Use of clomiphene citrate in women

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Ovulatory dysfunction is one of the most common causes of reproductive failure in sub-fertile and infertile couples. In the absence of other significant infertility factors, successful ovulation induction often will restore normal fertility. Clomiphene citrate (CC) is the best initial treatment for the large majority of anovulatory infertile women. The first clinical trial of CC therapy demonstrated successful ovulation induction in 80% of women, half of whom achieved pregnancy during treatment [1]. In subsequent years, results of CC treatment have not changed appreciably, despite the advent of modern immunoassays for steroid hormones, advances in ultrasound technology for cycle monitoring, and the introduction of commercial test kits that allow detection of the midcycle luteinizing hormone (LH) surge in urine.

This guideline will first describe the pharmacology, mode of action, and indications for CC treatment. Second, it will outline the pretreatment evaluation, standard and combination treatment regimens, and alternative strategies for the CC-resistant patient. Lastly, it will summarize the methods for monitoring therapy and review the results, side effects, and risks of CC treatment.

PHARMACOLOGY

Chemically, CC (like tamoxifen) is a nonsteroidal triphenylethylene derivative that exhibits both estrogen agonist and antagonist properties [2]. In general, estrogen agonist properties are manifest only when endogenous estrogen levels are extremely low. Otherwise, CC acts solely as a competitive estrogen antagonist. Clomiphene citrate is cleared through the liver and excreted in stool. About 85% of an administered dose is eliminated after approximately 6 days, although traces may remain in the circulation for much longer [3]. As currently manufactured, CC is a racemic mixture of two distinct stereoisomers, 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 [2, 4]. Enclomiphene levels rise rapidly after administration and fall to undetectable concentrations soon thereafter. Zuclomiphene is cleared far more slowly. Levels of this 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 [5].

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 [2]. 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 negative feedback trigger normal compensatory mechanisms that alter pulsatile hypothalamic GnRH secretion to stimulate increased pituitary gonadotropin release that, in turn, drives ovarian follicular activity. In ovulatory women, CC treatment increases GnRH pulse frequency [6]. In anovulatory women with polycystic ovary syndrome (PCOS) in whom the GnRH pulse frequency is already abnormally high, CC treatment increases pulse amplitude, but not frequency [7]. During CC treatment, levels of both LH and FSH rise, falling again after the typical 5-day course of therapy is completed [8]. In successful treatment cycles, one or more dominant follicles emerge and mature, generating a rising tide of E_2 that ultimately triggers the midcycle LH surge and ovulation.

Not surprisingly, tamoxifen also has been used successfully to induce ovulation in anovulatory infertile women [9]. Given its structural similarity to CC, its mechanism of action presumably is also similar [10]. Recent evidence suggests that letrozole, an orally active aromatase inhibitor, may have potential as an ovulation-inducing agent [11, 12]. In contrast to the central actions of CC and tamoxifen, letrozole acts in the periphery to inhibit ovarian follicular E_2 production, but the end result is similar—a decrease in central estrogen feedback action that stimulates a compensatory increase in pituitary gonadotropin secretion.

INDICATIONS
Anovulation

The causes of anovulation are many and varied. Whenever possible, treatment should be directed at correcting the underlying cause. Correct diagnosis may suggest specific treatment, and many conditions may have longer-term health consequences. Thyroid disease, pituitary tumors, eating disorders, extremes of weight loss and exercise, hyperpro-

lactinemia, PCOS, and obesity may be identified, but very often the immediate cause of anovulation cannot be confidently defined. CC is the initial treatment of choice for most anovulatory or oligo-ovulatory infertile women. However, given its hypothalamic site of action, CC is often ineffective in women with hypogonadotropic hypogonadism (hypothalamic amenorrhea). Women with other demonstrable endocrinopathies (diabetes mellitus, thyroid disorders, hyperprolactinemia, congenital adrenal hyperplasia) should first receive specific treatment and be offered CC only when that therapy fails to restore regular ovulatory cycles.

