Use of clomiphene citrate in infertile women: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

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This committee opinion describes the use of clomiphene citrate, including indications, use, monitoring, and side effects. There is also a discussion of adjuvants and alternatives to clomiphene citrate therapy. (Fertil Steril® 2013;100:341–8. ©2013 by American Society for Reproductive Medicine.)

Clomiphene citrate (CC) was first introduced as an agent to treat anovulatory infertility. With the better understanding of polycystic ovary syndrome (PCOS) and anovulation, adjuvant therapies have been developed to treat those women with anovulation who are resistant to CC. In addition, CC has been utilized in the treatment of unexplained infertility.

The purpose of this document is [1] to describe the pharmacology, mode of action, and indications for CC treatment; [2] to outline the pretreatment evaluation, standard and combination treatment regimens, and alternative strategies for the CC-resistant patient; [3] to summarize the methods for monitoring therapy; and [4] to review the results, side effects, and risks of CC treatment.

PHARMACOLOGY

Chemically, CC is a nonsteroidal triphenylethylene derivative that exhibits both estrogenic agonist and antagonist properties (1). In general, estrogenic agonist properties are manifest only when endogenous estrogen levels are extremely low. Otherwise, CC acts as a competitive estrogen antagonist. Clomiphene citrate is cleared through the liver and excreted in stool. Approximately 85% of an administered dose is eliminated after approximately 6 days, although traces may remain in the circulation for much longer (2). As currently manufactured, CC is a mixture, in approximately a 3:2 ratio, of 2 geometric isomers, enclomiphene and zuclomiphene. Available evidence indicates that enclomiphene is the more potent isomer and the one primarily responsible for the ovulation-inducing actions of CC (1, 3). Enclomiphene levels rise rapidly after administration and fall to undetectable concentrations soon thereafter. Zuclomiphene is cleared far more slowly; levels of the less-active isomer remain detectable in the circulation for more than a month after treatment and may accumulate over consecutive cycles of treatment, but there is no evidence of any important clinical consequence (4).

MODE OF ACTION

Structural similarity to estrogen allows CC to bind to estrogen receptors (ER) throughout the reproductive system. However, in contrast to estrogen, CC binds nuclear ER for an extended period of time and ultimately depletes ER concentrations by interfering with the normal process of ER replenishment (1). The drug's effectiveness in ovulation induction can be attributed to actions at the hypothalamic level. Depletion of hypothalamic ER prevents correct interpretation of circulating estrogen levels. Reduced levels of estrogen feedback trigger normal compensatory mechanisms that alter pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion to stimulate increased pituitary gonadotropin release that, in turn, drives ovarian follicular activity. In ovulatory women, CC treatment increases GnRH pulse frequency (5). In anovulatory women with PCOS in whom the GnRH pulse frequency is already abnormally high, CC treatment increases pulse amplitude but not frequency (6). During CC treatment, levels of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) rise, falling again after the typical 5-day course of therapy is completed (7). In successful treatment cycles, one or more dominant follicles emerge and mature. Most commonly, the LH surge occurs 5–12 days after the last dose of CC is taken.

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INDICATIONS

Anovulatory Infertility

The causes of anovulatory infertility are discussed in detail in another American Society for Reproductive Medicine (ASRM) Practice Committee document (8). Anovulation may be due to PCOS, obesity, hypothalamic dysfunction related to eating disorders, extremes of weight loss, exercise or other stress, hyperprolactinemia, pituitary tumors, or thyroid disease in some cases, but often the immediate cause cannot be determined. Clomiphene citrate is the initial treatment of choice for most anovulatory or oligo-ovulatory infertile women. However, given its mechanism of action, CC is often ineffective in women with hypogonadotropic hypogonadism (hypothalamic amenorrhea) in whom the hypothalamic–pituitary–ovarian axis is severely dysfunctional. Clomiphene citrate is also ineffective in women with hypergonadotropic hypogonadism. Women with other demonstrable endocrinopathies (diabetes mellitus, thyroid disorders, hyperprolactinemia, or congenital adrenal hyperplasia) should first receive specific treatment and be offered CC only when that therapy fails to restore regular ovulatory cycles. Clomiphene citrate also has been used for the treatment of luteal phase abnormalities, although diagnostic criteria for these disorders have not been validated (9). In the setting of anovulatory infertility, there is no benefit of intrauterine insemination (IUI) over timed intercourse for achieving pregnancy (10).

