

Ovulation induction with clomiphene citrate

INTRODUCTION - clomiphene citrate (clomid) has been the most widely used treatment for fertility enhancement for the past 40 years. clomiphene (clomid) was a revolutionary advance in reproductive medicine and quickly became popular for induction of ovulation because of its ease of administration and minimal side effects. Ironically, it was initially synthesized as a synthetic estrogen for possible use as a contraceptive.

The pharmacology, indications, and administration of clomiphene citrate will be reviewed here. Other drugs for induction of ovulation are discussed elsewhere.

PHARMACOLOGY — clomiphene (clomid) is a triphenylethylene derivative distantly related to diethylstilbestrol. It acts as a selective estrogen receptor modulator, similar to tamoxifen and raloxifene. All three drugs are competitive inhibitors of estrogen binding to estrogen receptors and have mixed agonist and antagonist activity depending upon the target tissue.

The commercially available form of clomiphene is the dihydrogen citrate salt (clomiphene citrate). It contains two stereoisomers: *zu*-clomiphene (38 percent) and *en*-clomiphene (62 percent), which were originally called the *cis*-isomer and *trans*-isomer, respectively. *En*-clomiphene is cleared rapidly, while *zu*-clomiphene has a long half-life. The two clomiphene isomers have mixed estrogenic and antiestrogenic effects that vary among species. *Zu*-clomiphene appears to have greater estrogenic activity than *en*-clomiphene.

¹⁴C-labeled clomiphene citrate is absorbed by the gastrointestinal tract. Fifty percent of the oral dose is excreted after five days, but radioactivity from labeled clomiphene appears in the feces up to six weeks after administration. However, the pharmacologic effect of clomiphene citrate is brief.

MECHANISMS OF ACTION - clomiphene (clomid) exerts its major effects on the hypothalamus, pituitary, ovary, and uterus. Hypothalamus and pituitary - Most evidence suggests that the primary site of clomiphene action is the hypothalamus, where it appears to bind to hypothalamic estrogen receptors, thereby blocking the negative feedback effect of circulating endogenous estrogen.

Elevated plasma concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) result from clomiphene treatment. When clomiphene is administered to normally cycling women, LH pulse frequency (but not amplitude) increases, suggesting an increase in hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency. In women with polycystic ovary syndrome, who have a high frequency pattern of LH pulses at baseline, the administration of clomiphene citrate produces an increase in LH pulse amplitude, as well as an increase in the daily plasma concentrations of LH and FSH.

In vitro data suggest that clomiphene citrate also has a pituitary site of action by increasing the gonadotropin response to GnRH.

Ovary — The ovarian actions of clomiphene are for the most part secondary to the effects of elevated FSH and LH on ovarian follicular development. Clomiphene (clomid) is an estrogen agonist in the absence of estrogen, thereby enhancing FSH stimulation of LH receptors in granulosa cells.

Direct effects of clomiphene on the ovary are not well understood but probably exist. As an example, clomiphene may activate aromatase, the enzyme that increases conversion of androstenedione to estrogen.

Uterus and cervix - clomiphene (clomid) acts primarily as an antiestrogen in the uterus, cervix, and vagina. The following findings have been noted, which may at least partially explain the low pregnancy rates observed in clomiphene-induced ovulatory cycles: The normal increase in uterine volume and endometrial thickening that occurs during spontaneous menstrual cycles is largely absent during clomiphene-induced cycles despite higher estrogen levels. Some, but not all, studies have found abnormal luteal phase endometrial morphology in clomiphene-induced cycles. clomiphene (clomid) citrate directly impairs implantation efficiency in mice. Data on the effect of clomiphene on cervical mucus are conflicting. While one study found no detrimental effect, another noted a decrease in the quality and quantity of cervical mucus at all clomiphene doses. In a meta-analysis, a detrimental effect was seen only with doses \geq 100 mg/day.

Other - clomiphene (clomid) citrate has no apparent progestational, corticotropic, androgenic, or antiandrogenic effects, nor does it interfere with adrenal or thyroid function.

CLINICAL INDICATIONS - clomiphene (clomid) citrate is used to induce ovulation in selected populations of anovulatory women, and in women with ovulatory infertility as a strategy to increase follicular number and enhance fertility.

Information on the use of clomiphene in men is found

elsewhere.

