

Ovulation and Decreased Ovulation



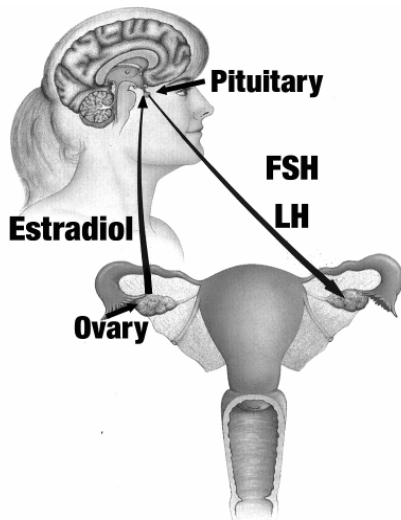
**Southern Ontario
Fertility Technologies**

Introduction

Decreased ovulation refers to situations where a woman **does not release an egg each month**. The usual sign that this is occurring is irregular menstrual cycles.

Regular menstrual cycles do not guarantee ovulation, but in general, the more regular the cycles, the more likely ovulation occurs in most cycles. The more irregular the cycles, the less likely ovulation occurs in many cycles.

The Normal Menstrual and Ovulatory Cycle



Each month the lining of the uterus (endometrium) builds up, and then sheds resulting in a period (menses). The average cycle is about 28 days but can be shorter or longer (usually 25-35 days). The menstrual flow lasts 3 to 7 days. This type of normal menstrual cycle is possible because of a complex interaction of hormones secreted from the pituitary and the ovary. If all goes well, the interaction of these hormones results in ovulation (release of an egg) about mid-cycle. If this occurs, estrogen is the dominant hormone in the first half

Notice that the title of this information sheet is decreased ovulation rather than anovulation. Although it is true that there are some women who hardly ever ovulate, it is usually not an all or nothing phenomenon. Usually, the more irregular the cycles are the less common ovulation. The women least likely to ovulate at all is the woman with no menstrual cycles. However, even in this situation, a rare ovulation can occur and therefore a spontaneous pregnancy can occur.

of the menstrual cycle and after ovulation, progesterone becomes dominant. If ovulation does not occur, the high levels of progesterone do not develop.

“Day one” of the cycle is considered the first day of bleeding requiring more than a panty liner. At this time, most of the reproductive hormones are at their lowest level. Follicle stimulating hormone (FSH) begins to rise. This usually results in the recruitment of a follicle in one of the ovaries. A follicle is the cystic structure containing an egg. The follicle, as it grows begins to produce estradiol; therefore, estradiol begins to rise. At some point, usually about day 13 of a 28 day cycle, a critical combination of FSH and estradiol causes an extremely rapid rise of luteinizing hormone (LH). The extremely rapid rise of LH (the LH surge) is necessary for the final maturation of the egg and its release from the follicle. Once the egg is released from the follicle, the FSH, estradiol and LH all decrease but the follicle becomes luteinized and produces progesterone. Progesterone levels rise for a short period, but if the egg is not fertilized and starts to implant in the endometrium (lining of the uterus) it falls and the cycle starts all over again.

Are You at Risk of Decreased Ovulation?

There are many ways of determining if ovulation occurs but none with the exception of a pregnancy is foolproof. The methods of determining ovulation will be discussed below. One of

the most common ways of determining ovulation is a “luteal phase progesterone”. This is a blood test that can be arranged by your doctor. If “luteal phase progesterone” is used as a measure of ovulation, the percentage of women who ovulate in any given cycle can be calculated. The results of this are presented in the table. What the table demonstrates is that in general, the more regular the cycles are, the more likely it is that ovulation will occur in any given cycle. It also demonstrates that even with extremely regular cycles, ovulation is not guaranteed in every cycle. Also, women with very irregular cycles probably do ovulate occasionally.

The shortcoming of using “luteal phase progesterones” to determine if ovulation occurred is that it is determined at day 21 of the cycle and therefore detects only ovulations which occur at the usual time of the cycle. We know from monitoring many cycles at S.O.F.T., that late ovulations can occur and can result in a pregnancy.