Unexplained Infertility

In couples whose infertility remains unexplained after careful and thorough evaluation, empiric treatment with CC combined with intercourse is no better than expectant management. Whereas an early study suggested that empiric CC treatment for unexplained infertility was significantly more effective than placebo (pregnancy rate over 4 cycles 19% vs. 0) (11), subsequent studies have observed little or no benefit (clinical pregnancy rate 5.6% per cycle with treatment vs. 1.3%–4.2% per cycle without treatment) (12). In a prospective, randomized trial, 387 women, with a mean age of 32 years and with greater than 2 years of unexplained infertility, were randomized to CC 50 mg per day on days 2–6 followed by ultrasound monitoring of the dominant follicle and human chorionic gonadotropin (hCG) to trigger ovulation, compared with expectant management (13). Because the goal in this study was monofollicular development, women in the treatment group were canceled if they had 3 or more follicles in a given cycle. Lower doses were used in subsequent cycles. In this study, as a result of the protocol, CC was associated with lower pregnancy rates than expectant management. The live birth rate for patients receiving CC was 14% vs. 17% for those women undergoing expectant management. There were no differences in time to live birth, multiple births, or miscarriage rate, but patients receiving CC were more likely to complain of nausea, abdominal pain, hot flashes, and headache. Although patients preferred intervention to expectant management as a plan, they were similarly satisfied with the outcome of either intervention. On the basis of the available data, empiric use of CC with intercourse for unexplained infertility should be discouraged. However, further studies are needed to assess the effectiveness of empiric CC for unexplained infertility.

When used in combination with IUI, CC seems to be beneficial compared with expectant management. One study randomized 67 women with unexplained infertility to CC/IUI or expectant management for up to 8 cycles (14). Fourteen patients achieved pregnancy with CC/IUI treatment over 148 cycles (9.5% pregnancy rate per cycle), compared with 5 patients managed expectantly (over 150 cycles; 3.3% pregnancy rate per cycle). In a more recent trial, 475 women were observed for up to 3 cycles of CC/IUI (15). There were 123 pregnancies over 1,294 cycles and 98 ongoing or live births (7.6% ongoing or live births per cycle). Up to three cycles is a common therapeutic regimen before progressing to more aggressive therapies.

PRETREATMENT EVALUATION

Diagnosis of ovulatory dysfunction may be established by menstrual history, timed serum progesterone determinations (during the putative luteal phase), monitoring urinary pregnanediol glucuronide excretion, or serial transvaginal ultrasound examinations. However, specific tests of ovulation are unnecessary when menstrual history alone is diagnostic (amenorrhea, oligomenorrhea). Once identified, anovulatory infertile women merit additional pretreatment evaluation to identify any underlying systemic illness that may require additional tests, counseling, or specific treatment.

A detailed medical history and physical examination may reveal evidence of other endocrine or metabolic disease. Screening for hypothyroidism (serum thyroid-stimulating hormone [TSH]) and hyperprolactinemia (serum prolactin) is justified because both disorders are best treated with medications other than CC (16, 17). Hirsutism warrants specific additional evaluation to exclude nonclassical congenital adrenal hyperplasia (NCAH) by evaluating 17α-hydroxyprogesterone concentration, whereas virilization warrants investigation for androgen-producing tumors of the ovary or adrenals by assessing testosterone and dehydroepiandrosterone sulfate (DHEAS) concentrations (18). Among amenorrheic women of any age, evaluation for ovarian insufficiency is indicated. Screening for impaired glucose tolerance (IGT) or frank diabetes is indicated in obese (body mass index [BMI] >30 kg/m^2) women with PCOS (19–21).

Ovulation induction with CC has little value when severe male, uterine, or tubal factors also are present. Early assessment of tubal patency via hysterosalpingography is indicated when clinical history raises suspicion of uterine or tubal pathology (pelvic infection or surgery, hydrosalpinx) but otherwise may be reserved for those anovulatory women who fail to conceive within 3 to 6 ovulatory treatment cycles. An earlier assessment is also prudent in older women (>35 years) to avoid ineffective treatment at a time when fertility is declining.