Oligoovulation or anovulation - The clinical approach to ovulation induction requires a uniform understanding of the causes and nomenclature of anovulation. The classification adopted by the World Health Organization (WHO) provides a practical guide to appropriate therapeutic intervention. The primary indication for clomiphene citrate is infertility secondary to oligoovulation or anovulation in normogonadotropic, normoprolactinemic, euthyroid women (WHO class 2). These women produce gonadotropin and estrogen (as evidenced by spontaneous menses or withdrawal bleeding in response to a progesterone challenge) and are therefore able to respond to clomiphene, which is the best initial treatment in this setting. This group includes women with polycystic ovary syndrome. In contrast, hypergonadotropic women (WHO class 3) with FSH concentrations at or above 40 mIU/mL who have diminished follicular reserve, have little or no response to clomiphene. Hypogonadotropic women (WHO class 1) with low FSH and low endogenous estrogen production (eg, exhibiting failure to respond to progesterone challenge) are also unlikely to respond successfully to clomiphene citrate, given their hypogestrogenemia.

In women with anovulatory infertility (in general those with polycystic ovary syndrome) an ovulatory rate of 80 percent and a pregnancy rate of 30 to 40 percent can be expected. Of those who ovulate, approximately 50 percent do so at a dose of 50 mg.

The ovulatory rate is lower with increasing age, body mass index, insulin resistance, and free androgen index.

Luteal phase defect - Luteal phase defect was initially described as a defect in the corpus luteum production of progesterone, but it can also be caused by a poor endometrial response to progesterone stimulation. An important problem in making this diagnosis is that luteal phase defect is often present in fertile women. Moreover, the body of available evidence demonstrates that the traditionally used endometrial histologic dating is not effective in differentiating fertile and infertile women and should not be used. As a result, luteal phase defect is now described as abnormally low levels of corpus luteum progesterone production or a short luteal phase. However, the existence of this entity has been questioned and the diagnostic criteria are not yet established. The potential mechanism of clomiphene's benefit in women with luteal phase defect is increasing serum FSH, follicular number, and therefore serum estradiol levels, which should lead to an increase in the number of corpora lutea and higher midluteal progesterone concentrations.

Two randomized trials comparing clomiphene with progesterone treatment for inadequate luteal phases demonstrated similar overall pregnancy rates (20 to 30 percent) with each treatment. clomiphene (clomid), unlike exogenous progesterone, does not prolong the luteal phase, thereby lessening the anxiety and period of uncertainty of infertile couples concerning possible conception.

Unexplained infertility - Unexplained infertility is the diagnosis applied to couples who have no identifiable etiology of their infertility after a comprehensive infertility evaluation. The estimated per cycle fecundity rate in couples with unexplained infertility followed expectantly is 1.3 to 4.1 percent compared with 20 to 25 percent in couples without infertility. Treatment strategies in these couples are empiric. Intrauterine insemination (IUI) either alone or in combination with superovulation is a viable option, keeping in mind the high spontaneous pregnancy rates in these patients.

The efficacy and limitations of clomiphene therapy in couples with unexplained infertility are illustrated by the following data from randomized trials: A randomized placebo-controlled crossover trial administered clomiphene or placebo for up to three months to 118 women with unexplained infertility. The greatest increase in three-month conception rates occurred when clomiphene was given to women with infertility lasting more than three years (14 versus 3 percent for placebo). The authors suggested that couples with unexplained infertility of less than three years duration are essentially normal, but there is often a subtle disorder of ovulation corrected by clomiphene therapy in those with more than three years of infertility. Another randomized trial evaluated whether treatment with clomiphene citrate and intrauterine insemination (IUI) resulted in increased fecundity when compared with periovulatory intercourse in 67 couples with either unexplained infertility or surgically corrected endometriosis. Fourteen pregnancies occurred in 148 treated cycles, which was significantly greater than the five pregnancies in 150 untreated cycles (fecundity 9.5 versus 3.3 percent). A third prospective, randomized, crossover trial of 26 couples with unexplained infertility compared LH-timed IUI treatment with clomiphene-stimulated, human chorionic gonadotropin-timed IUI. One pregnancy occurred in 20 cycles of the first treatment, whereas six pregnancies occurred in 23 cycles of the latter therapy. The authors concluded that clomiphene increased the pregnancy rate per cycle in this population. A Cochrane analysis of six clinical trials concluded that clomiphene/IUI treatment was superior to no treatment

or placebo for unexplained subfertility (odds ratio 2.5 for clinical pregnancy per treatment cycle).

