

Clomiphene Citrate



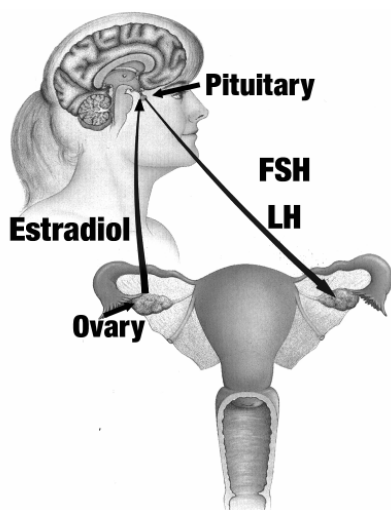
**Southern Ontario
Fertility Technologies**

Introduction

Once the “basic” infertility investigation is completed, clomiphene citrate is often used to promote fertility. Clomiphene has been one of the mainstays of infertility treatment since it was first used in 1963. It is not used if the fallopian tubes are blocked or if severe male factor infertility is present but essentially deserves a short trial in almost every other situation. For women who are **not ovulating** (producing an egg) every month clomiphene is usually the first treatment attempted. However, clomiphene is also useful in couples with “**idiopathic**” infertility, **mild male factor**, **endometriosis-associated infertility**, **mild tubal factor infertility**, **female age-associated infertility** or **cervical factor infertility**.

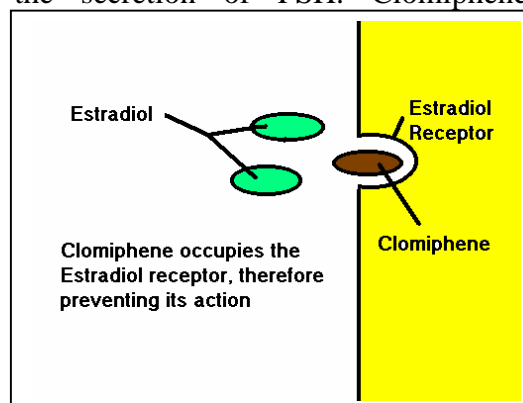
How many cycles of clomiphene with “timed intercourse” will be suggested depends on the diagnosis, the previously attempted infertility treatments, the length of infertility, and the female partner’s age. Clomiphene is effective for women who are not ovulating because it stimulates ovulation but it is also used in the other forms of infertility to mature more than one egg per month. Once clomiphene has been used with timed intercourse, it is often the first drug used combined with intrauterine insemination. An information sheet is available on intrauterine insemination.

How It Works



Menstruation and ovulation are complex processes depending on the action of hormones released from the ovary, pituitary and hypothalamus. An imbalance in the levels of these hormones can disturb normal ovulation and can contribute to infertility. **Follicle stimulating hormone (FSH)** is released by the pituitary and stimulates both egg maturation and production of estrogen (estradiol). The estradiol “feeds-back” to the pituitary to cause a decrease in the secretion of FSH. Clomiphene essentially works by fooling the body into

thinking there is less **estrogen**. It has the same three-dimensional shape as estradiol and fits into the estradiol **receptor** so that the receptor is unavailable to estradiol. Therefore the production of FSH is not turned off. More FSH is produced and more stimulation of the ovaries occurs.



How to Take Clomiphene

Clomiphene is taken as a pill(s) for five days beginning three days after the first day of menstrual bleeding (**day 3 to 7 of cycle**). Many physicians will use clomiphene from day 5 to 9 of the cycle. This is not wrong and depends more on where the physician was trained. In fact there has been a recent paper on using clomiphene from day 1 to 5 of the cycle and this paper demonstrates very similar results to what we are used to with the other regimes. More than one pill of clomiphene may be prescribed if ovulation hasn't occurred on the lower dose but if ovulation is already occurring, clomiphene is seldom increased above the initial starting dose. The first day of the cycle is considered the first day of bleeding sufficient to require sanitary protection as long as it occurs before midnight. Clomiphene may be started after medication (for example, **provera**) is given to bring on a period in women who are not having regular periods.