Luteal Phase Deficiency

Given that the corpus luteum derives from the follicle that ovulates, its functional capacity is, at least in part, dependent on the quality of preovulatory follicle development. In that context, CC is one logical treatment option for luteal phase deficiency (LPD) (13). Progesterone levels are typically higher after CC treatment than in spontaneous cycles, reflecting improved preovulatory follicle and corpus luteum development and/or the combined hormone production of more than one corpus luteum (14).

Unexplained Infertility

In couples whose infertility remains unexplained after careful and thorough evaluation, empiric treatment with CC may be justified, particularly in young couples with a short duration of infertility and in those unwilling or unable to pursue more aggressive therapies involving greater costs, risks, and logistical demands (15, 16). The efficacy of empiric CC treatment may be attributed to correction of subtle and unrecognized ovulatory dysfunction and/or "superovulation" of more than a single ovum (16). CC treatment is most effective when it is combined with properly timed intrauterine insemination (IUI), all in an effort to bring together more than the usual numbers of ova and sperm at the optimal time (17, 18).

PRETREATMENT EVALUATION

Infertile women who rarely or never ovulate are candidates for CC treatment. Diagnosis of ovulatory dysfunction may be established by:

- Basal body temperature recordings
- Timed serum P determinations
- Monitoring urinary LH excretion
- Timed endometrial biopsy
- 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.

Acanthosis nigricans is often observed in women with underlying insulin resistance or frank diabetes and merits formal evaluation to exclude these diagnoses (19). Screening for hypothyroidism (serum TSH) and hyperprolactinemia (serum prolactin) is reasonable since both disorders are best treated with medications other than CC (20, 21). Hirsutism that is severe or rapid in progression warrants specific additional evaluation to exclude non-classic congenital adrenal hyperplasia (CAH) and androgen-producing tumors of the ovary or adrenals (22).

Attempts at ovulation induction are generally futile in women with elevated serum FSH levels. Those with hypothalamic/pituitary dysfunction are also unlikely to respond to CC as its mechanism of action requires a functional hypothalamic/pituitary/ovarian feedback axis. Alternative treatments that will reestablish normal hypothalamic/pituitary communication (pulsatile exogenous GnRH) or stimulate the ovary directly (exogenous gonadotropins) will generally be required.

Ovulation induction has little value when severe male, uterine, or tubal factors are also present. Semen analysis should be performed to identify seminal abnormalities that also may require treatment. Hysterosalpingography is indicated when clinical history raises suspicion of uterine or tubal pathology (pelvic infection or surgery, ectopic pregnancy, inflammatory bowel disease), but may otherwise be reserved for those who fail to conceive within three to six ovulatory treatment cycles. An HSG is also prudent in older women (over 35 years) to avoid ineffective treatment at a time when fertility is steadily declining.

TREATMENT REGIMENS
Standard Therapy

CC is administered orally, typically starting on the third to fifth day after the onset of spontaneous or progestin-induced menses; ovulation rates, conception rates, and pregnancy outcome are similar regardless whether treatment begins on cycle day 2, 3, 4, or 5 (23). Although the dose required to achieve ovulation correlates with body weight, there is no reliable way to accurately predict what dose will be required in an individual woman (24). Consequently, CC induction of ovulation amounts to an empiric incremental titration in efforts 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 effective dose of CC ranges from 50 mg/day to 250 mg/day, although doses in excess of 100 mg/day are not approved by the Food and Drug Administration (FDA). Lower doses (e.g., 12.5 mg/day to 25 mg/day) deserve a trial in women who demonstrate exquisite sensitivity to CC or consistently develop large ovarian cysts that interfere with efficient cyclic treatment (25). Most women ovulate in response to treatment with 50 mg (52%) or 100 mg (22%); higher doses have been used, but also are less often successful (150 mg, 12%; 200

mg, 7%; 250 mg, 5%) (26). Some CC-resistant anovulatory women who fail to respond to a standard 5-day treatment regimen may respond to longer courses (8 days) of CC treatment (27), but such treatment should be considered only when alternative treatment with exogenous gonadotropins is rejected.

