Evaluation and Treatment of Anovulatory and Unexplained Infertility

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KEYWORDS

• Anovulatory disorders • Unexplained infertility • Polycystic ovarian syndrome
• Obesity

KEY POINTS

- A low-caloric diet and a structured exercise program should be recommended for obese anovulatory women.
- Clomiphene citrate is the initial treatment for most women with ovulatory dysfunction and unexplained infertility.
- Ovulation induction monitoring may be useful to document ovulation and for the timing of intercourse or intrauterine insemination.
- Letrozole is an option for women who have failed to ovulate or conceive as well as for those with thin endometrial lining or bothersome side effects using clomiphene citrate.
- Gonadotropins are second-line agents for anovulation and require close observation because of the high rates of multiple pregnancies.
- The role of laparoscopy in the evaluation and treatment of ovulatory disorders or unexplained infertility is unclear.

INFERTILITY AND OVULATORY DYSFUNCTION

With an average monthly fecundity rate of only 20%, human beings are not fertile compared with other mammals.[1] Overall, 10% to 15% of couples have difficulties conceiving, or conceiving the number of children they want, and many will seek specialist fertility care at least once during their reproductive lifetime. Infertility is

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a disease defined as the failure to conceive after 12 months of regular unprotected intercourse in a reproductive-aged couple. Beginning the fertility evaluation prior to one year of infertility is warranted when the woman has known or suspected anovulation or tubal factor, is older than 35 years, or if her partner has a suspected male factor.[2] Infertility affects a large number of couples. National surveys indicate that 11% of nulliparous married women younger than 29 years have nonvoluntary infertility and that rate increases to 27% of nulliparous married women aged 40 to 44 years.[3]

Ovulatory dysfunction is one of the major causes of infertility, affecting 25% of couples with infertility.[4] The World Health Organization (WHO) has classified anovulation into 3 categories.[5]

1. WHO I is anovulation with low gonadotropin levels, sometimes referred to as hypogonadotropic hypogonadism. Women with this form of anovulation have low levels of endogenous estrogen, do not develop an adequate endometrial lining, and will usually not bleed when given a progestin challenge to induce progestin withdrawal bleeding. Clinically, these women will often have a body mass index less than 20 and are involved in high-intensity exercise or have high stress levels. In addition, they usually do not respond to oral ovulation induction medications because of hypothalamic-pituitary dysfunction and will usually need injectable gonadotropins that directly stimulate the ovarian follicles to ovulate.
2. WHO II is anovulation with normal levels of gonadotropins. Women with this type of anovulation make endogenous estrogen and will usually respond with menstrual bleeding when given a progestin challenge. Polycystic ovarian syndrome (PCOS) is an example of this type of ovulatory disorder. Clinically, these women usually have a functioning hypothalamus and pituitary system and generally respond to oral ovulation induction medications.
3. WHO III is anovulation with elevated gonadotropins. Women of reproductive age who have elevated gonadotropins are usually a result of premature ovarian failure, either caused by unknown causes or caused by ovarian damage from chemotherapy, radiation, or surgery. Clinically, these women have limited ovarian follicles that are not responding to high endogenous follicle-stimulating hormone (FSH) stimulation. Similarly, they do not respond to additional ovarian stimulation through fertility medications and usually require third-party reproduction, such as an egg donor, to conceive.

POLYCYSTIC OVARIAN SYNDROME

Most women with anovulatory infertility have PCOS, and most women with PCOS are overweight or obese. This combination requires careful attention to the morbidities associated with obesity and the need for lifestyle intervention with exercise and dietary changes to achieve weight loss. PCOS prevalence in the population and impact on reproduction as well as overall health warrants special consideration. PCOS is covered in depth in the article by Bates and Propst elsewhere in this issue.