The efficacy of clomiphene citrate in couples with unexplained infertility has been attributed to correction of subtle ovulatory dysfunction and/or ovulation of more than one oocyte.

Controlled superovulation — In addition to being used as an empiric therapy for unexplained infertility, clomiphene has been used with assisted reproductive technologies. It promotes the development of multiple follicles when given to ovulatory women, leading to multiple ovulation and supraphysiologic luteal phase progesterone levels. It can be given alone, or it may be used to reduce the amount of more expensive gonadotropins administered for controlled superovulation in preparation for in vitro fertilization-embryo transfer, gamete intrafallopian transfer, or other assisted reproductive technologies.

HOW TO USE CLOMIPHENE CITRATE

Pretreatment evaluation - Absent or infrequent ovulation is the main indication for clomiphene citrate treatment. The menstrual history alone may be diagnostic of anovulation; however, if the diagnosis is uncertain, ovulatory dysfunction should be established by testing. Disorders of pituitary, adrenal, and thyroid origin that can cause anovulation should be excluded prior to the initiation of therapy as targeted treatment of these endocrinopathies can result in normal ovulation.

The pretreatment evaluation should include: A complete history and physical examination. Semen analysis to identify seminal abnormalities that also might require treatment. Hysterosalpingogram if the clinical history suggests uterine or tubal pathology may also be present, and in women over 35 years of age to avoid ineffective treatment when fertility is in decline. Serum FSH concentration for women older than 35 years of age and women at any age with unexplained infertility, a single ovary, or a history of ovarian surgery, endometriosis, or poor response to gonadotropins. Induction of ovulation with clomiphene is unlikely in women with elevated FSH concentrations. An endometrial biopsy may be useful to assess hyperplastic changes in women with chronic anovulation. A pelvic examination, or a pelvic ultrasound examination, may be performed prior to the treatment cycle to rule out ovarian cysts, especially in patients with known tendency to form functional cysts.

Initiation of therapy, duration and dosage — clomiphene (clomid) citrate therapy for ovulation induction is typically started on the fifth day of a cycle, following either spontaneous or induced bleeding. However, the results of therapy, in terms of ovulatory rates, pregnancy, or spontaneous miscarriage, are comparable when clomiphene is begun as early as day two. For in vitro fertilization, clomiphene is begun on the third day of the cycle because earlier administration is thought to stimulate the development of multiple follicles, which is desirable in this setting.

There are no laboratory or clinical parameters that predict the dose of clomiphene necessary to achieve ovulation. clomiphene (clomid) is initially begun empirically at a dose of 50 mg daily for five days; starting with a higher dose does not result in higher pregnancy rates. If ovulation does not occur in the first cycle of treatment, the dose is increased to 100 mg. Thereafter, dosage is increased by increments of 50 mg to a maximum daily dose of 250 mg (although 100 mg is the maximum dose approved by the FDA; the American College of Obstetricians and Gynecologists does not encourage the use of more than 150 mg) until ovulation is achieved, at which point the woman should attempt to conceive for four to six cycles. Longer courses (8 days) can be considered in clomiphene resistant women if exogenous gonadotropin therapy, the preferred therapy in this situation, is rejected or unavailable.

Most conceptions initiated by clomiphene citrate occur within the first six ovulatory cycles, approximately 50 percent occur at the 50 mg dose and another 20 to 25 percent at 100 mg and 10 percent at 150 mg. There is no benefit to increasing the clomiphene dose in subsequent cycles once ovulation occurs.

The LH surge occurs from 5 to 12 days after the last day of clomiphene administration. The day of ovulation is generally consistent in each cycle once ovulation has been established. The couple is advised to have intercourse every other day for one week beginning five days after the last day of medication.

Because of the observations that pregnancy rates are low after six cycles of treatment, and that 12 or more cycles may increase the risk of ovarian neoplasms, the American College of Obstetricians and Gynecologists has suggested that clomiphene treatment be limited to fewer than 12 cycles, and that the number of gonadotropin cycles be minimized as well.

