

Ovulation inducing medications help infertile women achieve a pregnancy by stimulating the development of multiple eggs within the ovaries. The medications are often used in conjunction with intrauterine inseminations with a washed sperm sample. This document explains ovulation inducing medications and intrauterine insemination treatment.

Pre-Treatment Recommendations

Patients should avoid any activity, medication, or behaviors that would reduce their chances of conception or increase the risk to the baby. Below are listed recommendations for all women/couples attempting pregnancy:

- Women should take a **prenatal vitamin** on a daily basis. This vitamin should contain folic acid which reduces the chance of giving birth to a child with a neural tube defect (e.g. spina bifida). Unless contraindicated, women should also take aspirin 81mg on a daily basis
- Smoking must be avoided before and during treatment. It is also contraindicated during pregnancy.
- Recreational drugs are absolutely contraindicated.
- Avoid ingestion of adult strength aspirin (325mg). Aspirin-like products (e.g. Motrin®, Advil®, Anaprox®, Naprosyn®, Aleve®, etc.) should be avoided during ovulation and Timed Intercourse (TIC)/Intrauterine Insemination (IUI) time. Tylenol® is a suitable alternative. After ovulation, Motrin® may be used as well.
- The use of alcohol should be eliminated, as it is contraindicated during pregnancy.
- The use of all prescription and over-the-counter medications should be discussed with a physician before starting a treatment cycle.
- Women should continue to get yearly Pap tests done with their primary care providers.
- Men should take a **multivitamin and antioxidant** (antioxidant supplements usually include vitamins E and C, beta carotene and selenium) on a daily basis.

Ovulation Induction

This treatment involves several steps as outlined below. Patients are not guaranteed success at any or all of these steps. If optimal results are not appreciated at any step, it may be recommended that the treatment be stopped and the cycle cancelled.

During a normal menstrual cycle, usually one mature follicle develops within the ovary, which results in the ovulation of a single egg. The growth of the ovarian follicle during the first half of a woman's cycle is influenced by several hormones, including follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH is the main hormone that stimulates the growth of the follicle, which produces estrogen. When the follicle is mature, a large amount of LH is released by the pituitary gland. This "LH surge" helps to mature the egg and leads to ovulation 36-40 hours after its initiation.

Medications

There are several medications that can be prescribed that will increase the chance of more than one egg to develop. Many of the medications used are administered by an injection.

- **Clomiphene citrate (Serophene®, Clomid®):** This is a pill that is taken daily for five to eight days. This medication stimulates the release of FSH and LH, which stimulates the development of follicles.
- **Letrozole (Femara®):** This is also a pill taken for five to eight days. It is similar in strength to Clomid® but works slightly differently. Femara® may work better in some patients
- **Gonadotropins:** These are injectable medications that contain hormones
 - **FSH (Gonal-F®, Follistim®):** These medications contain only FSH and are administered on a daily basis by subcutaneous injection.
 - **Human Menopausal Gonadotropins (Menopur®):** This medication contains equal amounts of FSH and LH, as well as a small amount of hCG, and are administered on a daily basis by subcutaneous injections.
- **Human Chorionic Gonadotropin [hCG] (Ovidrel®):** This medication contains the pregnancy hormone hCG, which functions similarly to LH. It is administered after there has been an adequate response and the ovarian follicles are deemed to be mature. This medication matures the eggs making them able to be fertilized and stimulates ovulation generally 36-40 hours after it is given.

Side Effects

The use of these medications can cause side effects such as nausea, vomiting, hot flashes, and headaches.

- **Ovarian Hyperstimulation:** Following administration of hCG, cysts can form within the ovaries. This will cause ovarian enlargement and, in some cases, lead to lower abdominal discomfort, bloating and distension. These symptoms generally occur five to ten days after either ovulation or the egg retrieval and usually resolve one to two weeks without intervention. A pregnancy can worsen the symptoms of ovarian hyperstimulation. Severe ovarian hyperstimulation is characterized by large ovarian cysts and fluid in the abdominal and, sometimes, chest cavities. Symptoms of severe ovarian hyperstimulation include abdominal distention and bloating along with weight gain, shortness of breath, nausea, vomiting and decreased urine output. Women with severe ovarian hyperstimulation (approximately 1-2% of all patients taking medications) may need to be admitted to the hospital for observation and treatment. Rare, but serious consequences of severe ovarian hyperstimulation include formation of blood clots that can lead to stroke, kidney damage and possibly death. Every woman who is administered these medications can develop ovarian hyperstimulation but the chance is higher in a woman with a high blood estradiol level and a large number of ovarian follicles. For this reason, in cases when the estradiol is significantly elevated, the cycle may be cancelled.
- **Ovarian Torsion (Twisting):** In less than 1% of all cases, a fluid filled cyst(s) in the ovary can cause the ovary to twist on itself. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary.
- **Ovarian Cancer:** In the general population, any woman has a 1 in 70 chance of developing ovarian cancer during her lifetime. Studies have shown that infertile women have a higher chance of developing ovarian cancer than fertile women. Controversial data exists that associates the use of ovarian induction drugs (e.g. clomiphene citrate, gonadotropins) with an

increased risk of ovarian cancer. However, a cause and effect relationship has not been clearly established at the present time.

Monitoring

During the ovulation induction phase of treatment, monitoring of follicular development is performed with a urinary ovulation predictor kit or periodic blood hormone tests and vaginal ultrasound exams. Monitoring helps the physicians to determine the appropriate dose of medication and the timing of the ovulation. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and, possibly, bruising, bleeding, infection or scar at the needle sites.

Intrauterine Inseminations (IUI)

Around the time of ovulation, couples receiving ovulation inducing medications will be instructed to have intercourse and/or intrauterine inseminations with a washed sperm sample.