TREATMENT REGIMENS

Standard Therapy

Clomiphene citrate is administered orally, typically for 5 days starting on the 2nd to 5th day after the onset of spontaneous

or progestin-induced menses. Ovulation rates, conception rates, and pregnancy outcome are similar regardless of whether treatment begins on cycle day 2, 3, 4, or 5 (22). Although the dose required to achieve ovulation correlates with body weight, there is no reliable way to predict accurately what dose will be required in an individual woman (23, 24). Consequently, CC induction of ovulation involves an empiric incremental titration to establish the lowest effective dose for each individual. Treatment typically begins with a single 50-mg tablet daily for 5 consecutive days, increasing by 50-mg increments in subsequent cycles until ovulation is induced. The standard effective dose of CC ranges from 50 mg/d to 250 mg/d, although doses in excess of 100 mg/d are not approved by the US Food and Drug Administration (FDA) and add little to clinical pregnancy rates. Lower doses (e.g., 12.5 mg/d to 25 mg/d) deserve a trial in small women and those who demonstrate exquisite sensitivity to CC or consistently develop large ovarian cysts (25). Most women (52%) ovulate in response to treatment with 50 mg. Those who do not ovulate with 50 mg CC may ovulate at higher doses using a step-up regimen with doses escalating 50 mg with each anovulatory cycle (22% with 100mg, 12% with 150mg, 7% with 200mg, and 5% with 250mg) (26). Higher doses may be required in patients with greater BMI (27). Among anovulatory women who ovulate with CC, the cumulative conception rates for 50 mg/d, 100 mg/d, or 150 mg/d at 3 months are 50%, 45%, and 33%, respectively, where conception rates at 6 months are 62%, 66%, and 38%, respectively (28, 29). In obese, anovulatory women with at least 2 years of infertility, success rates generally are lower, with 16% achieving live birth in women with BMI >35 kg/m^2 compared with 28% for women with BMI <30 kg/m^2 (30). If CC is used to induce ovulation, pregnancy is most likely to occur in the first 3 to 6 cycles, and therapy beyond 6 cycles is generally not recommended.

In general, in women treated with this conventional CC step-up regimen, a 55%–73% overall cumulative pregnancy rate can be expected (29). Increasing age and duration of infertility are associated with treatment failure.

ALTERNATIVE TREATMENT REGIMENS

In those women who fail to respond to traditional CC regimens, several alternative CC protocols exist. Limited evidence suggests that some CC-resistant anovulatory women may respond to longer courses (7 to 8 days) of CC treatment rather than the traditional 5-day course (31). For those who fail to respond to a given dose of CC, a progestin is traditionally given to induce menses, followed by administration of a higher dose of CC. Recently the "stair-step" protocol has been advocated. In this protocol, once failure to ovulate to a given dose is recognized by day 14–21, the higher dose of CC is started immediately without first inducing a withdrawal bleed with progestin (32). The advantage of this protocol is a shorter time to achieve ovulation when increasing doses of CC are required (32). In addition, inducing a menstrual bleed with progestins before clomiphene therapy in anovulatory women has been associated with a lower conception and live birth rate compared with women in whom CC was started in the follicular phase remote from spontaneous or induced menses (33).

ADJUNCTIVE TREATMENT REGIMENS

Women who prove resistant or refractory to standard CC treatment may ovulate in response to combined treatment regimens. A choice among them should not be arbitrary but be based on specific elements in the patient's history, results of laboratory evaluation, and/or observations in previous unsuccessful CC treatment cycles. These regimens also should not be considered as a prerequisite for use of more aggressive treatment strategies (e.g., exogenous gonadotropins and/or in vitro fertilization [IVF]). They are merely useful alternatives that merit consideration, depending on the patient's age, goals, available resources, and risk tolerance.

Clomiphene Citrate and Metformin

Some anovulatory/oligo-ovulatory women with PCOS may respond to CC combined with metformin (29, 34, 35). In a randomized, controlled trial, live birth rates were not significantly different for women treated with CC alone compared with women treated with CC and metformin (30). However, for those women who fail to ovulate with CC, metformin has been advocated to improve ovulation and pregnancy rates in response to CC. Several small randomized, controlled studies have shown that pretreatment with metformin in doses of 1,500 to 1,700 mg daily significantly improved ovulation rates (36–40) and pregnancy rates (41–45) in response to CC in women who had previously failed to ovulate with CC alone. Metformin pretreatment did not improve the ovulation rate in response to CC in one study (46), and in another study simultaneous treatment with extended-release metformin was not shown to reduce the lowest dose of CC that induces ovulation in women with PCOS (47). In obese women who have failed CC therapy or for couples for whom pregnancy is not an immediate goal, metformin combined with diet and exercise to achieve weight loss may be considered (48, 49).

Metformin therapy is associated with gastrointestinal side effects and rarely may induce hepatic toxicity or be complicated by lactic acidosis. Liver and renal functions should be evaluated before treatment and monitored periodically thereafter.