UNEXPLAINED INFERTILITY

Approximately 25% of couples will have no identifiable cause for their subfertility following a routine evaluation.[6] The diagnosis of unexplained infertility requires a normal semen analysis with evidence of tubal patency and ovulation. As one would surmise, the absences of an abnormal finding does not preclude the presence of an obstacle to normal reproduction (**Table 1**). However, exhaustive testing or pursuit of potential causes of infertility, in most cases, will not increase the efficacy of treatment

Table 1
Assessment of endocrine function in infertility patients

Endocrine System Screened	Laboratory Test
Thyroid	Thyroid stimulating hormone
Pituitary	Prolactin
Androgen excess	Total and free testosterone, DHEA-S
Congenital adrenal hyperplasia	17-OH progesterone
Cushing syndrome	24-h urine cortisol or overnight dexamethasone suppression test

Abbreviations: DHEA-S, Dehydroepiandrosterone Sulfate; 17-OH, 17-hydroxyprogesterone.
Data from Kamath MS, Bhattacharya S. Demographics of infertility and management of unexplained infertility. Best Pract Res Clin Obstet Gynaecol 2012 Aug 27. [Epub ahead of print].

or the potential for a successful delivery. Likewise, treatment aimed at achieving a successful pregnancy in women with unexplained infertility is by definition empiric, and much controversy surrounds the risk versus benefit of ovulation induction in this population. The clinician must weigh the potential benefit based on inconclusive data with the known risk of multiple gestations and other possible negative sequelae of supraphysiologic estrogen levels.

FERTILE WINDOW

There are a limited number of days in a menstrual cycle when a woman is fertile. In a landmark study that defined the fertility window, investigators looked at the timing of intercourse in relation to ovulation for 221 couples and evaluated subsequent pregnancy rates.[7] This study found that the fertile window begins 5 days before ovulation and ends on the day of ovulation. The highest likelihood of becoming pregnant is from 2 days before ovulation until the day of ovulation, with the pregnancy likelihood of approximately 35% on those 3 days. In a European study of 770 couples using natural family planning methods of contraception, 650 couples had intercourse at least once during the preovulatory period they were supposed to be abstaining, resulting in 433 pregnancies.[8] This study also found that the fertile window begins 5 days before ovulation and ends at ovulation, with the peak fecundity occurring with intercourse 2 days before ovulation. Women are most fertile the 2 days before ovulation and should be instructed to time intercourse during this period so that sperm are present in the genital tract before the follicle ovulates and releases the oocyte.

OVULATION INDUCTION MONITORING

When using medications for ovulation induction, it is imperative to document ovulation or lack thereof. Knowing whether or not ovulation has occurred allows not only for proper timing of intercourse or intrauterine insemination (IUI) but also helps define the method of therapy for subsequent cycles in the event ovulation does not occur. Several methods exist to access ovulation ranging from minimal to invasive testing.

1. The presence of regular menses and moliminal symptoms before menses is a sign that the woman is ovulatory. The luteal phase following ovulation to menses is typically 14 days, regardless of the length of time between menses. Ovulation typically occurs on day 10 of a 24-day menstrual cycle, day 14 of a 28-day menstrual cycle, and day 21 of a 35-day menstrual cycle.