Cycle Length Variability (Days)	Percent Ovulating (%)
0 -1	85
2 -4	60
5 - 10	40
10 - 20	25
> 20	<10

Determining if Ovulation Occurs

There are a number of ways of determining if ovulation occurs but none of them is 100% accurate except we know ovulation occurred if a pregnancy occurred. A regular cycle of about 28 to 30 days predicts that ovulation has occurred 85% of the time as demonstrated in the table above.

Chance of ovulating with different Cycle Patterns. Based on 1132 cycles analysed at S.O.F.T. from 2000 to 2002.

You can also detect ovulation by watching for changes in your **cervical mucous**, the fluid normally released from your vagina. At the start of the menstrual cycle, this mucus is sparse, tacky, and dense, but around the time of ovulation it becomes increasingly plentiful and slippery, with qualities very similar to the white of a raw egg.

Basal body temperature charts can perhaps indicate ovulation but are time consuming and intrusive. If it is done, at S.O.F.T., we recommend it is done one or twice at the most.

The **LH surge can be detected by urine tests or newer saliva tests**. Trying to choose among the dozen or so ovulation prediction kits now available at the drugstore can be dizzying. These kits detect a surge in luteinizing hormone, which signals ovulation will occur in the next 24 to 36 hours. OvuKit Self-Test © tends to be pricier (up to \$50) and more difficult to perform than other choices. It worth the extra time and expense for infertile couples undergoing finely timed intercourse since it is purported to be somewhat more accurate. However, under most circumstances, we don't recommend at S.O.F.T. trying to finely time intercourse. Clearplan Easy (about \$24), because they provide very reliable results and are very simple to perform -- all you do is hold the stick tester in your urine stream for several seconds, then wait five minutes for results." Similarly, the makers of OvuKit have now come out with two easier-to-use kits: OvuQuick One-Step (up to \$39) and Conceive (\$22). Still, if used correctly, all the home ovulation kits basically do their job.

When we are monitoring ovulation induction (giving a medication to promote ovulation and the chance of pregnancy), we will monitor with a **luteal phase progesterone (P4)**. This is a blood test done for progesterone in the last half of the cycle. It is a fairly accurate way of

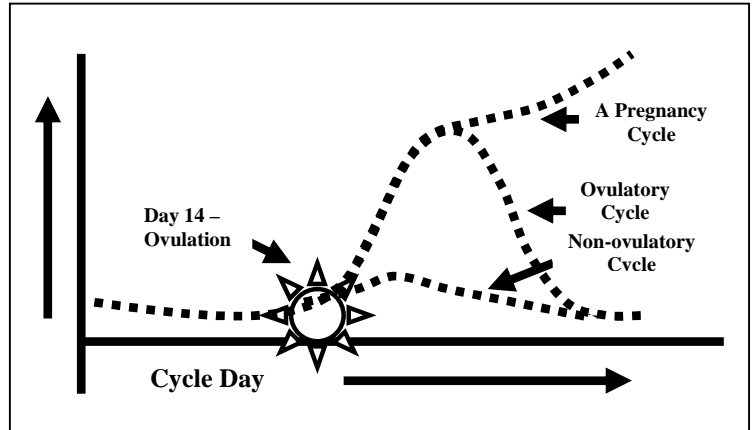


determining if ovulation occurred in that particular cycle. It is done 6 days before the next period is expected to occur. For example if the cycle is expected to be 28 days, the progesterone would be done on day 22, if the cycle was expected to be 32 days it would be done on day 26. **It is probably only important to know the progesterone level in usual cycle lengths as they are probably ovulatory.** If

the cycle lengths are extremely variable, ovulation is unlikely to occur in most of