Alternative and Combination Treatment Regimens

Many women who prove resistant or refractory to standard CC treatment may ovulate in response to alternative treatment regimens. A choice among them should not be arbitrary, but based on specific elements of 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). They are merely useful alternatives that merit consideration, depending on the patient's age, goals, available resources, and risk tolerance.

Insulin Sensitizing Agents Insulin resistance and hyperinsulinemia are common features in women with PCOS. Most women with PCOS will respond to CC, but many prove resistant and ultimately require alternative treatment. Among these, a large majority will have demonstrable insulin resistance (28). Insulin sensitizing agents (e.g., metformin) alone can restore menses and cyclic ovulation in many amenorrheic PCOS women (29, 30), although they are not currently approved by the FDA for this indication. Based on observations from open trials, some advocate metformin as primary therapy in anovulatory infertile PCOS women (1,000 mg/day to 2,000 mg/day in divided doses) and add CC only in those who fail to respond (29). Given the greater costs and complexity of metformin treatment and the frequency of severe gastrointestinal side effects (e.g., nausea, vomiting, diarrhea), others prefer to reserve metformin treatment for those who first prove resistant to CC. In either case, many who fail to ovulate in response to either alone will respond when the two are used in combination (29–31). Because metformin therapy may have hepatic toxicity or be complicated by lactic acidosis, liver and renal functions must be evaluated before treatment and monitored periodically thereafter. Although the safety of metformin treatment in pregnancy has not been established, preliminary evidence suggests that it may reduce the incident risk of spontaneous abortion and gestational diabetes in women with PCOS (32, 33).

Clomiphene and hCG Although exogenous hCG has been used to trigger ovulation and define the optimal time to perform IUI in CC-induced cycles, the practice is difficult to justify on a routine basis. Treatment requires costly monitoring with serial transvaginal ultrasound examinations that are otherwise unnecessary. The mean peak diameter of the preovulatory follicle in successful CC-induced ovulatory cycles ranges between 19 and 30 mm (median diameter: 25 mm) (34), and the optimum time to administer hCG is therefore difficult to determine. Most importantly, two randomized trials have demonstrated that IUI after exogenous hCG-triggered ovulation in CC-induced cycles is no more effective than IUI performed after detection of the endogenous LH surge (35, 36). Therefore, use of exogenous hCG is perhaps best limited to those women who require IUI and in whom a midcycle LH surge cannot reliably be detected.

Clomiphene and Glucocorticoids In some CC-resistant PCOS women, addition of glucocorticoids (e.g., dexamethasone 0.5 mg or prednisone 5 mg hs) to the CC treatment regimen may induce ovulation when CC alone has failed (37, 38). Adjunctive glucocorticoid treatment may be based on the serum DHEAS concentration (>200 μg/dL) (37) or empiric (38). Treatment may be continued (three to six cycles) when it is successful and should be promptly discontinued when it is not. There is no evidence that glucocorticoid treatment has any important side effects or risks when used in the doses or for the duration indicated.

Clomiphene and Gonadotropins CC-resistant anovulatory women who ultimately require exogenous gonadotropins to achieve ovulation and those with unexplained infertility might benefit from a trial of sequential CC/gonadotropin therapy using either traditional menotropins (hMG) or purified or recombinant FSH (39). Given the costs and risks of exogenous gonadotropin therapy, treatment should be offered only by those having the requisite training or experience. The typical cycle includes a standard CC treatment regimen (50 mg/day to 100 mg/day, cycle days 5–9), followed by low-dose hMG or FSH (75 IU/day, cycle days 9–12). Treatment is individualized thereafter, in the same way as with traditional gonadotropin therapy, based on transvaginal ultrasound examinations. Cycle fecundity with this approach is similar to that achieved with gonadotropins alone, but the dose and duration of treatment and the associated costs of monitoring may be significantly reduced. Treatment with exogenous gonadotropins alone is the obvious alternative. CC-resistant anovulatory women are often very sensitive to low doses of gonadotropins and treatment should be aimed at achieving ovulation of but a single mature follicle if possible. There is no indication for purposeful superovulation in the anovulatory infertile woman.

