries. It was only when urinary-derived products became available that this treatment gained popularity. The product, human menopausal gonadotropin (hMG), contains equal biological activity of FSH and LH (each 75 IU/ampoule) and has been used with impressive success for decades. In the mid-1990s, recombinant FSH products were introduced. The new recombinant products gradually replaced the urinary-derived ones for their advantages:

- High purity
- High specific activity
- Identical amino acid sequence compared to natural FSH
- No contamination with urinary proteins of undetermined origin
- No LH activity
- Reliable source for production, no need for cumbersome collection of urine

Recombinant FSH preparations also appear to be slightly superior to hMG based on the available evidence, although experience shows that ovarian stimulation in the face of no LH (endogenous or exogenously administered) is problematic. If GnRH agonist-induced pituitary downregulation results in very low LH levels, ovarian stimulation with recombinant FSH leads to very low estradiol levels and low pregnancy rates.

Recombinant LH is currently in its final stages of development; its marketing is anticipated in the near future.

Indications

The principal indication for gonadotropins is failure of PCOS patients to respond to antiestrogen therapy, mainly CC. In daily clinical practice, gonadotropins are also used in other situations:

1. Failure to achieve pregnancy with antiestrogens in PCOS patients, despite a favorable ovarian response leading to ovulation
2. Controlled ovarian stimulation before intrauterine insemination in "unexplained" or "mild male" infertility
3. Controlled ovarian stimulation for IVF
4. Treatment of male or female hypogonadotropic hypogonadism

Dose

The individualized treatment approach dictates tailoring the dose to the patient needs. The purpose of treatment in a PCOS patient is to reach ovulation of a single mature follicle (which hopefully contains a fertilizable oocyte). Consequently, a minimal starting dose is used (one ampoule, or even less), with dose increases as necessary. In contrast, the purpose of controlled ovarian stimulation in IVF is to obtain about 10 mature oocytes. In this situation, a higher starting dose is used (three ampoules). Recently, "soft" stimulation protocols have been advocated in IVF, aiming at achieving fewer oocytes, with transfer of only one or two embryos. This trend dictates a lower starting dose of only two ampoules.

Often, the starting dose is chosen based on previous performance of a given patient to gonadotropin treatment. A typical example is the high responder who needs only a minimal dose of gonadotropins for adequate response. Frequently, these patients are stimulated with a routine protocol to which they respond with a large number of growing follicles, and very high levels of E_2. A prudent approach in these situations is to abort the

cycle, given a high risk of OHSS. A reduced starting dose in subsequent stimulation cycles may lead to adequate ovarian response. In contrast, a known "low responder" can be safely stimulated with four ampules a day. In other word, detailed history of previous exposure to gonadotropins is very helpful. "Fine-tuning" of the dose from cycle to cycle will maximize the chances for success.

Protocols

For the typical PCOS patient, the "chronic low-dose" protocol has gained popularity in recent years. Based on the follicular threshold concept, a low starting dose is used (50 IU daily) for up to 14 d of stimulation. If a dominant follicle is not observed, the daily dose is increased by 25–50 IU for an additional 7 d. If a follicle of ≥11 mm is observed, the dose is kept unchanged until hCG is given (when the dominant follicle is ≥17 mm).

Ovarian stimulation of cycling patients usually starts with two ampoules. The ovarian response is assessed after 4–5 d of stimulation, and dose adjustments are done. The aim of ovarian stimulation in these patients is to reach up to four follicles of adequate diameter for ovulation. A larger number of ovulating follicles may increase the risk of multiple pregnancy and OHSS. This consideration advocates "softer" stimulation with a lower starting dose, although this approach may result in a lower pregnancy rate,; however, the risk of multiple pregnancy is not eliminated *(25)*. Because the number of ovulatory follicles (≥17 mm) is not predictive of high-order multiple pregnancy, ultrasonography may not be a valuable tool in reducing the risk of this outcome. Whether peak serum E_2 concentrations can be used to reduce this risk is also questioned *(25)*. The conclusion is that in these cases, pregnancy is a statistical event; therefore, patients must be aware that complications (i.e., multiple pregnancy and OHSS) cannot be totally eliminated. A practical approach may be to prefer IVF to IUI *(25)*, because it offers a higher pregnancy rate and leaves the decision of how many embryos to transfer to the uterus in the hands of the couple and the treating physician.

Gonadotropins in IVF are usually given after pituitary downregulation is established with a GnRH agonist. The usual starting dose is three ampoules, although deviations based on patients characteristics are common. If a GnRH antagonist is used, ovarian stimulation is started on d 2 or 3 of the cycle, and the antagonist is added after 5 d of stimulation or when the leading follicle reaches a diameter of 14 mm.