A Follicle

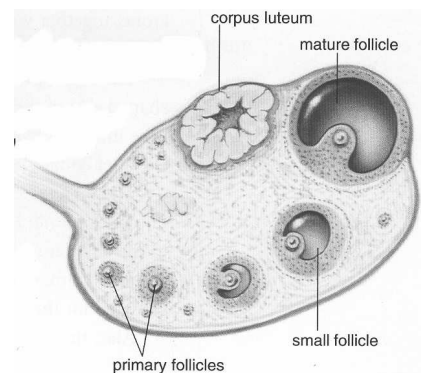
them and some treatment is indicated. Progesterone level of 16 or greater indicates ovulation. A progesterone level of less than 16 indicates that ovulation did not occur or did not occur at the usual time. The clinic only calls you if your progesterone is less than 16. If we don't call you, then the 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.



Ovulation is detected and timed at S.O.F.T. using a combination of blood tests (estradiol and LH) and vaginal ultrasounds. This is the "backbone" of our intrauterine insemination (IUI) program for which the exact prediction of when ovulation will occur can be critical. We don't believe that such precise monitoring of the cycle is necessary, however, occasionally, when the cycle is confusing we will do a **"biological or monitored cycle"** (an information sheet is available). This is where we monitor like an IUI cycle in order to time intercourse for the couple. The format of a biological cycle is presented below.

A biological cycle to clarify the timing of **ovulation or release of the egg from the ovary** or if there is something unusual about the cycle.

Usually, blood tests are performed daily from day 11 until an **"LH surge"** is detected. The "LH surge" refers to a rapid release of luteinizing hormone from the pituitary gland before ovulation occurs. We also do vaginal ultrasounds to follow the development of a follicle. In a spontaneous cycle, usually one follicle develops. It starts small and precipitates ovulation, usually when its diameter becomes greater than 20 mm. Intercourse should occur the day after the "LH surge". Unfortunately, the results of **the blood test required for this monitoring have to be available the same day.** This usually requires them to be done in London. The vaginal ultrasounds are also done in London. This can make undergoing a biological cycle very stressful and fatiguing. We will try and make this less

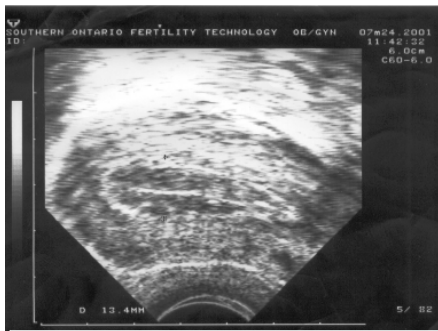


stressful by performing the monitoring blood tests at a convenient time of day and sometimes the blood testing can be arranged closer to home.

Blood testing, ultrasounds and inseminations may need to be performed 7 days a week. For this purpose, S.O.F.T. is open from 7:30 am to 4 pm weekdays and 8:30 am to 11 am on weekends. On weekends and holidays only the back door will be open.

A LH surge does not always occur in cycles being monitored. This can happen even if there is normal egg development. In natural cycles this has been named “luteinized, unruptured follicle syndrome” and is thought by some to contribute to some infertility. The term “follicle” refers to the fluid-filled structure surrounding the developing egg that can be seen by vaginal ultrasound. If an LH surge does not occur, an artificial one can be given with an injection of **HCG (Profasi HP, Pregnyl)**. Usually if you are monitored for a spontaneous cycle and no LH surge occurs, some form of ovulation induction will be recommended in the next cycle. This is usually done with clomiphene citrate. Clomiphene is a pill taken from day 3 to 7 of your cycle and costs about \$35.00 in its lowest dose. We may also suggest this after a biological cycle.

Vaginal ultrasound monitoring of cycles is important. It is sometimes employed in spontaneous cycles but is more commonly used in cycles employing some form of medication. In spontaneous cycles an ultrasound is



Ultrasound of a normal endometrial lining.

done on day 11 to see determine the endometrial thickness and to make sure the body has recruited as follicle for ovulation. The endometrium should be at least 6mm in diameter and a recruited follicle should be at least 11 mm in diameter. It is important in cycles were a spontaneous LH surge does not occur and

helps to determine when HCG

should be given. In spontaneous cycles were a LH surge does not occur by day 14, a vaginal ultrasound can be performed on day 15 to determine if an appropriate sized follicle is present. If it is, HCG (Profasi HP) can be given to create an artificial LH surge. If a good size follicle has not developed, it is most appropriate to cancel the cycle and try next month with clomiphene.