Cost of Clomiphene

Clomiphene at the lowest dose is usually about **\$35.00**. It is important to note that **some drug plans cover a given number of cycles of infertility treatment**. Clomiphene does not work for everybody and you may have to move on to more expensive medication. Before submitting clomiphene to your drug plan, check exactly your coverage. If your drug plan covers only a number of cycles you may consider paying for the clomiphene in order to have more expensive cycles covered later on.

Before starting any infertility treatment, make yourself familiar with the details of your drug plan!

Alternative Medications

Several alternatives do exist to clomiphene. **Tamoxifene citrate** and **Letrosole** (Femara) may be very helpful as alternatives. In the clinic we often will use femara as an alternative to clomiphene especially if clomiphene is causing endometrial thinning or is not able to cause ovulation.

The Success Rate When Not Ovulating

Clomiphene is very effective at promoting ovulation in women where the reason for not ovulating is miscommunication between the pituitary and the ovary (usually referred to as polycystic ovary syndrome or PCOS – a separate information sheet is available). Clomiphene will not work for women with pituitary or ovarian failure. These different causes of not ovulating will be evaluated with your initial infertility investigation. Between **50 - 90%** of women who take clomiphene will ovulate. Not everyone will be successful with the lowest dose (50 mg / day X 5 days). We will begin with this dose but will increase the daily dose by 50 mg for the next month if ovulation does not occur. A dose of 50 mg, 100 mg, and 150 mg or higher may be tried. Approximately **50%** of women who ovulate will become pregnant, usually within the first three to six cycles. A maximum of six ovulatory cycles / pregnancy are indicated before other infertility treatments are considered.

The Success Rate with Other Causes of Infertility

In couples with “idiopathic”, mild male-factor, endometriosis-associated, mild tubal-factor, or cervical-factor infertility, clomiphene can be used to stimulate more than one egg and is associated with a **doubling to tripling** of the monthly pregnancy rate. There is no evidence that increasing the 5-day dosage above 50 mg is beneficial in this situation. Clomiphene has both beneficial and non-beneficial effects for pregnancy and increasing the dose above what is required to produce extra eggs may have detrimental effects on the cervical mucous or endometrium.

How Long To Try Clomiphene?

Clomiphene is indicated for a maximum of **six ovulatory cycles** in patients who are not ovulating. How we determine whether ovulation occurs or not is covered later in this information sheet. Once six ovulatory cycles have been documented without a pregnancy, it becomes increasingly less likely that clomiphene alone will be successful and it is probably time to consider a different treatment.

Clomiphene is indicated for a maximum of **12 cycles for other forms of infertility** but is seldom used more than 6 cycles. The reason for this is that most research indicates that a benefit (higher chance of pregnancy) cannot be demonstrated past 12 cycles and it is time to add something else to the treatment.

In many situations you may be advised to do **less than the suggested number of cycles**. With an increased length of infertility, increased dose of clomiphene required to produce ovulation or in older women, fewer cycles may be suggested as time may necessitate moving on to a more intensive treatment earlier. Fewer cycles may also be suggested with certain diagnoses such as mild male-factor or mild tubal-factor infertility as these may be associated with a lower chance of success with clomiphene. We will probably move on to more intensive treatments sooner in female age-related infertility.

In a few circumstances, **more cycles than mentioned above may be recommended**. If clomiphene has produced a pregnancy but it has unfortunately ended in miscarriage it will often be tried again. In anovulatory women who cannot afford more intensive treatment or for patients whose endometriosis has been treated at the time of laparoscopy, more cycles may be considered.

Lastly, the exact number of cycles of clomiphene to be tried will be modified by **how you feel about it**. Clomiphene is usually attempted first because it is inexpensive, easy (less time consuming), and requires less intervention. Side effects are very few (to be discussed) and the risk of multiple pregnancies is lower than many other infertility treatments. However, if your particular preference is to avoid clomiphene, this will be discussed and respected.