2. Basal body temperature measurements are an inexpensive method of detecting ovulation.[9] The body temperature will increase slightly after ovulation in response to an increase in endogenous progesterone. The cumbersome nature of monitoring daily temperatures first thing in the morning and because the temperature increase will occur only after ovulation and the fertility window is closed make charting basal body temperature less useful than other ovulation detection methods.
3. Urine luteinizing hormone (LH) detection kits detect the endogenous LH surge that occurs 36 to 48 hours before ovulation.[10] This method seems to be an easy and reliable method that patients are compliant with. Testing should begin 4 days before expected ovulation, based on the cycle length. Digital and nondigital ovulation predictor kits are available. The digital kits are more expensive but easier to interpret and are preferred by volunteers over the nondigital kits.[11] Once LH has been detected in the urine, patients should be instructed to have intercourse that day and the following day or scheduled for an IUI. Detection of ovulation and proper timing of intercourse doubled the chances of conception (odds ratio 1.89) in a cohort of women with no known obstacles to pregnancy.[12] This finding raises the possibility that a subset of unexplained infertility may be caused by poorly timed intercourse.
4. Luteal serum progesterone levels can also be measured to confirm that ovulation has occurred. When ovulation has occurred, the midluteal phase serum progesterone is greater than 3 ng/mL and preferably greater than 10 ng/mL. Serum progesterone should be measured approximately 1 week after expected ovulation. This practice will document ovulation but provides no guidance in the timing of intercourse or IUI.[13]
5. For patients that have difficulty detecting ovulation by ovulation predictor kits, ovarian follicular development can be monitored by ultrasound. When the lead follicle is 20 mm or more, ovulation can be induced with an injection of human chorionic gonadotropin (hCG). A recent retrospective study found a higher pregnancy rate when the lead follicle was 23 to 28 mm when given hCG.[14] Intercourse or an IUI can be timed for 12 to 36 hours following the hCG injection. Alternatively, the IUI can be scheduled after detecting ovulation using an LH detection kit. However, using LH testing results in higher rates of canceled cycles because of a false-negative rate of approximately 15% with LH testing.[15]

MEDICAL AND SURGICAL TREATMENT OPTIONS

Clomiphene Citrate

A variety of medications can be used to induce ovulation in women with ovulatory dysfunction. The most common initial ovulation induction medication is clomiphene citrate (CC), which can be combined with timed intercourse or IUI. CC is a nonsteroidal triphenylethylene derivative that has both estrogen agonist and antagonist properties.[9] CC was approved for clinical use in 1967 and predominately acts as an estrogen antagonist. CC binds to the estrogen receptors primarily in the hypothalamus. The prolonged binding of CC to the estrogen receptors interrupts the negative feedback of the increasing estrogen level and results in continued production of FSH, which stimulates follicular growth and maturation.[9] It is indicated for use in anovulatory women with normal thyroid and prolactin and who produce endogenous estrogen. It is also indicated for the empiric treatment of women with unexplained infertility when it is most effective when combined with IUI.[9]

CC is administered orally, beginning 3 to 5 days after the onset of a spontaneous or progestin-induced menses.[9] Contrary to traditional practice, a recent study suggested

that women with anovulatory women with PCOS who began CC without first having a progestin withdrawal had significantly higher conception and live birth rates than women who took a progestin to induce menses before starting CC.[16] Treatment typically begins with a single 50-mg tablet daily for 5 days. Ovulation usually occurs within 5 to 10 days after the last dose of CC. It is important to confirm ovulation in patients that are using CC and to continue with the lowest dose that achieves ovulation. There is no benefit to increasing the dose if patients ovulate but do not get pregnant during that cycle. If patients remain anovulatory, the dose should be increased. Most patients that will ovulate on CC will ovulate at the 100-mg dose or less, with decreasing rates of ovulation at higher doses for patients resistant at the 100-mg dose. The United States Food and Drug Administration's maximum recommended dose is 100 mg/d for 5 days; however, some physicians will continue to increase the dose in 50-mg increments up to 250 mg until ovulation is achieved.[9] Some CC-resistant women who fail to ovulate with a 5-day regimen of 250 mg/d may respond to an 8-day course of the same dose.[17]

The use of CC in anovulatory women results in ovulation rates of approximately 75% and overall pregnancy rates of 50% to 70% of those who ovulate and continue the medication for up to 12 cycles.[18,19] Cycle fecundity is approximately 15% in anovulatory women who ovulate in response to CC. Most conceptions occur within the first 6 ovulatory cycles. Most women (88%) who conceive with the assistance of CC do so at doses of 150 mg or less and 52% conceive at doses of 50 mg.[19] If ovulation has not occurred at 100-mg or 150-mg doses, complimentary or alternative medications for ovulation induction should be implemented, which is discussed later.