Ultrasound of an ovary with many small follicles but one central follicle, which has become larger

Cycle Day	Estradiol E ₂	LH	Follicle Size (mm)
Day 1	50	4	2
Day 3	100	3	5
Day 6	200	4	8
Day 8	250	3	11
Day 10	320	4	14
Day 11	400	3	15
Day 12	550	6	17
Day 13	600	42	19
Day 14	300	25	21

Cycle Dynamics

The dynamics of a spontaneous cycle is presented in this table. At the beginning of a cycle (day 1 is the first day of menstrual bleeding requiring protection), estrogen and LH levels are

Monitoring of a Spontaneous Cycle

estrogen and LH levels are

very low and the ovary should contain only very small follicles. In most cycles the estrogen increases each day while the LH stays low. During this same time, one or more follicles (depending on ovarian response and medication) will grow. Once the estrogen reaches a certain level or a follicle becomes a certain size; a LH surge occurs (a doubling or tripling of the level). The LH surge is then used to time the insemination. In spontaneous cycles the LH surge usually occurs on day 12 or 13. Once the LH surge has occurred the estradiol usually drops.

Cycle Monitoring – Day By Day

Cycle Day	Instructions	Patient Notes
Day 1-3	Call S.O.F.T. (519-685-5559) and inform us that your cycle has started	
Day 2-4	Baseline blood and/or vaginal ultrasound (Only if necessary – the default is none)	
Day 11	Blood and ultrasound	
Day 12-14	Daily blood testing until LH surge	
Day 15	Blood and ultrasound if no LH surge	
Day 16 or 17	If no LH surge and good size follicle(s), inject HCG (will be discussed at ultrasound)	
Day 17 on	If medium-sized follicles, continue monitoring until adequate size follicle develops If no good follicles – cancel cycle	
Day 1 or 2 after LH surge or HCG	IUI or intercourse – day after LH surge or 2 days after HCG injection If IUI male needs to produce sample	
Day 28-32	If no menses, serum BHCG	
40 days after insemination	If pregnancy test positive, an early pregnancy vaginal ultrasound	

Timing Ovulation to Promote Pregnancy

The above methods are used to determine if **ovulation is occurring**. They can also be used, with the exception of luteal phase progesterone, to time ovulation. **Timing ovulation in order to know “when to do it”** is controversial. There are many articles written and many proponents of this. However, our philosophy at S.O.F.T. is that it is better to have frequent intercourse over the time if potential ovulation than to try and time it. This philosophy only changes to timing ovulation when we advance to intrauterine insemination.

The reasons for frequent intercourse rather than timing intercourse and ovulation are the following:

- 1) timing ovulation can be stressful
- 2) Intercourse “on demand” when ovulation is occurring is usually not fun
- 3) Several studies have indicated that couples who have intercourse more often, no matter when in their cycle, get pregnant faster. In fact, the Environmental Health Sciences study found that the more sex you have, the greater your chances of getting pregnant.
- 4) Intercourse should be relationship building
- 5) Newer studies indicate intercourse is good for general health in both men and women

- 6) Frequent intercourse probably promotes sperm production
- 7) According to a groundbreaking 1995 study by the National Institute of Environmental Health Sciences a woman's fertile period lasts six days: the five days leading up to, and the day of, ovulation. Therefore, if a couple waits until the LH surge, they have lost 4 of the 6 days!
- 8) What's more, the same study showed that the likelihood of pregnancy decreased from about 36 percent (if intercourse occurred two days before and/or on the day of ovulation) to 10 percent (if it occurred four to six days before). Since sperm may live up to five days, even "old" sperm can fertilize an egg, although it's not as likely.