Clomiphene Citrate and Glucocorticoids

In some anovulatory women, addition of glucocorticoids to the CC treatment regimen may induce ovulation successfully. One prospective, randomized trial involved 64 anovulatory women who had not received CC previously (50). Half received CC 50 mg per day, increasing as needed to 150 mg per day on days 5–9, whereas the other half received CC plus dexamethasone 0.5 mg daily. Of those receiving CC only, 14 of 22 ovulated and 8 of 14 conceived, whereas of those receiving CC plus dexamethasone, 23 of 23 ovulated and 17 of 23 conceived ($P<.05$). The benefit was most notable in women with DHEAS serum concentrations of 200 μg/dL or

greater. Two large trials evaluated CC-resistant anovulatory patients with normal DHEAS levels. Of those treated with dexamethasone on cycle days 3–12 and CC, 75%–88% ovulated and 40% conceived, whereas of those treated with CC alone, 15%–20% ovulated and 5% conceived (51, 52). Treatment may be continued (3 to 6 cycles) when it is successful and should be promptly discontinued when it is not. Glucocorticoid treatment has significant side effects and risks that must be addressed should this regimen be used.

Clomiphene and Gonadotropins

Clomiphene citrate-resistant anovulatory women and women with unexplained infertility may benefit from a trial of sequential CC/gonadotropin therapy (53). Given the costs and risks of exogenous gonadotropin therapy, treatment should be offered only by clinicians having the requisite training or experience. The typical cycle includes a standard CC treatment regimen, followed by low-dose human menopausal gonadotropin (hMG) or follicle-stimulating hormone (FSH) (75–150 IU/day for 3 days). Treatment is individualized thereafter in the same way as with traditional gonadotropin therapy, on the basis of transvaginal ultrasound examinations with or without serum estradiol assessment. Cycle fecundity in women so treated has been reported to be similar to that achieved by treatment with gonadotropins alone in some (53–55), but not all, studies (56). There are no data directly comparing ovulation and pregnancy rates to those with exogenous gonadotropins alone. Advantages of combined CC and gonadotropin therapy include a reduction in the dose of gonadotropin and a potential reduction in the associated costs of monitoring. Clomiphene citrate–resistant anovulatory women often are very sensitive to low doses of gonadotropins, and treatment should be aimed at achieving ovulation of a single mature follicle whenever possible, because there is no indication for purposeful superovulation in anovulatory infertile women except for IVF.

ALTERNATIVE TREATMENTS FOR CLOMIPHENE CITRATE RESISTANCE

Alternatives to CC therapy in CC-resistant patients include aromatase inhibitors (57–66), tamoxifen (67–70), insulin-sensitizing agents (35, 36, 71, 72), ovarian drilling (73–75), gonadotropins (29), and IVF (29).

CLOMIPHENE CITRATE TREATMENT MONITORING

Objective evidence of ovulation is key to successful treatment. In the setting of unexplained infertility, assessment of ovulation is done to optimize the timing of IUI. Methods to detect ovulation that may be used to time IUI include ovulation predictor kits, ultrasound, and serum measurement of estradiol, LH, and/or progesterone. Furthermore, hCG can be used to time ovulation with IUI, obviating the need for an endogenous LH surge.

Urinary ovulation predictor kits identify the midcycle LH surge, which correlates with the interval of peak fertility (76, 77). The surge is typically observed between 5 and 12 days after treatment is completed, most often on cycle day 16 or 17, when CC is administered on days 5–9 (78). Serial transvaginal ultrasound can reveal the size and number of developing follicles and provide presumptive evidence of ovulation (progressive follicular growth, sudden collapse of the preovulatory follicle, and an increase in cul-de-sac fluid volume) and luteinization (loss of clearly defined follicular margins and appearance of internal echoes) (79). However, ultrasound is costly and logistically demanding and is generally reserved for patients in whom less complicated methods fail to provide the necessary information.

A meta-analysis of 7 studies comparing triggering ovulation with hCG (1,461 patients) with urinary LH testing to identify the endogenous LH surge (1,162 patients) for timing IUI for women with unexplained infertility treated with CC reported that there were lower odds of pregnancy when an hCG trigger was used (139 of 1,461) compared with LH surge monitoring (138 of 1,162; odds ratio [OR] 0.74; 95% confidence interval [CI] 0.57–0.96) (80, 81). Therefore, use of exogenous hCG is best reserved for women who require IUI and in whom LH monitoring proves difficult or unreliable. Ultrasound evaluation may be beneficial for determining optimal follicular size should an hCG trigger be used. Higher pregnancy rates may occur when the leading follicle sizes are 23–28 mm in diameter (82).