**You should try _____
cycles of clomiphene.**

Timing of Ovulation and Intercourse

Release of the egg(s) usually happens 8 to 10 days after the last dose of clomiphene (day **15 to 17** of the cycle). If a pregnancy does not occur, menstruation will probably occur 23 or 25 days after the last dose of clomiphene (giving a **30 to 32** day cycle). Clomiphene tends to lengthen your existing cycle. The above prediction is based on a person who had a 28 day cycle. Women, who usually have a 24 day cycle, may

experience an ovulatory cycle which is only 26 or 28 days long. Women, who have extremely long cycles or no cycles at all, may ovulate in very long cycles.

Intercourse should occur **whenever you feel like it**. One of the more stressful aspects of infertility is that intercourse tends to become regimented and only for the purpose of conceiving. There is no good evidence that having intercourse, even frequently outside of the “fertile window” will decrease the chances of pregnancy. In fact, on the contrary, there is good evidence that couples that **have more frequent intercourse become pregnant faster**. Intercourse also has relationship building and stress relieving benefits. Recent evidence has also indicated general health benefits and improvement of sperm counts from frequent intercourse.

There is also no evidence that any particular sexual frequency clustered at ovulation is better. Advice has been given in the past that intercourse every two days will allow a higher sperm count. It is true that when we request a semen analysis, you are asked to abstain for 48 hours so that we can estimate the maximal sperm count. However, ejaculation into the vagina allows the number of sperm in the female to be additive and of different ages.

One of the misconceptions about infertility is that intercourse should be only every other day in order to maintain a high sperm count. An example might help to clarify this. A couple has intercourse in the morning and 100 million sperm are deposited in the vagina. The couple then has intercourse later that same day and only 75 million sperm are deposited in the vagina because the sperm count is decreased by the earlier ejaculation that day. However, there are now 175 million sperm in the vagina, thus increasing the total number of sperm where it counts!

We believe sperm live in the female reproductive tract about 48 hours. If intercourse occurs **at least every other day from the 12th to the 20th day of the cycle** there should always be sperm available when the egg is released. This recommendation is based on the usual scenario of clomiphene making the cycle 30 to 32 days long. In circumstances where we think ovulation is occurring, but the cycle length is different than this, the recommendation for frequent intercourse times may have to be modified. For example, in the woman who’s usual cycle is 24 days and clomiphene lengthens this to 27 days, intercourse should occur from day 9 to 17 of the cycle.

In rare circumstances when intercourse is not possible frequently (illness or work commitments which require separation of the partners), detection of ovulation may be important to time intercourse. In these circumstances, basal body temperature charts, urine based ovulation detection kits (I.E. Clearplan Easy or Ovukit), or the newer saliva kits may be used. Often this may be an indication for earlier graduation to intrauterine insemination (Information sheets are available) or we may offer to monitor your cycle at S.O.F.T. in order to pinpoint ovulation.

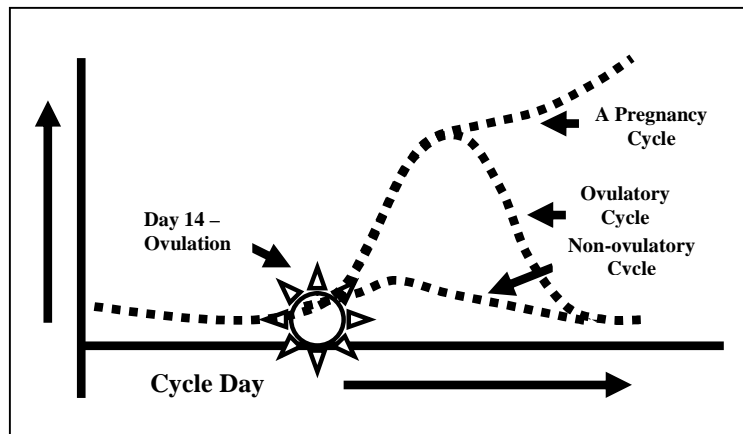
Determining If Ovulation Occurs

It may not be critical to determine when ovulation occurs but it is important to determine whether ovulation is occurring. If menstruation occurs about 30 or 32 days after the first day of the last period, then ovulation has likely occurred. In this program, we prefer to confirm ovulation with “**luteal phase progesterone**”. This is usually done 6 days before the next period is expected to occur, if a pregnancy does not occur. Because