Our recommendation at S.O.F.T. is not to try timing intercourse. This is reserved for when you have to get to the level of intrauterine insemination. Our recommendation is to have intercourse as often as possible over an **8 day period which shifts slightly depending on the length of the cycles**. For example, if the cycle is 28 days long usually, we recommend intercourse as frequently as possible from day 10 to 18. If the cycles are usually only 24 days long, intercourse should be between day 6 and 14 and if 32 days long, between day 14 to 22.

The next question of course is how often during this period of time. It's long been thought that a man should abstain from sex for several days prior to his wife's fertile time in order to "build up" his sperm count. Part of this presumption is true in that studies have shown that the more frequently a man ejaculates over a period of several days, the lower his sperm count. But, although the husband's sperm count may get lower the more often he has intercourse, it's still plenty high enough for achieving pregnancy. It has been found that couples who had intercourse every other day during their fertile days still had a 22 percent chance of conceiving per cycle, compared to 25 percent for those who had sex every day. However, couples who made love weekly reduced their chances of conception to 10 percent per cycle, since they were more likely to miss the key baby-making window of opportunity.

Therefore, because we believe **sperm last in the female genital tract about 48 hours** and because the pregnancy rate is not much different between every day and every other day, we recommend intercourse **at least every other day over the fertile period of time**. This at least takes a little of the pressure of but allows some spontaneity if there is a holiday away in the fertile period.

Causes of Decreased Ovulation

Irregular cycles and decreased ovulation have **three general causes**. Either the ovaries do not work. The pituitary does not work or the pituitary and ovaries do not 'talk' to each other. If the ovaries do not work it is referred to as ovarian failure (or in younger women, premature ovarian failure). If the pituitary (or hypothalamus: the hypothalamus is the part of the brain that directs the pituitary) is not working, it is referred to as hypothalamic amenorrhea. If the ovary and pituitary are not talking to each other, it is referred to as polycystic ovary syndrome. Information sheets are available on each of these situations but they are briefly outlined below.

The different causes of decreased ovulation can sometimes be suspected by the clinical circumstances. For instance, if a woman is less than her ideal weight and/or exercises a great deal,

Polycystic ovary syndrome makes up 90%. It is not a disease but a diagnostic category meaning the women who have it may not be similar at all. Premature ovarian failure and ovarian failure make up 9%. Hypothalamic amenorrhea make up only 1%.

hypothalamic anovulation may be present. If a woman is trying to start a family when she is older and her periods have become less frequent than when she was younger, ovarian failure may be present. Classically women with PCOS were overweight and perhaps had increased male pattern hair growth. However, many women do not fit this picture and are initially thought to belong to this category because they don't fit the other two and because this is by far the most common. **The three causes of decreased ovulation can usually be differentiated with the day three blood work.** If the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) are low (IE <2) then pituitary failure is present. If the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) are high (IE >10) then ovarian failure is present. If the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) are in the intermediate range (IE usually >2 and <10, but not always) then polycystic ovary syndrome is likely present.

PCOS

The diagnosis of PCOS is based on criteria put in place by the Modified Consensus of the National Institute of Child Health and Human Development in 1990. Up until this conference, many different ways of diagnosing PCOS existed. To diagnose PCOS, **two major criteria or one major and two minor criteria should be present.** Major Criteria include chronic anovulation (not releasing an egg each month), hyperandrogenemia (increased male hormone), clinical signs of hyperandrogenemia, ultrasound evidence PCOS (see below), and exclusion of other causes. Minor Criteria include insulin resistance, perimenarcheal (at the time of puberty) onset of hirsutism (increased hair growth in the male distribution) and/or obesity, elevated LH/FSH ratio (see below).

Do You Qualify?

