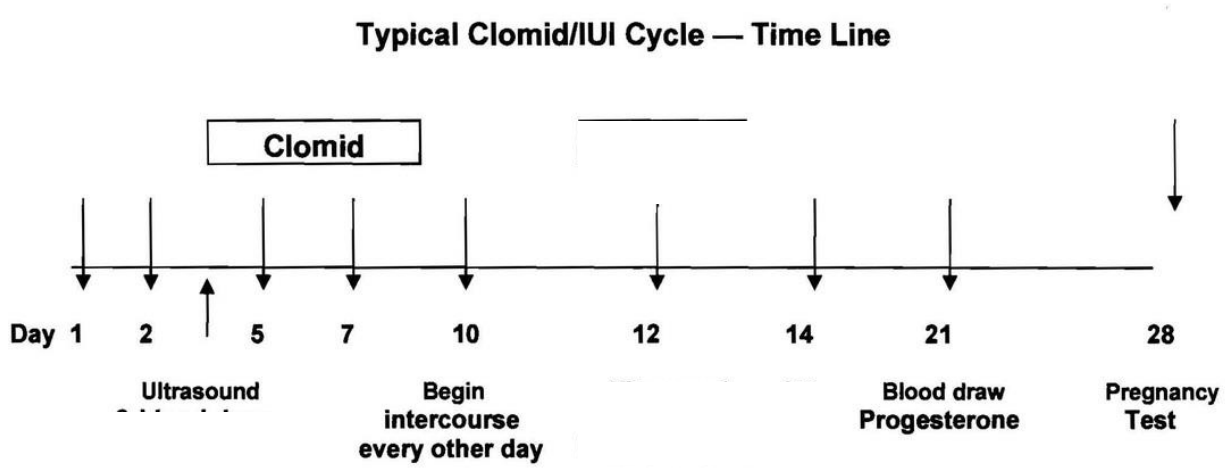
Ovulation Induction with Clomid or Femara



ORAL AGENTS.

Letrozole — Letrozole, an aromatase inhibitor, blocks the conversion of testosterone and androstenedione to estradiol and estrone, respectively (unlike clomiphene, which blocks estrogen action), thereby reducing negative estrogenic feedback at the pituitary and thus increasing follicle-stimulating hormone (FSH) output (figure 2). In contrast to clomiphene citrate, letrozole appears to be free of the adverse effects on endometrial and cervical mucus attributed to clomiphene citrate [18]. (See "Ovulation induction with letrozole".) For oligoovulatory women with polycystic ovary syndrome (PCOS) undergoing ovulation induction, we now suggest letrozole as first-line therapy over clomiphene citrate, regardless of the patient's body mass index (BMI). Before starting letrozole, the clinician **must** discuss that this use of the drug is not US Food and Drug Administration (FDA) approved and that there is an available alternative (clomiphene citrate). This recommendation is consistent with current American College of Obstetrics and Gynecology (ACOG) guidelines for choice of ovulation induction agents in women with PCOS [19].

A randomized trial [20] and a meta-analysis of 20 trials in nearly 4000 anovulatory women with PCOS [21] have both reported that letrozole results in higher live birth rates compared with clomiphenetherapy. In contrast, clomiphene citrate is

approved for ovulation induction and has been widely used for over 50 years [22]. Efficacy and safety of letrozole is reviewed in detail separately. (See "Ovulation induction with letrozole".)

Clomiphene citrate — In 1958, the nonsteroidal antiestrogen MER-25 was found to induce menstruation in an amenorrheic woman receiving the drug as an experimental treatment for endometrial cancer [23]. The next year, 43 anovulatory women given another antiestrogen, clomiphene citrate, also ovulated. Clomiphene, like tamoxifen and raloxifene, belongs to the category of compounds known as selective estrogen receptor modulators (SERMs). These drugs are competitive inhibitors of estrogen binding to estrogen receptors and have mixed agonist and antagonist activity, depending upon the target tissue. While they could be used for ovulation induction, tamoxifen and raloxifene are less effective than clomiphene, so are not typically used for this purpose.

Clomiphene citrate has been the most widely used agent for ovulation induction for over 50 years. Most, but not all, women with PCOS ovulate in response to clomiphene citrate. However, clomiphene is no longer considered to be first-line therapy for women with PCOS. (See 'Letrozole' above and "Ovulation induction with letrozole".)

Sixty to 85 percent of anovulatory women, typically with PCOS, ovulate in response to clomiphene citrate. Of those who ovulate, approximately 50 percent do so at a dose of 50 mg daily for five days, often cycle days 3 to 7. Twin and triplet gestations occur in approximately 7 to 9 and 0.3 percent, respectively, of clomiphene-induced pregnancies. The incidence of miscarriage and birth defects appears to be similar to that in spontaneous pregnancies, and the rate of ectopic pregnancy is probably not increased. The risk of ovarian hyperstimulation syndrome (OHSS) is less than 1 percent. (See "Ovulation induction with clomiphene citrate", section on 'Outcomes'.)

Predictors of ovulation in one study included a lower free androgen index (FAI), a calculation of testosterone not bound to sex hormone-binding globulin (SHBG), lower body mass index (BMI), presence of oligomenorrhea (as opposed to amenorrhea), and lower ovarian volume [24]. Of those who ovulate, 30 to 40 percent conceive. In the study noted [24], predictors of pregnancy with clomiphene included younger age, low BMI, low FAI, and oligomenorrhea rather than amenorrhea. A nomogram has been developed to help predict chances for live birth based upon simple, initial screening characteristics (figure 3).

There is general agreement that obese women respond less favorably to clomiphene citrate ovulation induction.
Ovulation induction with clomiphene is reviewed in greater detail elsewhere. (See "Ovulation induction with clomiphene citrate" and "Treatment of polycystic ovary syndrome in adults", section on 'Ovulation induction medications'.)