Ovarian "Drilling" A contemporary version of the classic ovarian wedge resection is another treatment option in CC-resistant, hyperandrogenic, anovulatory women (e.g., PCOS). The technique involves laparoscopic cautery, diathermy, or laser vaporization of the ovaries at multiple sites, the objective being to decrease circulating and intraovarian androgen levels by reducing the volume of ovarian stroma. Data derived from randomized controlled trials suggest that initial ovulation and pregnancy rates after ovarian drilling are similar to those achieved by treatment with exogenous gonadotropins, and the risk of multiple pregnancy is lower (40). When it does not result in spontaneous ovulation, ovarian drilling may help to restore sensitivity to CC treatment. Ovarian drilling is a reasonable option for clomiphene-resistant anovulatory women, but the temporary effects of treatment

and the risks of postoperative adhesions or diminished ovarian reserve should be carefully considered.

Treatment Monitoring

Objective evidence of ovulation and normal luteal function is key to successful treatment. Ovulation can be documented using any one of a number of methods. The choice may vary and should be tailored to meet the needs of the individual patient.

Basal body temperature (BBT) recordings provide a simple and inexpensive method for evaluating response to treatment, but may be tedious. Test kits that can identify the midcycle LH surge in urine more precisely define both the interval of peak fertility and luteal phase duration (41). 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 (34). Whereas any P level greater than 3 ng/mL provides presumptive evidence of ovulation (42), a midluteal phase concentration offers more information regarding the quality of luteal function. Best results are observed when concentrations exceed 10 ng/mL (43).

Endometrial biopsy revealing a secretory endometrium also provides evidence of ovulation. Endometrial "dating" using established histologic criteria may reveal evidence of LPD (44), although controversies persist regarding the accuracy of traditional diagnostic criteria. 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) (45). However, because of the cost and logistical demands involved, the method generally is reserved for patients in whom less complicated methods fail to provide the necessary information. In CC/IUI cycles in couples with unexplained infertility, transvaginal ultrasound is useful to confirm that treatment successfully promotes development of more than one mature follicle. A recent study that compared cycle fecundity in CC-induced cycles monitored with BBT, urinary LH excretion, or serial ultrasound examinations could demonstrate no clear advantage for any one of these methods (46).

In the past, examination to exclude any significant residual ovarian enlargement has been recommended before each new treatment cycle. Although it is prudent to postpone further treatment when symptoms lead to discovery of a large cyst or grossly enlarged ovaries, clinical studies (34) and accumulated clinical experience suggest that routine "baseline" physical or ultrasound examinations are not always necessary. Nevertheless, regular contact 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.

Results of Treatment

CC treatment will successfully induce ovulation in approximately 80% of properly selected candidates. Likelihood of response declines with increasing age, body mass index (BMI), and free androgen index (47). Overall, cycle fecundity is approximately 15% in anovulatory women who respond to treatment. In the absence of any other infertility factors, cycle fecundity is higher (22%), and comparable to that seen in fertile women after discontinuation of diaphragm contraception (25%) and in those with male factor infertility who receive inseminations with donor sperm. Approximately 70% to 75% of anovulatory women who respond to CC (50 mg/day to 150 mg/day, as required) may be expected to conceive within six to nine cycles of treatment (48, 49). Amenorrheic women are more likely to conceive than oligomenorrheic women, probably because those who already ovulate (47), albeit inconsistently, are more likely to have other co-existing infertility factors. In infertile women with luteal phase deficiency, CC treatment increases luteal phase duration (13) and serum P levels (14, 50) and improves fecundity (13, 14, 50).

Fecundability declines with advancing age; and prolonged treatment with CC is unjustified in women in their latter reproductive years. The failure to conceive within a maximum of six CC-induced normal ovulatory cycles is a clear indication to expand the diagnostic evaluation to exclude other infertility factors or to change the overall treatment strategy if evaluation is already complete.