Preparations

The use of gonadotropins in fertility treatment became widespread when large-scale industrial production from urine collected from postmenopausal women was established. The relative biological activity of LH and FSH (75 IU each) was not changed from those early days. The product is sold today by manufacturers under different trade names (Pergonal®, Humegon®, Menogon®, and others). Further chemical purification steps have resulted in the production of urinary-derived FSH, sold under the names Metrodin®, Metrodin HP® (highly purified), and others. Parallel to the global trend of using recombinant DNA technology to synthesize human peptides, recombinant human FSH became available in the mid-1990s. Preparations like Puregon® and Gonal-F® were extensively studied and found to be safe and effective *(26)*. Recombinant LH was also synthesized and used successfully in the experimental setting *(27)*; its marketing debut is expected soon.

Monitoring

Objective assessment of ovarian response to gonadotropins relies on blood hormonal levels and ultrasound. The purpose of monitoring is to achieve the degree of ovarian stimulation that suits the individual patient needs. This may range from a single growing follicle in a PCOS with patient up to 10 mature follicles in an IVF case. In most cases, E_2 measurement after the fourth gonadotropin dose is used. A transvaginal ultrasound scan with a high-frequency probe allows for detailed and accurate assessment of the ovarian response. In addition, ultrasound is used to document the endometrial response to ovarian stimulation. Gonadotropin dosage is changed based on those two parameters. hCG (5000–10,000IU) is frequently given to trigger ovulation when the leading follicle reaches a diameter of ≥18 mm. A spontaneous LH surge may occur (in cycles during which a GnRH agonist or antagonist are not used to neutralize the pituitary). Therefore, if accurate timing of ovulation is needed (to plan IUI), P and LH measurements are obtained as the patient approaches the presumed ovulation date. If an oocyte-retrieval procedure is planned (i.e., for IVF), hCG is given 35 h before the procedure.

It is the responsibility of the treating fertility expert to minimize the risk of OHSS based on the monitoring plan and his best clinical judgment. If in her or his best judgment the patient is at risk, the cycle should be aborted and a new one planned. In this case, intercourse should be avoided, because if pregnancy is achieved, OHSS is a threat even though hCG was not given.

In most cases, luteal phase support is not needed; therefore, scheduled monitoring is not indicated. In high-risk situations for OHSS, the patient is instructed to limit physical activity until the results of the cycle are known and to report any symptoms that may indicate the development of OHSS.

In failed cycles, menses occurs earlier than expected based on a 14-d luteal phase duration. To avoid redundant and meaningless pregnancy tests, a blood hCG level is taken if menses does not occur 14 d after IUI (or scheduled intercourse).

Outcomes

Most PCOS patients (up to 95%) will respond to gonadotropin treatment. Stimulation cycles in these patients will yield one or two ovulatory follicles if a gentle, patient approach is used. Once ovulation is achieved, about a 20% clinical pregnancy rate is expected per ovulatory cycle. This rate decreases with the patient's age. A 30% early (≤12 wk), pregnancy loss can be expected. If three or more leading follicles are observed serious consideration should be given to aborting the cycle because of the risks of OHSS and multiple pregnancy.

In other indications for gonadotropin treatment, multifollicular response is commonly achieved; the pregnancy rate depends on other variables (i.e., patient age, sperm quality, history of previous pregnancy, anatomical or mechanical pelvic anomalies). Generally speaking, a 15% pregnancy rate per cycle can be expected.

PREMATURE OVARIAN FAILURE

Premature ovarion failure (POF) is a major source of frustration for both the patient and the fertility expert. Although numerous etiologies are known for this condition (iatrogenic, infections, genetic, autoimmune), in most cases we are left with an idiopathic condition, facing a wide choice of treatments and protocols with a narrow chance for success.

Meaningful success rates in POF patients can only be obtained using donated oocytes. This sad truth should be conveyed honestly to the patient, before embarking on any stimulation protocol. Most patients may choose to "role the dice" for the slim chance of having their own genetic child. For those patients, a wide range of treatment protocols have been advocated, some of which were tested in controlled studies *(28)*. The following therapeutic maneuvers try to enhance follicular recruitment and growth:

1. Suppression of pituitary FSH with estrogens and/or GnRH-a followed by ovarian stimulation (rebound phase)
2. Initiation of ovarian stimulation with GnRH-a followed by gonadotropins (the "flare" effect)
3. High doses of gonadotropins
4. Immune suppression with corticosteroids

The combined data of observational and controlled studies indicate that a POF patient has a 5–10% of conceiving after the diagnosis is made. Unfortunately, there is no evidence, at this stage, that any treatment can improve this pregnancy rate *(28)*.