Similar to ovulatory women, the fecundity rate for women using CC decreases with age. In a large retrospective analysis of 4000 CC cycles with IUI of anovulation and unexplained infertility, the per-cycle fecundity rates were 10% for women younger than 35 years but 4% or less for women aged 41 years or older.[20]

Empiric treatment with CC for couples with unexplained infertility is a first-line therapy. CC or IUI as individual treatments do not improve the baseline chance of conception each month (fecundity) compared with historical controls, but the combination of CC with IUI can double the monthly fecundity rate.[21]

The incidence of multiple gestations with the use of CC is approximately 8% and most of these are twins. Triplet or higher-order multiple births are rare but can occur.[9] The most common side effect is vasomotor symptoms, which occur in approximately 10% of women taking CC. Less common side effects include mood swings, breast tenderness, headaches, and nausea. Visual disturbances occur in less than 2% but occasionally can be permanent, and CC use should be stopped in patients who have them.

There is not an increase of congenital anomalies or birth defects in the children conceived by women taking CC. Although some retrospective studies have reported an increased risk of ovarian cancer, overall there does not seem to be an increase in the incidence of ovarian or breast cancer in infertile women who have taken CC.[22,23]

Letrozole

Letrozole is an aromatase inhibitor that blocks the conversion of androgens to estrogens. Letrozole is indicated for the treatment of postmenopausal women with hormone-receptor-positive or unknown breast cancer. However, it is increasingly being used off label for ovulation induction. Letrozole's mechanism of action for ovulation induction is thought to be the release of the hypothalamus and the pituitary from the negative feedback of estrogen (**Fig. 1**).[24] With a lower estradiol level, there is less negative feedback on the hypothalamus and pituitary and the levels of GnRH and,

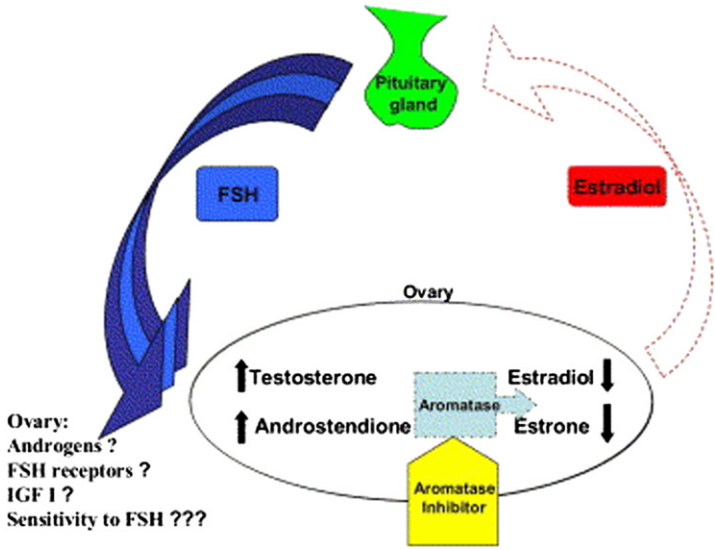

Fig. 1. Hypothalamic Pituitary Ovarian Axis and Aromatase Inhibition. IGF, Insulin like Growth Factor. (*From* Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006;85(2):277–84; with permission.)

therefore, FSH is increased, which leads to further stimulation of follicular development. Letrozole can be used to stimulate ovulation in women who do not respond to CC or in women that have side effects with CC, such as uncomfortable vasomotor symptoms, visual changes, or headaches.[25] These side effects are rare in patients using letrozole for ovulation induction. Some patients will have a thin endometrium (less than 7 mm) when taking CC. The proliferation of the endometrium is stimulated by estrogen. Because CC acts as an estrogen antagonist, in some women the endometrial lining is thin, which may reduce implantation. Letrozole does not have the same antiestrogen effect on the endometrium.[26,27] Letrozole can be used in combination of timed intercourse or IUI.