In randomized trials, cycle fecundity in women with unexplained infertility treated with empiric CC has ranged from 3.4% to 8.1% (15, 16). The benefits of CC treatment alone are relatively small—one additional pregnancy for every 40 cycles of treatment. Based on observations in clinical trials, cycle fecundity in couples with unexplained infertility treated with CC/IUI is approximately 8.5% to 9.5%, at least twofold higher than in those who receive no treatment (17, 18). CC/IUI yields one additional pregnancy for every 16 cycles of treatment.

SIDE EFFECTS AND RISKS

CC is generally 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. Although CC treatment does have intrinsic risks, they are typically modest and manageable.

Side Effects

Vasomotor flushes (hot flashes) occur in approximately 10% of CC-treated women, but typically abate soon after treatment ends. Mood swings are also common. Visual disturbances, including blurred or double vision, scotomata, and light sensitivity, are generally uncommon (<2% prevalence) and reversible, although there are isolated reports of persistent symptoms and more severe complications such as optic

neuropathy (51). 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% to 5% of CC-treated women.

Numerous studies have suggested that in addition to the desirable central actions responsible for its efficacy as an ovulation inducing agent, CC exerts undesirable and unavoidable adverse antiestrogenic effects in the periphery (endocervix, endometrium, ovary, ovum, and embryo) that explain the "discrepancy" between the ovulation and conception rates observed in CC-treated patients. However, there is little or no compelling evidence to support these notions. The quality and quantity of cervical mucus production in CC treatment cycles may sometimes be reduced (52), but rarely to an extent that risks interference with the effective capture, survival, or transport of sperm. Limited endometrial proliferation has been observed in some CC-treated patients (1), but the effect is minor or not at all evident in the large majority of women (53–55). When reduced endometrial thickness is observed in CC-induced ovulatory cycles, tamoxifen (9) or letrozole (10) may offer an alternative method for ovulation induction that may avoid this effect. Although some studies have suggested that fecundity may relate to endometrial thickness, others have failed to demonstrate any significant correlation. CC has indeed been shown to inhibit steroid hormone production by cultured avian (56), ovine (57), and human granulosa/luteal cells (58), but estrogen and P levels in CC-induced cycles are typically significantly higher, not lower, than in spontaneous cycles. Adverse effects of CC on mouse ovum fertilization and embryo development have been demonstrated in vitro (59), but circulating levels of CC never reach the concentrations required to produce these effects, even after several consecutive treatment cycles (5). Taken together, available evidence and accumulated clinical experience suggest that any adverse antiestrogenic effects of CC present no significant obstacle in the majority of treated women.

Risks and Complications

Multiple Gestation Multifollicular development is relatively common during CC treatment and the risk of multiple gestation is clearly increased to approximately 8% overall (60, 61). The overwhelming majority of multiple pregnancies that result from CC treatment are twin gestations; triplet and higher order pregnancies are rare but may occur.

Congenital Anomalies There is no evidence that CC treatment increases the overall risk of birth defects or of any one anomaly in particular (61, 62).

Spontaneous Abortion Early studies suggested that the incidence of spontaneous abortion in pregnancies resulting from CC treatment was increased over that observed in spontaneous pregnancies. However, a number of more recent studies have described abortion rates that are not different from those observed in spontaneous pregnancies (10% to 15%) (63, 64).

Ovarian Hyperstimulation Syndrome The incidence of ovarian hyperstimulation syndrome (OHSS) in CC-treated women is difficult to determine, as 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.

Ovarian Cancer Two epidemiologic studies published early in the last decade suggested that the risk of ovarian cancer might be significantly increased in women exposed to ovulation inducing drugs (65, 66), but subsequent studies have failed to corroborate those findings (67–70). A recent pooled analysis of eight case-control studies concluded that neither fertility drug use nor use for more than 12 months was associated with invasive ovarian cancer (71). 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. In any case, prolonged treatment with CC is generally futile and should therefore be avoided.