REFERENCES

1. Webster J, Piscitelli G, Polli A, et al. A Comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 1994;331:904–909.
2. Verhelst J, Abs R, Maiter D, et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab 1999;84:2518–2522.
3. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. Drug Saf 1996;14:342.
4. Colao A, Di Sarno A, Sarnacchiaro F, et al. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 1997;82: 876–883.
5. Christian GM, Randolph JF, Kelch RP, Marshall JC. Reduction of GnRH pulse frequency is associated with subsequent selective FSH secretion in women with polycystic ovarian disease. J Clin Endocrinol Metab 1991;72:1278–1285.
6. Hopkins CC, Hall JE, Santoro NF, et al. Closed intravenous administration of gonadotropin releasing hormone (GnRH): safety of extended peripheral intravenous catheterization. Obstet Gynecol 1989;74:267–270.
7. Schriock ED, Jaffe RB. Induction of ovulation with gonadotropin-releasing hormone. Ob Gyn Sur 1986;41:414–423.
8. Martin K, Santoro N, Hall J, et al. Management of ovulatory disorders with pulsatile gonadotropin-releasing hormone. J Clin Endocrinol Metab 1990;71:1081A–1081G.
9. Crowley Jr. WF, McArthur JW. Stimulation of the normal menstrual cycle in Kallmann's syndrome by pulsatile administration of luteinizing hormone-releasing hormone (LHRH). J Clin Endocrinol Metab 1988;66:327.
10. Filicori M, Santoro N, Merriam GR and Crowley Jr. WF. Characterization of the physiologic pattern of episodic gonadotropin secretion throughout the human menstrual cycle. J Clin Endocrinol Metab 1986;62:1136–1144.
11. Filicori M, Flamigni C, Meriggiola MC, et al. Ovulation induction with pulsatile gonadotropin-releasing hormone: technical modalities and clinical perspectives. Fertil Steril 1991;56:1–12.
12. Filicori M, Flamigni C, Dellai P, et al. Treatment of anovulation with pulsatile gonadotropin-releasing hormone: prognostic factors and clinical results in 600 cycles. J Clin Endocrinol Metab 1994;79:1215–1220.
13. Hopkins CC, Hall JE, Santoro NF, at al. Closed intravenous administration of gonadotropin releasing hormone (GnRH): safety of extended peripheral intravenous catheterization. Obstet Gynecol 1989; 74:267–270.
14. Smith YR, Randolph JF Jr, Christman GM, et al. Comparison of low-technology and high technology monitoring of clomiphene citrate ovulation induction. Fertil Steril 1998;70:165–168.
15. Boostanfar R, jain JK, Mishell DR Jr, Paulson RJ. A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. Fertil Steril 2001;75:1024–1026.

16. Mitwally MF, Casper RF. Use of aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305–309.
17. Randall JM, Templeton A. Transvaginal sonographic assessment of follicular and endometrial growth in spontaneous and clomiphene citrate cycles. Fertil Steril 1991;56:208–212.
18. Unfer V, Costabile L, Gerli S, et al. Low dose of ethinyl estradiol can reverse the antiestrogenic effects of clomiphene citrate on endometrium. Gynecol Obstet Invest 2001;51:120–123.
19. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in polycystic ovary syndrome. N Engl J Med 1998;338:1876–1880.
20. Mitwally MF, Kuscu NK, Yalcinkaya TM. High ovulatory rates with use of troglitazone in clomiphene-resistant women with polycystic ovary syndrome. Hum Reprod 1999;14:2700–2703.
21. Vendermolen DT, Ratts VS, Evans WS, et al. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertil Steril 2001;75:310–315.
22. Ng EHY, Wat NM, Ho PC. Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blind placebo controlled trial. Hum Reprod 2001;16:1625–1631.
23. Lewit N, Kol S, Manor D, Itskovitz-Eldor J. Comparison of GnRH analogs and hCG for the induction of ovulation and prevention of ovarian hyperstimulation syndrome (OHSS): a case-control study. Hum Reprod 1996;11:1399–1402.
24. Ben-Chetrit A, Eldar-Geva T, Gal M, Huerta M, Mimon T, Algur N, Diamant YZ, Margalioth EJ. The questionable use of albumin for the prevention of ovarian hyperstimulation syndrome in an IVF programme: a randomized placebo-controlled trial. Hum Reprod 2001;16:1880–1884.
25. Gleicher N, Oleske DM, Tur-Kaspa, I, et al. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. N Engl J Med 2000;343:2–7.
26. Out HJ, Mannaerts BMJL, Driessen SGAJ, Coelingh Bennink HJT, for the European Puregon collaborative IVF study group. A prospective, randomized assessor-blind, multicenter study comparing recombinant and urinary follicle-stimulating hormone (Puregon vs. Metrodin) in in-vitro fertilization. Hum Reprod 1995;10:2534–2540.
27. The European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. J Clin Endocrinol Metab 2001;86:2607–2618.
28. van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review of therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 1999;5:483–492.