Letrozole is typically prescribed at a starting dose of 2.5 to 5.0 mg and can be increased by increments of 2.5 mg.[28] The highest commonly used dose is 7.5 mg. It is given for 5 consecutive days like CC and can be started as early as day 3 of the cycle. A recent publication reported using letrozole at higher doses, up to 12.5 mg/d, with high rates of ovulation among patients who did not respond to lower doses.[29]

The first report of letrozole being used as an ovulation induction medication was published in 2001 and looked at 12 women who had failed to ovulate with CC treatment and an additional 10 women who ovulated on CC but who had an endometrial thickness of 5 mm or less.[26] Letrozole 2.5 mg was given for 5 days (day 3 to 7). The rate of ovulation increased from 44% while taking CC to 75% with letrozole. The endometrial thickness went from 5 mm or less with CC to a mean endometrial thickness of 8 mm with letrozole.

Several studies have looked at letrozole versus CC as a first-line therapy in women with anovulatory infertility (**Table 2**).[28] Begum and colleagues[27] looked at the rate of ovulation, endometrial thickness, and pregnancy rates between 64 women who failed to ovulate when taking CC 100 mg. These women were randomly assigned to either CC 150 mg or letrozole 7.5 mg for 5 days. This study showed higher rates of ovulation (62.5% vs 37.5%) endometrial thickness, and overall pregnancy rate (40.6% vs 18.8%) in to the letrozole group compared with the CC group.

Table 2
RCTs comparing letrozole versus clomiphene as first line for anovulatory women

S. No.	Authors	Study Design	Treatment Arms	Numbers Cycles	Endometrial Thickness (mm)	Ovulation Rates (%)	Pregnancy Rates (%)
1	Atay et al,[30] Turkey, 2006	RCT	Letrozole 2.5 mg vs clomiphene 100 mg	51 vs 55	8.4 ± 1.8 vs 5.2 ± 1.2	82.4 vs 63.6	21.6 vs 9.1
2	Bayar et al,[10] Turkey, 2006	RCT	Letrozole 2.5 mg vs clomiphene 100 mg	99 vs 95	8[a] vs 8[a]	65.7 vs 74.7	9.1 vs 7.4
3	Badawy et al,[31] Egypt, 2009	RCT	Letrozole 5 mg vs clomiphene 100 mg	540 vs 523	8.1 ± 0.2 vs 9.2 ± 0.7	67.5 vs 70.9	15.1 vs 17.9

Abbreviation: RCT, randomized controlled trial.
[a] Values represent median.
Data from Kamath MS, George K. Letrozole or clomiphene citrate as first line for anovulatory infertility: a debate. Reprod Biol Endocrinol 2011;9:86.

Atay and colleagues[30] performed a randomized controlled trial (RCT) that evaluated 106 women with PCOS to receive either letrozole (2.5 mg) or CC (100 mg) for 5 days. The ovulation rates (82.4% vs 63.6%) and clinical pregnancy rates (21.6% vs 9.1%) were significantly higher in the letrozole group. However, in the largest RCT, involving more than 400 women and 1000 cycles, Badawy and colleagues[31] compared letrozole versus CC for women with PCOS and found similar ovulation (67.5% vs 70.9%) and pregnancy rates (15.1% vs 17.9%). The investigators concluded that there was no benefit for letrozole over CC, especially because letrozole is more expensive than CC.

A review of clinicaltrials.gov shows that several trials are underway that evaluate CC versus letrozole, including 2 by the National Institutes of Child Health and Human Development's The Reproductive Medicine Network. The first, Pregnancy in Polycystic Ovarian Syndrome II, is comparing letrozole versus CC for women with PCOS, whereas the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation trial is assessing the risk and benefit of superovulation with letrozole, CC, or gonadotropins in women with unexplained infertility.