Major Criteria		Minor Criteria	
Chronic anovulation		Insulin resistance	
Hyperandrogenemia		Perimenarcheal onset of hirsutism and obesity	
Clinical signs of hyperandrogenemia		Elevated LH/FSH ratio	
Exclusion of other causes			
Ultrasound evidence PCOS			

Most commonly the diagnosis is placed in this category because of irregular cycles (therefore chronic anovulation) and exclusion of other causes (IE FSH and LH in the normal range on day three of the cycle).

An information sheet is available on PCOS.

Premature Ovarian Failure and Ovarian Failure

Ovarian failure is usually diagnosed because of irregular cycles and an elevated day three follicle stimulating hormone level. The most common situation for this to occur is in the **older woman trying to start a family.** The average age of running out of eggs that will produce a pregnancy is 41 years old. The most common pattern of menstrual changes to occur is actually for the cycle to become shorter (IE 24 days), then to become irregular and longer (IE 32 to 50 days).

At S.O.F.T. we have an approach to this situation which happens quickly. It involves proceeding with a basic infertility investigation as quickly as possible, usually in the cycle as you

are assessed. This involves the usual day three blood work, a hysterosalpingogram and a semen analysis. However, this is often combined with a “clomiphene challenge test”. A clomiphene challenge test involves giving clomiphene citrate at a double dose of 100 mg from day three to seven of the cycle and repeating the FSH level on day 10. The clomiphene challenge test gives us more information about the ovarian reserve (the number of eggs that are left). If the day three FSH is elevated, the ovarian reserve is decreased. However, the day 10 FSH indicates if the ovary was able to respond to the fertility drug. If it is elevated, the prognosis (chance of a pregnancy) is worse but if it goes down, the chance is better.

The significance of an elevated day three FSH is different depending on the age at which it occurs. In a woman about 41 years old it indicates the natural progression in the depletion of the number of eggs. At puberty, a woman usually has about 40,000 eggs. Each menstrual cycle 20 to 40 of these eggs have the potential of being recruited and if not recruited go through pre-programmed cell death (apoptosis). In younger years, the eggs used are probably healthier and more vigorous. In later years, they are less healthy. Some but not all are genetically abnormal. This means that each individual egg that is recruited in a younger woman has a higher chance of not being viable.

If the FSH becomes elevated at a younger age it still means that there are a reduced number of remaining eggs. However, depending on the reason for the reduced number of eggs, they may not be less healthy.

This makes the approach to treatment different. In older women we try to produce as many eggs as possible, knowing that many of them will be incapable of producing a pregnancy. One of the best approaches in older women with slightly elevated FSH levels has been medium stimulation intrauterine insemination. For a full discussion of this, please refer to the information sheet on ovarian failure.

In younger women with an elevated FSH, any egg which develops could be viable. Therefore, the therapeutic approach is to try to produce one or at most two eggs and optimize the chance of these fertilizing and implanting. Again, refer to the full discussion of this in the information sheet on ovarian failure.

An information sheet is available on decreased ovarian function.

Hypothalamic Amenorrhea

This condition means that the pituitary cannot make FSH and LH to stimulate egg production and release from the ovary. It can occur because of pituitary disease, however this is very rare. For example a tumor or infection which destroyed the pituitary would cause this. Elevated prolactin levels can interfere with the release of FSH and LH. We always check for this with the day three bloodwork.

More commonly this condition occurs in women who are extremely thin or sometimes in women who are exercising to extreme. Periods can become irregular as a woman becomes lighter but eventually will stop all together. There is an increased tendency for young women to be thin.

The basal mass index (BMI) is a common medical way to express body composition. The BMI is the weight in kilograms squared over the height in centimeters.

For example, a thin person will have a BMI of 17 as opposed to an obese person who will have a BMI of 35. Menstrual cycles may become irregular at a BMI of 15 and stop at 14 or 13 but they will not become regular again until a BMI of 17 to 19! In other words, there seems to be some inertia to re-establishing regular cycles.

Many times this will lead to irregular cycles. However, it is usually not until a woman becomes very thin that the periods stop all together.