the usual clomiphene cycle is 32 days long, this would be day **24 to 26 of the cycle** but will be sooner in the cycle if clomiphene produced a shorter cycle (I.E. day 22 in a 28 day cycle, day 18 in a 24 day cycle). If this information sheet has been given to you at the clinic with a prescription for clomiphene, you will also be given instructions on how to do your progesterone level. This can be done in at a lab near you or at S.O.F.T. if you live close to us. The results will automatically be sent to the clinic and arrive about a week later. **It is probably only important to know the progesterone level if clomiphene is not producing the usual cycle lengths.** Progesterone level of 16 or greater indicates ovulation. A progesterone level of less than 16 indicates that ovulation did not occur or did not occur at the usual time.

For example, if your period was 30 to 32 days in length and the progesterone is 16 or greater, you probably released an egg (ovulated). If another cycle of clomiphene has been prescribed, you should repeat the same cycle as long as it is within the pre-agreed number of cycles. If your period was outside this range and/or the progesterone was less than 16 and your pregnancy test is negative, you probably didn't ovulate or didn't ovulate at the usual time. We will likely advise you to increase your clomiphene dose. If the clomiphene dose has already been increased, we may change your medication or do something to make clomiphene work better. Call S.O.F.T. (519-685-5559) for instructions. The clinic only calls you if your progesterone is less than 16. If we don't call you, then the progesterone level was likely over 16. In this case you will have to call the clinic if you want to know your exact level. Higher is not necessarily better although occasionally very high progesterone levels may foreshadow a pregnancy. That is not because a higher progesterone indicates a better ovulation but because in a cycle were a pregnancy occurs, the progesterone continues to rise rather than having the usual "bell curve shaped" rise (see diagram opposite).

If your period does not come in 35 days, call the clinic for a lab requisition for a pregnancy test. (BHCG) Pregnancy tests are usually run the same day at S.O.F.T. If your BHCG is positive, please call S.O.F.T. for an early pregnancy ultrasound.



What If Ovulation Does Not Occur?

If you had regular cycles and clomiphene was given to you to promote the production of more than one egg but appears to have caused you not to ovulate it may not be the right medicine for you. Sometimes the lowest dose will be tried one more or a modest increase (IE 75 mg

Clomiphene is associated with a doubling to tripling of the pregnancy rate in women who are already ovulating because it increases the number of eggs. However, in a small minority of ovulatory women (<5%), it causes them to not ovulate. In this case, it is of no benefit and other forms of treatment should be perused.

from day 3 to 7) will be tried but usually clomiphene will be abandoned early in favor of another treatment. If this occurs we will often monitor a cycle with blood tests and ultrasound, much like we monitor for intrauterine insemination. This will tell us exactly what is happening to your cycle and allow us to choose alternate treatments. Information on how this monitoring is done is available in the information sheet on intrauterine insemination with clomiphene citrate.

Some women, who are not ovulating naturally, will not ovulate with clomiphene. If you don't ovulate with the lowest dose of clomiphene, a higher dose will be tried. Usually, the highest dose that is attempted is 150 mg from day 3 to 7 of the cycle. Even though higher doses may cause ovulation, they are less likely to cause pregnancy because of the negative effects of clomiphene on the endometrium and cervical mucous at higher doses.

If this happens, some treatments are available to make them more sensitive to clomiphene or alternative medications such as letrozole or tamoxifene may be tried. Sometimes the addition of injectable fertility medication will allow ovulation to occur with a previously unsuccessful level of clomiphene. This of course is only done with careful monitoring of the cycle and usually includes intrauterine insemination.

In up to 60% of women with polycystic ovary syndrome have **insulin resistance**? Insulin resistance occurs when the body is required to produce more insulin to keep the blood sugar normal than usual. It is not diabetes but predisposes to diabetes later in life or during a pregnancy. If your cycles are irregular or you have a family history of diabetes, you will likely be tested for insulin resistance with your day three blood work done for your initial workup. Treatment of this with metformin or advandia will often make ovulation more likely to occur with clomiphene. Recently, several reports have indicated that metformin treatment may be beneficial even if the initial insulin resistance testing is within normal limits. An information sheet is available on decreased ovulation.