Monitoring — The response to treatment should be monitored. A basal body temperature (BBT) chart is effective and does not increase the cost of treatment. Conversion of a uniphasic to a biphasic basal temperature curve suggests ovulation has occurred. However, a BBT charting can

be tedious for some patients and is not useful for timing of intercourse as the temperature rise occurs one to five days after the midcycle LH surge and up to four days after ovulation. A midluteal (one week after ovulation or one week before the expected menses) serum progesterone concentration greater than 3 ng/mL (ideally greater than 10 ng/mL) provides reliable evidence that ovulation has occurred. An endometrial biopsy to confirm the adequacy of the luteal phase is not recommended. Determination of the ovulatory LH surge by urinary LH kits is useful in women with inconclusive BBT charts. In addition, urinary LH monitoring provides additional information on appropriate timing of intercourse during a given cycle. The LH surge typically occurs 5 to 12 days after clomiphene administration is completed. Ovulation generally occurs 14 to 26 hours after the detection of the urinary LH surge, and almost always within 48 hours. Therefore, the interval of highest fertility is the day of the LH surge and the following two days.

Serial transvaginal ultrasound can be used to monitor the number and size of developing follicles and to time human chorionic gonadotropin administration if necessary. Serial transvaginal ultrasound may also provide evidence of ovulation (follicle enlargement followed by collapse suggests ovulation). Some advocate ultrasound monitoring of just the first CC cycle in order to exclude hyperresponse. However, adding ultrasonographic monitoring and urinary LH testing is costly and does not appear to improve pregnancy rates significantly.

Ovarian enlargement — Routine physical and ultrasound examinations to detect ovarian enlargement are not always necessary before every new treatment cycle, but should be considered in symptomatic patients.

The management of ovarian enlargement/theca lutein cysts from ovarian stimulation is controversial. We recommend withholding clomiphene in these cases until the cyst(s) disappear either spontaneously or after suppression with oral contraceptive pills or GnRH agonists.

RESULTS OF THERAPY

Overview — Results of clomiphene therapy by specific indication are discussed above: anovulation, luteal phase defect, and unexplained infertility.

A literature review including data from over 5000 patients with a variety of indications for clomiphene therapy reported an ovulation rate of 73 percent and a pregnancy rate of 36 percent. Of patients who became pregnant, the miscarriage rate was approximately 20 percent and the multiple pregnancy rate was 8 to 13 percent. Almost all of the pregnancies that did not miscarry resulted in a live birth. A theoretical projection of the results of clomiphene induction of ovulation in 100 women concluded that 25 of the 100 would succeed in delivering a singleton healthy baby. The discrepancy between the ovulation and pregnancy rates may be partly explained by the peripheral anti-estrogenic effects of clomiphene on cervical mucus (impairing fertilization) and the endometrium (impairing implantation) or by hypersecretion of LH. High LH levels can compromise pregnancy rates.

After six months of treatment, the pregnancy rate per cycle falls substantially despite regular ovulation. In addition, pregnancy rates are lower among women who ovulate only after receiving higher doses of clomiphene. Failure to conceive despite ovulatory cycles, particularly at higher doses, may be due to clomiphene's antiestrogenic effects on the quantity and quality of cervical mucus and on the endometrium. A hysterosalpingogram should be performed, if not already done, in any woman who fails to conceive within three to six treatment cycles. Failure to conceive after a maximum of six ovulatory treatment cycles indicates a need to further evaluate for factors potentially causing infertility or to change to another treatment strategy. In view of the low pregnancy rate after six or more cycles of therapy and the possibility that 12 or more cycles may increase the risk of ovarian neoplasms, the American College of Obstetricians and Gynecologists has suggested limiting clomiphene treatment to fewer than 12 cycles, as well as minimizing the use of gonadotropin administration.

Pregnancy and perinatal outcome — The probability of multifetal pregnancy is increased: twins have been reported in 6.9 to 9 percent of pregnancies, triplets in 0.3 to 0.5 percent, quadruplets in 0.3 percent, and quintuplets in 0.13 percent. The risk may be reduced by ultrasound monitoring and withholding hCG, IUI, or intercourse if more than two follicles >15 mm diameter are seen. Additional information on outcomes of multiple gestations is discussed elsewhere.