The periods can stop in women who are not quite as thin but are exercising a great deal. This is common in athletes at international or Olympic levels. Decrease in the exercise level will usually re-instate the periods.

In women who stop menstruating because of low weight, weight increase is important and can be tried. However, this is not usually enough to re-instate the cycles. Most young women in this circumstance will try to gain weight but more weight gain is necessary to re-instate the cycles than weight that was lost when the cycles stopped.

Treatment of Decreased Ovulation

Ovulation Induction

Ovulation induction (promotion of ovulation or egg production is one of the cornerstones of infertility treatment. Usually it can be accomplished easily by using simple medications but sometimes can be one of the most difficult things we do in the clinic.

Ovulation induction as described here is done for women with **PCOS and mild ovarian failure**. If you have advanced ovarian failure or hypothalamic amenorrhea, there are information sheets especially on these topics.

Clomiphene citrate is used to induce ovulation when infertility is a complaint. Approximately 80% of patients with PCOS will ovulate on clomiphene. If the lowest dose of 50 mg from day 3 to 7 of the cycle is not sufficient to cause ovulation, it is increased to 100 mg in the next cycle and 150 mg in the cycle after that. If ovulation does not occur at the 150 mg dose, then we move on to another step. This is because clomiphene has positive (causes ovulation) and negative effects (makes the cervical mucous hostile and decreases the implantation rate by effecting the endometrium). However, only 50% of those that ovulate will get pregnant and the pregnancy rate is higher per ovulation if ovulation can be promoted at the lower doses.

Clomiphene is indicated for six ovulatory cycles. It is important to demonstrate ovulation on clomiphene and this is done using a luteal phase progesterone level. A complete description of clomiphene is available on the clomiphene information sheet.

A newer medication sometimes used in a similar fashion to clomiphene is **letrozole** (femara). The initial results with this drug have been very exciting with at least the same or perhaps a higher pregnancy rate than clomiphene. We use it at S.O.F.T. when clomiphene has not produced ovulation or a pregnancy with six cycles, when clomiphene causes excessive thinning of the endometrium or when higher doses of clomiphene have been necessary to induce ovulation.

Tamoxifene is another ovulation induction agent which works very similarly to clomiphene. Some reports in the literature indicate that tamoxifene can produce ovulation in clomiphene resistant patients. There are also several reports of using clomiphene and tamoxifene together.

A new approach which we have found very successful in the clinic is to use **clomiphene and letrozole together**. These two ovulation induction agents work in a similar fashion but by slightly different mechanisms. The combination has proved very successful for us and a separate information sheet is available on this.

Sixty percent of patients with PCOS have **insulin resistance**. Insulin resistance refers

Metformin can be beneficial to treat insulin resistance. When insulin resistance is present, use of metformin will sometimes allow the resumption of normal ovulatory cycles and sometimes a spontaneous pregnancy. Three such pregnancies occurred in the first year of operation of S.O.F.T.

It is also very helpful in PCOS, which is resistant to ovulation induction with clomiphene. Early results of a clinical trial demonstrated that in 19 consecutive patients with infertility, PCOS and insulin resistance who did not ovulate with cc in a dose of up to 150 mg., metformin 500 mg. p.o. t.i.d. allowed 4 patients to ovulate at 100 mg and 2 patients at 150 mg. (31.6%). Two pregnancies occurred. Since then many more pregnancies have occurred in the same circumstances.

Metformin is given in a dose of 500 mg. This is begun at once a day for a week, then twice a day for a week, then three times a day for a week to avoid the side effects of heartburn and diarrhea. The insulin resistance test is usually repeated at the end of the first week of the three times a day dosage. Other medications are available if the insulin resistance doses not respond to metformin. An information sheet is available on insulin resistance.