One advantage of letrozole is that it has a lower incidence of multiple pregnancies when compared with CC or gonadotropins.[32] Several years ago, there was some concern raised about higher rates of birth defects in women conceived after taking letrozole. An abstract presentation at the American Society for Reproductive Medicine in 2005 suggested an increased risk of congenital malformation compared with a low-risk obstetric control group. The manufacturer of letrozole (Novartis) subsequently sent a warning letter to doctors that letrozole was not to be used as an ovulation induction medication. However, a succeeding Canadian study of more than 900 infants that compared the birth defects of infants born to mothers taking letrozole versus CC found similar rates of defects in the letrozole infants and the CC infants (2.4% vs 4.8%).[33] Patients should be informed that letrozole is being prescribed off label so they can make an informed decision and are not concerned when they read the package instructions.

Gonadotropins

The administration of exogenous FSH or human menopausal gonadotropin is considered the second line of therapy for ovulation induction for patients who do not respond to oral therapy or have been unsuccessful in achieving a pregnancy.[34] Gonadotropins are the first line of treatment of ovulation induction in the WHO I category of hypogonadotropic hypogonadism because patients are not producing adequate levels of FSH and LH and do not respond to oral medications, such as CC or Letrozole.[5]

When starting gonadotropins, patients must understand the expense of the medications as well as the commitment required in monitoring the effects of the medication. Close monitoring of serum estradiol levels and follicular number and growth by an experienced physician is mandatory to minimize the risks of high-order multiple pregnancies (HOMP). The key is to start with lower dosages of medication, 50 to 100 IU daily. Clinical judgment is necessary in dosing the medication and adjusting the dose throughout the cycle according to estradiol levels and follicular growth.

There are significant risks of twins (11%) and high-order multiples (3.0%–4.1%) when using gonadotropins.[35] HOMP are positively related to the use of high doses of gonadotropin, higher number of 7- to 10-mm preovulatory follicles, and higher estradiol.[36] HOMP are also more common in younger patients. For women aged younger than 32 years, HOMP was 6% for 3 to 6 follicles and 20% for 7 or more follicles. For women aged 32 to 37 years, HOMP was 5% for 3 to 6 follicles and 12% for 7 or more follicles. HOMP are also most likely to occur in the first gonadotropin treatment cycle and were rare after the second treatment cycle.[37]

Strategies successful in reducing HOMP include using CC earlier in the cycle before starting gonadotropins, using low gonadotropin doses, cancellation for more than 3 follicles that are more than 10 to 15 mm. By using a conservative strategy, 5% to 20% of cycles may be canceled but HOMP rates can be less than 2% and pregnancy rates can average 10% to 20% per cycle.[36]

Metformin

Metformin is an antihyperglycemic that is widely used off label as an adjunct to ovulation induction or superovulation. The net effect of lowering serum glucose in women who are anovulatory is a reduction of androgens and potential resumptions in ovulation.[38] Although numerous case series and cohort studies have demonstrated a favorable impact on pregnancy rates following ovulation induction, randomized trials have yielded mixed results.[39–41] Metformin has not been shown to increase the chances of a live birth in women with unexplained infertility. The role of metformin in the treatment of PCOS and ovulation induction is examined at length in the article by Bates and Propst elsewhere in this issue.

Glucocorticoids and Clomiphene Citrate

In cases of CC resistance in the setting of normal and elevated dehydroepiandrosterone, daily dexamethasone (0.5–2.0 mg) or prednisone (5 mg) during the follicular phase have been used adjunctively with CC. The combination of glucocorticoids and CC has been shown to significantly increase the rate of ovulation and pregnancy when compared with CC alone in randomized trials.[42–44]

Oral Contraceptives and Clomiphene Citrate

Two months of oral contraceptive pill treatment before ovulation induction with CC may improve the observed rate of ovulation and pregnancy.[45] Treatment with Oral Contraceptive Pills (OCPs) is associated with lower levels of testosterone and androstenedione, which probably accounts for the improved ovarian response to CC.