SUMMARY AND CONCLUSIONS

- CC is the best initial treatment for the majority of women whose infertility is associated with ovulatory dysfunction (anovulation, luteal phase deficiency). Combined with appropriately timed IUI, CC treatment also increases cycle fecundity in couples with unexplained infertility.
- CC treatment generally should be limited to the minimum effective dose and to no more than six ovulatory cycles. Failure to conceive after successful CC-induced ovulation is indication for further evaluation to exclude other contributing causes of infertility.
- Combination therapies involving CC and other agents (metformin, glucocorticoids, exogenous gonadotropins) may be effective when treatment with CC alone fails to induce ovulation. Alternative strategies for the CC-resistant woman include treatment with aromatase inhibitors or exogenous gonadotropins and, in selected patients, ovarian drilling.
- CC treatment should be monitored (BBT, serum P concentration, urinary LH excretion) to ensure its effectiveness in ovulation induction.
- Side effects of CC treatment are generally mild and well tolerated. The principal risk of CC treatment is an increased incidence of multifetal gestation (<10%).

American Society for Reproductive Medicine, and the Board of Directors of the American Society for Reproductive Medicine.

REFERENCES

1. Greenblatt RB. Chemical induction of ovulation. Fertil Steril 1961;12: 402–4.
2. Clark JH, Markaverich BM. The agonistic-antagonistic properties of clomiphene: a review. Pharmacol Ther 1982;15:467–519.
3. Mikkelson TJ, Kroboth PD, Cameron WJ, Dittert LW, Chungi V, Manberg PJ. Single-dose pharmacokinetics of clomiphene citrate in normal volunteers. Fertil Steril 1986;46:392–6.
4. Van Campenhout J, Borreman E, Wyman H, Antaki A. Induction of ovulation with cisclomiphene. Am J Obstet Gynecol 1973;115:321–7.
5. Young SL, Opsahl MS, Fritz MA. Serum concentrations of enclomiphene and zuclomiphene across consecutive cycles of clomiphene citrate therapy in anovulatory infertile women. Fertil Steril 1999; 71:639–44.
6. Kerin JF, Liu JH, Phillipou G, Yen SS. Evidence for a hypothalamic site of action of clomiphene citrate in women. J Clin Endocrinol Metab 1985;61:265–8.
7. Kettel LM, Roseff SJ, Berga SL, Mortola JF, Yen SS. Hypothalamicpituitary-ovarian response to clomiphene citrate in women with polycystic ovary syndrome. Fertil Steril 1993;59:532–8.
8. Rebar R, Judd HL, Yen SSC, Rakoff J, VandenBerg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. J Clin Invest 1976;57:1320–9.
9. 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;75:1024–6.
10. Tajima C, Fukushima T. Endocrine profiles in tamoxifen-induced ovulatory cycles. Fertil Steril 1983;40:23–30.
11. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305–9.
12. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril 2002;78:280–5.
13. Quagliarello J, Weiss G. Clomiphene citrate in the management of infertility associated with shortened luteal phases. Fertil Steril 1979;31: 373–7.
14. Guzick DS, Zeleznik A. Efficacy of clomiphene citrate in the treatment of luteal phase deficiency: quantity versus quality of preovulatory follicles. Fertil Steril 1990;54:206–10.
15. Fisch P, Casper RF, Brown SE, Wrixon W, Collins JA, Reid RL, et al. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. Fertil Steril 1989;51:828–33.
16. Glazener CM, Coulson C, Lambert PA, Watt EM, Hinton RA, Kelly NG, et al. Clomiphene treatment for women with unexplained infertility: placebo-controlled study of hormonal responses and conception rates. Gynecol Endocrinol 1990;4:75–83.
17. Deaton JL, Gibson M, Blackmer K, Nakajima ST, Badger GJ, Brumsted JR. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. Fertil Steril 1990;54:1083–8.
18. Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, et al. Efficacy of treatment for unexplained infertility. Fertil Steril 1998;70:207–13.
19. Practice Committee Report. Use of insulin sensitizing agents in the treatment of polycystic ovary syndrome. Birmingham, AL: American Society for Reproductive Medicine, 2000.