Increasing the dose of clomiphene is helpful in non-ovulatory women who do not ovulate on the lowest dose of clomiphene because higher doses may cause ovulation and therefore make pregnancy possible. There is however a down side to this. The higher the dose of clomiphene required to produce ovulation, the fewer pregnancies that occur per ovulation. This is because of the negative effects of clomiphene on the cervical mucous and endometrium and is why we will usually move on to a different treatment if ovulation dose not occur with 150 mg of clomiphene for 5 days.

Sometimes combinations of drugs will be tried. One combination we have found successful in the clinic is femara with clomiphene. Using the two drugs together appears to harness the ovulation induction ability of both while keeping the side effects of each to a minimum (separate information sheet available).

Other specific medications may be used in circumstances where there is increased production of androgens from the adrenal glands. A recent study has demonstrated that dexamethazone can be used to decrease the adrenal glands production of male hormones in the first half of the cycle to promote ovulation. We are about to initiate a clinical trial to determine if there are predictors of when this approach will be useful.

Ovarian cautery or drilling at the time of laparoscopy may also be considered. Ovarian cautery or drilling has been demonstrated to cause the resumption of normal ovulation or cause an improved response to clomiphene in many patients. Although this sounds crazy, it works very well. It was discovered serendipitously like many things are in medicine (see box). Additional information sheets are available on laparoscopy and ovarian cautery.

Determining If Pregnancy Has Occurred

If a period does not occur after **35 days** from the first day of your last period, a **pregnancy test** should be done. You should call the clinic for a requisition for *BHCG* (blood pregnancy test) can be called or faxed in for you. (A pregnancy test can also be done at the clinic and usually the results will be available the same day – Therefore *“it’s worth the drive to London”*.) If you are pregnant, the test will be positive but may take a few days to get to our office if done elsewhere. If you would like to know the results of your test faster, you may wish to write “copy to your family doctor or local gynecologist” in the forth box down on the left hand side of the requisition. If you are pregnant, you will be offered a vaginal ultrasound at the clinic to evaluate the pregnancy and especially to diagnose a twin pregnancy. If you are not pregnant and your period is delayed, it is unlikely that you have ovulated. You should contact the clinic so that medication to bring on a period (Provera 5 mg X 5 days) and the dose of clomiphene can be increased or some other change can be made for the next cycle. **If ovulation has not occurred on a given dose of clomiphene, that dose should not be continued;** a higher dose should be prescribed or other forms of treatment employed.

What If It Doesn’t Work

Clomiphene is often considered the first line of infertility treatment. It is worth trying in almost any couple as long as at least one fallopian tube is open and extremely severe male-factor infertility is not present. In most studies the pregnancy rate per cycle using clomiphene is about 5 to 10%. Although this may not seem very high, it is still very reasonable first line treatment as 6 cycles will allow up to 50% of women who are not ovulating, and 30% of women who are ovulating a pregnancy.

However, clomiphene doesn’t always work. Many options may be considered but the most common is the **intrauterine insemination**. This may originally be combined with clomiphene or stronger medications. An information sheet on intrauterine insemination is available.

Side Effects

The major side effect of clomiphene is an increase in the frequency of multiple births. **Twins occur in 5 %** of these pregnancies and triplets are extremely uncommon.

Clomiphene usually causes the ovaries to become larger as they are making more eggs. This does not cause pain but you may be aware that there is more going on in that area of your body and often gives the sensation of bloating or pressure. However, occasionally, abnormal **enlargement of the ovaries** or a persistent cyst can occur. This is very rare and can be easily diagnosed in the clinic with a vaginal ultrasound. If it does occur, it will respond to withdrawal of the drug for a cycle or two. Extremely rarely

(0.1%), patients will over-respond to clomiphene, forming many cysts. This can also easily be diagnosed at the clinic using a vaginal ultrasound. In this case, the dose of clomiphene is reduced or an alternate treatment will be suggested. In the past, patients on clomiphene required pelvic examinations between each cycle, but there is good evidence now that this is not necessary.