Timed Intercourse Versus IUI

The decision to proceed with timed intercourse or IUI has to do with the quality of the partner's semen; the presence of a cervical factor, such as cervical stenosis; and the previous treatment history of the patient. Semen analyses can vary based on illness, stress, and recent ejaculations. A long abstinence interval increases the sperm count but decreases the percent motile and IUI pregnancy rates.[46] Higher pregnancy rates are seen in daily or every-other-day intercourse versus once weekly because the percentage of normal sperm seems to correlate with the frequency of ejaculations.[10]

If an abnormal semen analysis is obtained, it is best to repeat it 6 to 8 weeks later. After 3 cycles of ovulation and timed intercourse, IUI should be recommended. However, if the total motile sperm count is less than 10 million, in vitro fertilization or intracytoplasmic sperm injection is the most cost-effective treatment.[47]

For women with anovulation and a partner with a normal semen analysis, timed intercourse after ovulation induction is the authors' recommended first-line treatment. For couples with unexplained infertility, IUI will improve success rates with both CC and gonadotropins compared with timed intercourse or intracervical insemination.[21,48]

Laparoscopy

Laparoscopy has become the gold standard for the diagnosis and surgical treatment of pelvic pathology. However, its role in the evaluation and treatment of infertility has become less clear with the advent and success of assisted reproductive technologies

(ART). Some investigators argue that the diagnosis of unexplained infertility cannot be made without a surgical or laparoscopy confirmation of normal pelvic anatomy. A recent trial of diagnostic laparoscopy found pelvic pathology in 83% of women with a normal routine fertility evaluation who failed to conceive following 3 months of ovulation induction. The investigators also suggested that surgical intervention increased the chances of pregnancy.[49] Others have argued that even in the presence of tubal occlusion due to prior tubal ligation, adhesions and/or endometriosis, surgical intervention is inferior to ART.[50]

One possible exception to the purported demise of reproduction surgery can be found in laparoscopic ovarian drilling (LOD). This use of thermal energy to damage the ovarian cortex and reduce production of androgen has been recommended as the second-line therapy for patients with PCOS who are resistant to ovulation induction.[34] Although LOD has a significantly lower risk of multiple pregnancies, the live birth rate is also lower when compared with ovulation induction agents.[51] Nonetheless, laparoscopy and LOD may play a role in properly selecting women for whom advanced ovulation induction is not practical or available or for those who wish to avoid the risk of multiple gestations and/or the use of gonadotropins.

SUMMARY RECOMMENDATIONS

- A low-caloric diet and a structured exercise program should be recommended for obese anovulatory women. These lifestyle changes can result in weight loss and spontaneous ovulation.
- CC is the initial treatment for most women with ovulatory dysfunction and unexplained infertility. CC should be started at 50 mg for 5 days of the cycle, starting between the third and fifth day of the cycle. The dose can be increased by 50 mg if patients do not ovulate but should not be increased if ovulation is occurring.
- Once ovulation induction methods are prescribed, some type of ovulation induction monitoring should be performed and ovulation should be documented.
- Letrozole is an option for women who have failed to ovulate using CC. It is typically started at a dosage of 2.5 to 5.0 mg for 5 days of the cycle, starting between the third and fifth day of the cycle. Letrozole is also beneficial when patients have an endometrial lining of 6 mm or less on CC or patients have bothersome side effects on CC.
- Gonadotropins are second-line agents for anovulation. They should be used with caution because of the high rates of multiple pregnancies and require close observation of the developing follicular size and number.
- Laparoscopic ovarian diathermy may play a limited role as a second-line intervention for patients with PCOS. Laparoscopy's role in the evaluation of unexplained infertility is controversial.

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