20. Cuellar FG. Bromocriptine mesylate (Parlodel) in the management of amenorrhea/galactorrhea associated with hyperprolactinemia. Obstet Gynecol 1980;55:278–84.
21. Lincoln SR, Ke RW, Kutteh WH. Screening for hypothyroidism in infertile women. J Report Med 1999;44:455–7.
22. Practice Committee Report. Evaluation and treatment of androgen excess. Birmingham, AL: American Society for Reproductive Medicine, 2000.
23. Wu CH, Winkel CA. The effect of therapy initiation day on clomiphene citrate therapy. Fertil Steril 1989;52:564–8.
24. Lobo RA, Gysler M, March CM, Goebelsmann U, Mishell DR Jr. Clinical and laboratory predictors of clomiphene response. Fertil Steril 1982;37:168–74.
25. Dodge ST, Strickler RC, Keller DW. Ovulation induction with low doses of clomiphene citrate. Obstet Gynecol 1986;67:63S–65S.
26. Gysler M, March CM, Mishell DR Jr, Bailey EJ. A decade's experience with an individualized clomiphene treatment regime including its effect on the postcoital test. Fertil Steril 1982;37:161–7.
27. Lobo RA, Granger LR, Davajan V, Mishell DR Jr. An extended regimen of clomiphene citrate in women unresponsive to standard therapy. Fertil Steril 1982;37:762–6.
28. Legro RS, Finegood D, Danaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998;83:2694–8.
29. Heard MJ, Pierce A, Carson SA, Buster JE. Pregnancies following use of metformin for ovulation induction in patients with polycystic ovary syndrome. Fertil Steril 2002;77:669–73.
30. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med 1998;338:1876–80.
31. Velazquez E, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 1997; 90:392–5.
32. Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. Fertil Steril 2001;75:46–52.
33. Glueck CJ, Wang P, Kobayashi S, Phillips H, Sieve-Smith L. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. Fertil Steril 2002;77:520–5.
34. Opsahl MS, Robins ED, O'Connor DM, Scott RT, Fritz MA. Characteristics of gonadotropin response, follicular development, and endometrial growth and maturation across consecutive cycles of clomiphene citrate treatment. Fertil Steril 1996;66:533–9.
35. Deaton JL, Clark RR, Pittaway DE, Herbst P, Bauguess P. Clomiphene citrate ovulation induction in combination with a timed intrauterine insemination: the value of urinary luteinizing hormone versus human chorionic gonadotropin timing. Fertil Steril 1997;68:43–7.
36. Zreik TG, Garcia-Velasco JA, Habboosh MS, Olive DL, Arici A. Prospective, randomized, crossover study to evaluate the benefit of human chorionic gonadotropin-timed versus urinary luteinizing hormone-timed intrauterine inseminations in clomiphene citrate-stimulated treatment cycles. Fertil Steril 1999;71:1070–4.
37. Daly DC, Walters CA, Soto-Albors CE, Tohan N, Riddick DH. A randomized study of dexamethasone in ovulation induction with clomiphene citrate. Fertil Steril 1984;41:844–8.
38. Isaacs JD Jr, Lincoln SR, Cowan BD. Extended clomiphene citrate (CC) and prednisone for the treatment of chronic anovulation resistant to CC alone. Fertil Steril 1997;67:641–3.
39. March CM, Tredway DR, Mishell DR Jr. Effect of clomiphene citrate upon the amount and duration of human menopausal gonadotropin therapy. Am J Obstet Gynecol 1976;125:699–704.
40. Farquhar C, Vandekerckhove P, Lilford R. Laparoscopic "drilling" by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev 2001:CD001122.
41. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. N Engl J Med 1995;333:1517–21.
42. Wathen NC, Perry L, Lilford RJ, Chard T. Interpretation of single progesterone measurement in diagnosis of anovulation and defective

luteal phase: observations on analysis of the normal range. BMJ 1984;288:7–9.

43. Hull MG, Savage PE, Bromham DR, Ismail AA, Morris AF. Value of a single serum progesterone measurement in the miduteal phase as a criterion of a potentially fertile cycle ("ovulation") derived from treated and untreated conception cycles. Fertil Steril 1982;37:355–60.

44. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril 1950;1:3–25.

45. De Crespigny LC, O'Herlihy C, Robinson HP. Ultrasonic observation of the mechanism of human ovulation. Am J Obstet Gynecol 1981;139: 636–9.