The frequency of congenital malformations and spontaneous abortion do not appear to increase in pregnancies after clomiphene therapy. This was illustrated in a report that examined 1034 pregnancies and 935 newborns after clomiphene-induced ovulation. Spontaneous abortion and visible congenital malformations occurred in 14.2 and 2.3 percent, respectively, rates comparable to those in mothers who spontaneously ovulated. Rates of ectopic

pregnancy are not increased with clomiphene. A specific association between clomiphene and hypospadias was suggested and refuted. There is no evidence of developmental delays or learning disabilities in children whose mothers took clomiphene. Several studies have found a mildly increased risk of preterm birth in pregnancies (singleton and multiple) after assisted reproduction compared with natural pregnancies. This effect has not been shown to be specific to clomiphene and is likely to be due, at least in part, to comorbidities in subfertile women, rather than the ovulation stimulation.

There does not appear to be an increase in cancer risk in children conceived using ovulation induction drugs.

ADVERSE EFFECTS

General — Drug-induced side effects are not dose-related, as they can occur at the 50 mg dose. Uncomplicated ovarian enlargement develops in approximately 14 percent of women, but true ovarian hyperstimulation syndrome is rare. We withhold clomiphene in women with ovarian enlargement and/or cyst(s) until the ovaries return to pre-treatment size. Ovarian enlargement can be assessed by symptoms and pelvic examination; routine ultrasound monitoring is unnecessary.

Hot flashes are common, occurring in 10 to 20 percent of women. They may be due to hypoeestrogenism at the hypothalamic level due to clomiphene blockade of estrogen receptors. By comparison, problems related to the hyperestrogenic environment induced by clomiphene citrate include abdominal distention and pain (5.5 percent), nausea and vomiting (2.2 percent), and breast discomfort (2 percent). Side effects rapidly abate soon after cessation of therapy. Visual symptoms, such as blurring, double vision, and/or scotomata, develop in 1 to 2 percent of women and are usually reversible. However, persisting visual symptoms have been described. As a result, visual symptoms warrant discontinuation of therapy. Mood swings, depression, and headaches can occur, but are rarely serious enough to consider terminating treatment.

Luteal phase defect — clomiphene (clomid) citrate, while used to improve luteal function, may also cause an iatrogenic luteal phase defect when used to induce ovulation in anovulatory women. The mechanism may be related to antiestrogenic effects of clomiphene citrate on the endometrium or inhibition of steroidogenesis in granulosa and lutein cells. Increasing the dose of clomiphene does not correct the luteal phase defect. However, preovulatory hCG and/or supplemental progesterone may prevent the problem.

Ovarian cancer — The use of fertility drugs has been associated with neoplasia, particularly borderline ovarian tumors, in some, but not all, studies. In one series, the risk appeared to be only in women who had undergone more than 12 cycles of clomiphene citrate therapy. The apparent association between fertility drug use and epithelial ovarian cancer appears to be related to the fact that these drugs are more likely to be used in infertile women, who are known to be at higher risk of developing ovarian cancer. This issue is discussed in more detail elsewhere.

Because of the observations that pregnancy rates are low after six cycles of treatment, and that 12 or more cycles may increase the risk of ovarian neoplasms, the American College of Obstetricians and Gynecologists has suggested that clomiphene treatment be limited to fewer than 12 cycles, and that the number of gonadotropin cycles be minimized as well.

Breast cancer — There does not appear to be an increased risk of breast cancer in women treated with fertility drugs. However, interpretation of the available data is limited by several factors, such as survey information, small subgroup numbers, lack of evaluation by drug type/dose or cause of infertility, and confounding by the presence of other risk factors for breast cancer. Women taking infertility drugs can be reassured that these drugs probably do not increase their risk of breast cancer, although it is not clear whether some subgroups may be at increased risk. Further investigation is required.