Hot flashes are the most common side effect while you are taking the drug. This occurs because clomiphene works by fooling the body into thinking there is less estrogen. With less estrogen the body can simulate symptoms of menopause.

Other adverse reactions, occurring less frequently (1% or less of patients), include breast tenderness, headache, nervousness, dizziness, nausea and vomiting, fatigue and temporary visual disturbances.

Overall most women find clomiphene gives very few side effects and is easily tolerated. If you are experiencing many side effects or finding taking clomiphene unpleasant, please discuss this with us. If you have pain in the last half of a clomiphene cycle, please call the clinic and ask for a vaginal ultrasound.

Safety

Clomiphene has been in clinical use since 1963. For most of that time it has functioned as the usual first step in fertility treatment except for couples with blocked fallopian tubes or severe male factor infertility. No one knows how many pregnancies have occurred using clomiphene but it is probably in the hundreds of thousands, if not in the millions. No clinical trial has ever demonstrated an increase in congenital abnormalities using clomiphene. Clomiphene does cause an increase in the twinning rate from 1.2% to 5%. Twins are a more difficult pregnancy and associated with more complications.

Is Clomiphene Right for You?

Who knows? All the epidemiological data has been discussed earlier in this information paper but epidemiological studies describe the results in large groups of patients. This data will be used to decide how many cycles of clomiphene should be used. However, individuals get pregnant and it has been my experience that in individuals there is a **key to obtaining a pregnancy**. It is not always possible to predict what that key is. Sometimes, “just clomiphene” has produced some remarkable results. Therefore unless the fallopian tubes are blocked or there are very few sperm, clomiphene is worth trying at least briefly.

Clomiphene with Timed Intercourse Cycle – Day By Day

Cycle Day	Instructions	Patient Notes
Day 1	This is the first day of menstrual bleeding requiring protection (as long as the bleeding occurs before midnight)	
Day 1 (cycle 1)	Call for hysterosalpingogram (only if asked)	
Day 3 (cycle 1)	“Day 3 blood-work” (only if asked)	
Day 3-7 (5-9)	Take clomiphene citrate as prescribed. The starting dose is 50 mg. If you don’t ovulate this is	

	increased each cycle by 50 mg.	
Day 2 to 13	Hysterosalpingogram (only if asked)	
Day 12 to 20	Have intercourse a minimum of every two days.	
Day 24, 25 or 26	Go to the lab and for serum progesterone. You will be given a "Laboratory Requisition" with this information sheet. You can call S.O.F.T. for this result about a week after it is done. If you would like the result faster the test can be done at S.O.F.T.	
Day 35	If your period does not begin, call the clinic or your family doctor for a BHCG (pregnancy test). Pregnancy tests are done at S.O.F.T. on the same day.	
Day 54-56	If pregnancy test positive, an early pregnancy vaginal ultrasound	

When you're Pregnant

After a positive pregnancy test, you will be asked to attend the clinic about 40 days after conception or ovulation for a vaginal ultrasound (usually 26 days after a missed period). By this time we should be able to clearly see the gestational sac (bag of waters) inside the uterus. A multiple pregnancy can also be diagnosed.

It also is possible to diagnose problems with the pregnancy such as a miscarriage or ectopic pregnancies.

Although a perfectly normal ultrasound cannot guarantee a normal pregnancy because it cannot predict the future, it is very reassuring. At least 90% will go on to be normal.

When the ultrasound is done, your due date will be calculated and a report will be sent back to your referring physician informing them of your pregnancy and asking them to take over your obstetrical care. After your ultrasound you are still considered our patient. Especially early in your pregnancy, if you have any concerns, perhaps because you have had bleeding or pain, we are more than happy to repeat your ultrasound.

It is at this time we will also remind you of the **Clinic Rules**. "Rule one" is you have to send us a birth announcement and "rule two" is that you have to bring the baby to visit us.



Normal "luteal day 40" or "early pregnancy" ultrasound of a single pregnancy

James Martin MD ©

S.O.F.T.

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Check out our web page at www.soft-infertility.com