46. Smith YR, Randolph JF Jr, Christman GM, Ansbacher R, Howe DM, Hurd WW. Comparison of low-technology and high-technology monitoring of clomiphene citrate ovulation induction. Fertil Steril 1998;70: 165–8.

47. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. J Clin Endocrinol Metab 1998;83:2361–5.

48. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility. J Clin Endocrinol Metab 1999;84:1617–22.

49. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. Fertil Steril 2002;77:91–7.

50. Hammond MG, Talbert LM. Clomiphene citrate therapy of infertile women with low luteal phase progesterone levels. Obstet Gynecol 1982;59:275–9.

51. Purvin V. Visual disturbance secondary to clomiphene citrate. Arch Ophthalmol 1995;113:482–4.

52. Maxson WS, Pittaway DE, Herbert CM, Garner CH, Wentz AC. Antiestrogenic effect of clomiphene citrate: correlation with serum estradiol concentrations. Fertil Steril 1984;42:356–9.

53. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern of fecundity in ovulation cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. Fertil Steril 1993;59:756–60.

54. Eden JA, Place J, Carter GD, Jones J, Alaghband-Zadeh J, Pawson ME. The effect of clomiphene citrate on follicular phase increase in endometrial thickness and uterine volume. Obstet Gynecol 1989;73:187–90.

55. Randall JM, Templeton A. Transvaginal sonographic assessment of follicular and endometrial growth in spontaneous and clomiphene citrate cycles. Fertil Steril 1991;56:208–12.

56. Sgarlata CS, Mikhail G, Hertelendy F. Clomiphene and tamoxifen inhibit progesterone synthesis in granulosa cells: comparison with estradiol. Endocrinology 1984;114:2032–8.

57. Opsahl MS, Fitz TA, Rexroad CE Jr, Fritz MA. Effects of enclomiphene and zuclomiphene on basal and gonadotrophin-stimulated progesterone secretion by isolated subpopulations of small and large ovine luteal cells. Hum Reprod 1996;11:1250–5.

58. Olsson JH, Nilsson L, Hillensjo T. Effect of clomiphene isomers on progestin synthesis in cultured human granulosa cells. Hum Reprod 1987;2:463–8.

59. Schmidt GE, Kim MH, Mansour R, Torello L, Friedman CI. The effects of enclomiphene and zuclomiphene citrates on mouse embryos fertilized in vitro and in vivo. Am J Obstet Gynecol 1986;154:727–36.

60. Schenker JG, Jarkoni S, Granat M. Multiple pregnancies following induction of ovulation. Fertil Steril 1981;35:105–23.

61. Ahlgren M, Kallen B, Rannevick G. Outcome of pregnancy resulting from clomiphene therapy. Acta Obstet Gynecol Scand 1976;55:371–5.

62. Correy JF, Marsden DE, Schokman FC. The outcome of pregnancy resulting from clomiphene induced ovulation. Aust NZ J Obstet Gynaecol 1982;22:18–21.

63. Gysler M, March CM, Mishell DR Jr, Bailey EJ. A decade's experience with an individualized clomiphene treatment regime including its effect on the postcoital test. Fertil Steril 1982;37:161–7.

64. Dickey RP, Taylor SN, Curole DN, Rye PH, Pyrzak R. Incidence of spontaneous abortion in clomiphene pregnancies. Hum Reprod 1996; 11:2623–8.

65. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992;136:1184–203.

66. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. N Engl J Med 1994;331:771–6.

67. Venn A, Watson L, Lumley J, Giles G, King C, Healy D. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. Lancet 1995;346:995–1000.

68. Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, et al. Cancer incidence in a cohort of infertile women. Am J Epidemiol 1998;147:1038–42.

69. Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Infertility, fertility drugs, and invasive ovarian cancer: a case-control study. Fertil Steril 1997;67:1005–12.

70. Potashnik G, Lerner-Geva L, Genkin L, Chetrit A, Lunenfeld E, Porath A. Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. Fertil Steril 1999;71:853–9.

71. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol 2002;155:217–24.