To start Metformin you will be given a repeating prescription of 100 tablets. Metformin will often cause diarrhea and to a lesser extent, heartburn. Introducing the medication slowly can minimize these side effects. To do this you will be asked to start a single tablet once per day. After a week, any side effects should have just about gone. If this is the case, you should increase metformin to two tablets per day. If the side effects at the end of the first week are still continuing, don't increase the dose but wait until things do settle down. Similarly, increase metformin to three per day after another week as long as the side effects are minimal. After taking metformin at three per day for a week the fasting blood sugar with insulin level should be repeated. You will be given a requisition for this blood test.

Treatment options after a trial of clomiphene ± treatment of insulin resistance include injectable fertility medications or laparoscopic ovarian cautery. Patients with PCOS tend to under or over respond to injectable fertility medication creating a higher risk of multiple pregnancies or ovarian hyperstimulation syndrome. Very careful monitoring is necessary to avoid these complications. Ovarian cautery or drilling will sometimes cause the resumption of ovulatory cycles. If this does not occur it does make ovulation induction more successful and treatment with injectable infertility medications more predicable and controllable.

What If Ovulation Does Not Occur?

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 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.

In up to 60% of women with polycystic ovary syndrome have **insulin resistance**? Insulin

Polycystic Ovary Syndrome was called Stein-Leventhol Syndrome after two gynecologists who first investigated women who did not ovulate. They took wedge biopsies from the ovaries of these women. However, they found that when they did the biopsies, the women would often start to ovulate! This is now believed to work because it decreases the intra-ovarian male hormone level and can be more easily done by burning the surface of each ovary in 6-10 places during a laparoscopy.

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. 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 (500 mg three times per day) 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.

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.

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.

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). More information is available on laparoscopy and ovarian cautery in the information sheet on laparoscopy.

Occasionally, women who are ovulating spontaneously will react unusually to clomiphene. Instead of causing them more vigorous ovulation, it will cause them not to ovulate. 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.

Ovarian Hyperstimulation

Ovarian Hyperstimulation or “controlled ovarian hyperstimulation” (COH) refers to the use of injectable follicle stimulating hormone (FSH) to stimulate the production of eggs. This is the only way to stimulate egg production if the cause of the decreased ovulation is hypothalamic amenorrhea. However, it can also be used for the other two causes.

COH for **hypothalamic amenorrhea** involves the daily injection of FSH until a follicle or follicles develop. The follicles can then be ovulated by giving a human chorionic gonadotropins (HCG) injection. This is usually combined with IUI or IVF.

COH for hypothalamic amenorrhea is very tricky because it often involves a threshold response. This means if too little FSH is given, no follicles will be recruited. If only slightly more is given, many follicles may develop. This is critical in IUI as high order multiple pregnancies can occur. The danger is somewhat lessened by IVF because the number of embryos that are put back can be controlled even if many eggs develop. Sometimes, cycles originally designed to be completed by IUI must be “converted” to IVF to reduce the risk. Full information sheets are available on intrauterine insemination with injectable fertility medications and in vitro fertilization.

If COH is used for PCOS or ovarian failure, it can be combined with some form of ovulation induction. This reduced the overall dose of FSH required (and therefore the cost) and often can improve the response. The ovulation induction agents fool the body into making more FSH and then injectable FSH is added. (This cannot be done in hypothalamic amenorrhea because the pituitary cannot make FSH.) This gives a “double whammy” of FSH.

This is usually done as aggressively as possible in older women with **ovarian failure** and somewhat aggressively in younger women with ovarian failure because the object is usually to make as many eggs as possible. Some care has to be exercised in the younger woman in that more of the eggs may be good and multiple pregnancies can occur.

In women with **PCOS**, care has to be exercised because they respond (like the women with hypothalamic amenorrhea) in a threshold fashion. A woman with ovulation induction resistant PCOS may reach the threshold and respond by producing many eggs. This again is another situation where conversion from IUI to IVF may be necessary to decrease the risk of a multiple pregnancy.

Conclusion

A common contributor to infertility is decreased ovulation. The most common reason for decreased ovulation is PCOS. Other causes are ovarian failure or hypothalamic amenorrhea. Most decreased ovulation can be treated. Specific information sheets are available for each of the causes.

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