In the past, examination to exclude any significant residual ovarian enlargement has been recommended before each new treatment cycle but it is no longer recommended. Although it is prudent to postpone further treatment when symptoms lead to discovery of a large cyst or grossly enlarged ovaries, clinical research (78) and accumulated clinical experience suggest that routine "baseline" physical or ultrasound examinations are unnecessary. Nevertheless, regular contact with the patient should be maintained to review response to treatment and to ensure that any additional evaluation or alternative treatment that may be required is not delayed.

SIDE EFFECTS OF CLOMIPHENE CITRATE THERAPY

Clomiphene citrate generally is very well tolerated. Some side effects are relatively common, but rarely are they persistent or severe enough to threaten completion of the usual 5-day course or next cycle of treatment.

Mood swings are the most common side effect (64%–78% [83, 84]), whereas vasomotor flushes (hot flashes) occur in approximately 10% of CC-treated women. These side effects typically abate soon after treatment ends. Visual disturbances, including blurred or double vision, scotomata, and light sensitivity, generally are uncommon (<2% prevalence) and reversible, although there are isolated reports of persistent symptoms and more severe complications, such as optic neuropathy (85). Whenever visual disturbances are identified, it is prudent to stop treatment and consider alternative methods of ovulation induction. Less specific side effects include breast tenderness, pelvic discomfort, and nausea, all observed in 2%–5% of CC-treated women.

RISKS AND COMPLICATIONS OF CLOMIPHENE CITRATE THERAPY

Multiple Gestation

Multifollicular development is relatively common during CC treatment, and the risk of multiple gestation is increased to approximately 8% overall for anovulatory women (86, 87) and 2.6%–7.4% in women treated for unexplained infertility (88, 89). The overwhelming majority of multiple pregnancies that result from CC treatment are twin gestations; triplet and higher-order pregnancies are rare (0.08%–1.1%) but may occur (15, 90).

Congenital Anomalies

There is no evidence that CC treatment increases the risk of birth defects (87, 91).

Miscarriage

Early studies suggested that the incidence of miscarriage in pregnancies resulting from CC treatment was increased over that observed in spontaneous pregnancies. However, more recent studies have described miscarriage rates that are not different from those observed in spontaneous pregnancies (10%–23%) in both anovulatory and unexplained infertility patients (28, 30, 92–94).

Ovarian Hyperstimulation Syndrome

The incidence of ovarian hyperstimulation syndrome (OHSS) in CC-treated women is difficult to determine, because definitions of the syndrome vary widely among studies. Whereas mild OHSS (moderate ovarian enlargement) is relatively common, severe OHSS (massive ovarian enlargement, progressive weight gain, severe abdominal pain, nausea and vomiting, hypovolemia, ascites, and oliguria) is rarely observed (95, 96).

Ovarian Cancer

Two epidemiologic studies suggested that the risk of ovarian cancer was significantly increased in women exposed to a heterogeneous group of ovulation-inducing drugs that included CC (97, 98), but subsequent studies have failed to corroborate those findings (99–103). A pooled analysis of 8 case–control studies concluded that neither fertility drug use nor use for more than 12 months was associated with invasive ovarian cancer (104). Patients with concerns should be counseled that no causal relationship between ovulation-inducing drugs and ovarian cancer has been established, and no change in prescribing practices is warranted.

SUMMARY

- Clomiphene citrate is an effective first-line treatment for the majority of women with anovulatory infertility.
- Clomiphene citrate treatment combined with intercourse does not increase cycle fecundity in couples with unexplained infertility compared with expectant management.
- Clomiphene citrate treatment in combination with IUI seems to increase cycle fecundity in couples with unexplained infertility compared with expectant management.
- Side effects of CC treatment generally are mild and well tolerated. The principal risk of CC treatment is an increased incidence of multifetal gestation (<10%).

CONCLUSIONS

- Failure to conceive after 3 to 4 successful CC-induced ovulation cycles is indication for further evaluation to exclude other contributing causes of infertility, particularly in women >35 years of age.
- Combination therapies involving CC and other agents (metformin, glucocorticoids, and exogenous gonadotropins) may be effective when treatment with CC alone fails to induce ovulation.
- Clomiphene citrate treatment should be monitored (menstrual calendar, serum progesterone concentration, urinary LH excretion) to ensure its effectiveness in ovulation induction. The choice of monitoring should be tailored to the needs of the specific patient.

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This document was reviewed by ASRM members, and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

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