Metformin — Correction of hyperinsulinemia with metformin has been shown to have a beneficial effect in anovulatory women with PCOS by increasing menstrual cyclicity and improving spontaneous ovulation. However, it does **not** appear to improve live-birth rates when given alone or in combination with clomiphene citrate. This topic is discussed separately. There is some experience with the use of another insulin-sensitizing drug, (myo)inositol. Results of well-designed studies of sufficient sample size should be awaited.
(See "Metformin for treatment of the polycystic ovary syndrome", section on 'Anovulatory infertility'.)

Pretreatment evaluation — Before initiating therapy, the presence of ovulatory dysfunction must be established. The menstrual history alone may be diagnostic (eg, one can be confident that ovulatory dysfunction is present in women with amenorrhea or irregular menses [>45 day intermenstrual interval]). It is possible that women with cycles in the 35- to 45-day range have intermittent ovulations. We suggest that these women try to conceive on their own without therapy for several months. If they are unsuccessful, they should be referred for ovulation induction. If the diagnosis of ovulatory dysfunction is uncertain, additional testing should be performed. This can include simple, noninvasive tests such as basal body temperature and/or urinary luteinizing hormone (LH) monitoring, although a luteal phase serum progesterone level is more definitive (table 2). (See "Evaluation of the menstrual cycle and timing of ovulation".)

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. (See "Overview of infertility".)
The pretreatment evaluation should include [1]:

- A complete history and physical examination.
- Laboratory testing – Human chorionic gonadotropin (hCG), thyroid-stimulating hormone (TSH), and prolactin (PRL) to exclude pregnancy, thyroid disease, and hyperprolactinemia as causes of the ovulatory dysfunction, respectively, because these require different treatments. Serum follicle-stimulating hormone (FSH) should also be measured [1] as women diagnosed

with primary ovarian insufficiency are unlikely to respond to clomiphene. (See "Evaluation and management of secondary amenorrhea", section on 'Follow-up testing based upon initial results' and "Clinical manifestations and diagnosis of spontaneous primary ovarian insufficiency (premature ovarian failure)".)

- Women with polycystic ovary syndrome (PCOS) and hirsutism should have a 17-hydroxyprogesterone measured; if nonclassic 21-hydroxylase deficiency is diagnosed, glucocorticoid therapy is a potential alternative for ovulation induction. (See "Diagnosis and treatment of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on '17-hydroxyprogesterone'.)
- Women with PCOS and obesity should be screened for diabetes and encouraged to lose weight before considering ovulation induction.
- Semen analysis of the partner to identify seminal abnormalities that might contribute to the infertility. (See "Evaluation of female infertility", section on 'Semen analysis'.)
- 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. In women with no risk factors for tubal disease, the hysterosalpingogram can be postponed but should be performed if women have not conceived after three ovulatory cycles. (See "Evaluation of female infertility", section on 'Hysterosalpingogram'.)
- An endometrial biopsy may be indicated to assess hyperplastic changes in women with chronic anovulation. This is not routine, however. Indications are described separately. (See "Abnormal uterine bleeding: Management in premenopausal patients".)
- A pelvic examination or a pelvic ultrasound to rule out ovarian cysts, especially in patients with known tendency to form functional cysts.
- Some experts suggest an assessment of ovarian follicle pool in women over age 37 years. A low serum anti-müllerian hormone (AMH) less than 1 ng/mL would identify a woman with a diminished pool of oocytes who would likely be triaged to assisted reproductive interventions (instead of clomiphene citrate). (See "Evaluation of female infertility", section on 'Anti-müllerian hormone'.)

Starting a cycle — Clomiphene 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 started on cycle day 2, 3, 4, or 5 [18,19].

There are no laboratory or clinical parameters that predict the dose necessary to achieve ovulation. The initial dose, empirically, is 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, the dose is increased by increments of 50 mg to a maximum daily dose of 150 mg (100 mg is the maximum dose approved by the US Food and Drug Administration [FDA], and the American Society for Reproductive Medicine [ASRM] suggests that doses >100 mg add little to clinical pregnancy rates) [1]. Once ovulation is achieved, the same dose should be continued for four to six cycles.
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 [20], the American College of Obstetricians and Gynecologists (ACOG) has suggested that clomiphene treatment be limited to fewer than 12 cycles and that the number of gonadotropin cycles be minimized, as well [21]. We suggest further evaluation and/or a change in therapy for women who do not conceive after three to six ovulatory clomiphene citrate cycles.

Monitoring — The response to treatment should be monitored. Determination of the ovulatory LH surge by urinary LH kits is what most clinicians recommend in practice. Urinary LH monitoring also provides information on appropriate timing of intercourse during a given cycle [22]. 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 [23]. Therefore, the interval of highest fertility is the day of the LH surge and the following two days.

A basal body temperature chart can also be used and does not increase the cost of treatment. Conversion of a uniphasic to a biphasic basal temperature curve suggests retrospectively that ovulation has occurred. However, basal body temperature 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 mid-luteal (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.
Some expert groups, such as the Royal College of Obstetricians and Gynecologists (RCOG) and the National Institute for Health and Clinical Excellence (NICE), suggest serial transvaginal ultrasound to monitor the number and size of developing follicles and to time hCG 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 clomiphene cycle in order to exclude hyper-response [24,25]. However, adding ultrasonographic monitoring is costly and does not appear to improve pregnancy rates significantly [26]. (See "Evaluation of the menstrual cycle and timing of ovulation".)

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 gonadotropin-releasing hormone (GnRH) agonists.

Source: UpToDate – as of 10/2/21