Uterine cancer — A retrospective cohort study including over 8000 women evaluated for infertility between 1965 and 1988 suggested there may be an association between clomiphene use and development of uterine cancer. Data from questionnaires and registries were used. The major findings from this study were: infertile study participants had a significantly higher risk of developing uterine cancer than women in the general population, standardized incidence ratio (SIR): 1.56 (95% CI 1.1-2.1). Infertile women who used clomiphene had a significantly higher risk of developing uterine cancer than women in the general population, SIR 2.14 (95% CI 1.3-3.3); however, infertile women who did not use clomiphene were not at significantly increased risk: SIR 1.24 (95% CI 0.8-1.9). The relative risk of uterine cancer was not significantly increased for infertile users compared to infertile nonusers: RR 1.79 (95% CI 0.9-3.4). One explanation for these findings is that infertile women who used clomiphene were more likely to have underlying chronic anovulation, which is strong risk fac-

tor for development of endometrial cancer, than infertile women not exposed to clomiphene. The latter group was likely enriched by women with nonhormonal causes of infertility (eg, tubal obstruction) who would be expected to have a lower risk of developing uterine cancer. The relatively small number of uterine cancers and incomplete ascertainment of cases preclude a definite conclusion regarding uterine cancer risk. This study does not provide sufficient evidence to change current recommendations for clomiphene use.

SUPPLEMENTARY AND ALTERNATIVE TREATMENTS

Modified regimens — High-dose clomiphene citrate (200 to 250 mg daily) may be given for 8 to 10 days in women who are refractory to standard doses. This extended regimen of clomiphene is particularly well suited for woman who cannot receive exogenous gonadotropins, but the overall experience is limited and the dose exceeds current FDA recommendations.

Human chorionic gonadotropin — An absent or inadequate midcycle LH surge may result in a failure to ovulate or a short luteal phase, despite clomiphene-induced follicular development. In this situation, exogenous hCG (single dose 10,000 IU IM) may be added to the regimen. It is given when transvaginal ultrasonography (TVS) shows that the leading follicle has reached 18 to 20 mm in diameter. It should be noted that premature administration of hCG acts like a premature LH surge and may result in follicular atresia. In many institutions, hCG is routinely used to induce ovulation and to time intrauterine insemination. However, routine administration of exogenous hCG is not recommended for women in whom an endogenous LH surge can be detected, as it does not enhance the efficacy of clomiphene-IUI treatment in these women.

A progressive rise in the serum estradiol concentration is also evidence for advancing follicular development and maturation, but serial TVS to monitor follicle size is superior and should be used to time hCG administration. Ovulation occurs approximately 36 to 44 hours after the injection.

Bromocriptine — Bromocriptine is indicated for ovulation induction in women with galactorrhea or hyperprolactinemia (show table 1). It has also been tried in women with normal serum prolactin and no galactorrhea who have failed clomiphene therapy. However, there is only anecdotal evidence to support its use in this setting.

Infertility in PCOS — Obese anovulatory women with polycystic ovary syndrome (PCOS) and hyperinsulinemia are sometimes unresponsive to clomiphene treatment. Weight loss (5 to 10 percent) alone or in combination with exercise is associated with reduced hyperinsulinemia and hyperandrogenism and a high rate of resumption of ovulation in these women. Other options include metformin and dexamethasone.

Metformin — Many women with PCOS and ovulatory infertility are insulin resistant. (See "Clinical manifestations of polycystic ovary syndrome in adults"). In these women, elevated insulin secretion may directly stimulate ovarian androgen secretion and result in anovulation. Reducing insulin secretion with an insulin sensitizing agent such as metformin may lower ovarian androgen secretion, increase the rate of spontaneous ovulation.

Dexamethasone or oral contraceptives — Anovulatory women in WHO group 2 appear to have reduced ovulation and pregnancy rates when they are treated with clomiphene. Some studies suggest that treatment with clomiphene plus dexamethasone or pretreatment with oral contraceptives improves pregnancy rates in these women.

Ovarian drilling — Laparoscopic ovarian drilling may be considered in women with PCOS who fail to ovulate despite an adequate trial of clomiphene citrate.

Aromatase inhibitors — The potential role of aromatase inhibitors in ovulation induction is discussed separately.

Alpha-glucosidase inhibitors — Addition of acarbose (an alpha-glucosidase inhibitor), to clomiphene therapy in clomiphene-resistant women may result in an improvement in ovulatory rates. However, in one trial, acarbose was not as effective as metformin.

Gonadotropins — In clomiphene resistant women, another option is sequential therapy with a standard clomiphene citrate regimen (50 to 100 mg/day cycle days 5 to 9) followed by low dose gonadotropins (menotropins [hMG] or recombinant FSH). Combination treatment may be safer and is less costly, but not more effective, than gonadotropins given alone. This therapy should be administered by physicians with relevant expertise because of the high costs and risk of complications.

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