- Inseminations are generally performed on one or two days (12-36 hours) after taking hCG. On the day of the IUI treatment, the male partner will be asked to produce a fresh semen specimen. Alternatively, the semen sample can be produced at home as long as it can be brought back to SpringCreek within thirty minutes after it is produced. Semen samples should be collected by masturbation into a sterile specimen cup. Lubricants should not be used and contamination with other bodily fluids should be avoided. It is important to keep the sample at body temperature during transport. The semen sample will then be washed and prepared. In cases where the mail has a significant reduction in the quantity or quality of sperm (or if there is no male partner), the patient may elect (prior to the initiation of the cycle) to use donor sperm.
- The IUI procedure is simple. Prior to insemination, the female patient will be asked to verify the correct identity of the labeled sperm sample. A speculum is placed in the vagina and the cervix is visualized. Sperm are loaded into a catheter, which is inserted through the cervical canal and into the uterine cavity. The woman will be asked to lie on her back for a period of time before being discharged. Following the insemination, normal activity can be resumed. Because a catheter is inserted into the uterine cavity during the insemination treatment, there is a small (<1%) risk of pelvic infection following the treatment. Symptoms of an infection include fever, vaginal bleeding, chills, and abdominal pain. If any of these symptoms occur you should contact your physician. In rare cases, hospitalization with intravenous antibiotics and/or surgery (to remove ovaries, fallopian tubes, or the uterus) may be necessary. Fertility may be impaired in some cases.

Treatment Following Ovulation

- Progesterone is a natural hormone made by the ovary that prepares the lining of the uterus for implantation. Women may have their blood serum progesterone level monitored after ovulation.
- If pregnancy occurs, the progesterone level will be monitored, and if the level is low, progesterone may be started, and in some cases continued until the 12th week of pregnancy. Progesterone supplements are not FDA –approved for this purpose. It should be noted,

however, that studies have shown that there is no increased risk of congenital anomalies or health risks to a woman who takes natural progesterone supplements during pregnancy.

- Fourteen days after conception has been attempted, either by timed intercourse or intrauterine insemination, a pregnancy test may be done. If this test is positive, a repeat pregnancy test may be done two to three days later. If the test results are encouraging, a vaginal ultrasound will be done approximately four to five weeks after treatments to determine the status of the pregnancy. Because of the potential for complications following ovulation induction, the woman should have access to medical care up to the time of the pregnancy test, and beyond if pregnancy is established. If travel is necessary, it should be discussed with a physician.

Treatment Outcomes

The success (the delivery of a live born infant) following a cycle of treatment with the administration of ovulation induction medicines is between 5-25% per cycle. The development of a pregnancy following this treatment is dependent on many factors, some of which include the age of the woman, the diagnosis, the number of previous cycles of treatment, the number of follicles that develop, and the quality of the sperm. Some other possible complications include:

- **Miscarriage:** The risk of miscarriage in the general population is about 20%. The risk of miscarriage in the population using fertility medications is estimated to be up to 30%. The risk of miscarriage increases with the age of the women. For women over 40 years of age, the risk may exceed 50%. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require treatment. In some cases, however, complete removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilatation and curettage (D&C). This procedure is usually performed under anesthesia in the operating room.
- **Tubal (Ectopic) Pregnancy:** An ectopic pregnancy may result following this treatment. The majority of ectopic pregnancies are present in the fallopian tubes. The chance of tubal pregnancy is greater in women with damaged tubes. If a woman has a tubal pregnancy, she may need surgical treatment, which may involve the removal of the involved tube. Medical treatment with Methotrexate may be an option in selected cases.
- **Multiple Pregnancy:** The administration of ovulation induction medications can result in the ovulation of more than one egg, which increases the chance of a multiple pregnancy. The chance of a multiple pregnancy ranges from 5-10%, which is in part dependent on the medication that is used. Following clomiphene citrate treatment, the multiple pregnancy rate is about 5%. Of those multiple pregnancies, approximately 98% are twins. When the injectable medications are used (gonadotropins), the multiple pregnancy is about 10%. Of the multiple pregnancies, there is a slightly higher chance of a triplet pregnancy. All multiple pregnancies are associated with an increased risk of every complication of pregnancy, including, but not limited to miscarriage, toxemia, congenital anomalies, gestational diabetes in the mother and premature labor and birth. Premature birth is the single greatest cause of death or disability in newborn infants. In contrast to a single intrauterine pregnancy, a multiple pregnancy may pose increased emotional and financial hardship.
- **Other Risks:** Most infants who have been born following fertility treatment are normal. The rate of congenital abnormalities (birth defects) in the general population is 2-3% and is not different in babies following conceived following this treatment. It is important to be aware that genetic

abnormalities, structural abnormalities, mental retardation and other abnormalities may occur following this treatment just as they do in pregnancies conceived naturally.

- **Psychological Risks:** undergoing infertility treatment can be psychologically stressful. Anxiety and disappointment may occur at any point during and after treatment. Significant commitment of time and finances may be required. All couples are encouraged to seek emotional support before, during and/or after a treatment cycle. Individual and couples counseling support groups and books on infertility may be beneficial in helping couples cope with infertility treatment.

There are many complex and sometimes unknown factors, which may prevent the establishment of pregnancy. Known factors which may prevent the establishment of pregnancy include, but are not limited to, the following:

- The ovaries may not respond to the medications or the ovarian follicles may not develop in the cycle
- The ovaries may over-respond to the medication and the cycle may be cancelled because of the increased risk of ovarian hyperstimulation or multiple pregnancy
- The male partner may be unable to ejaculate or the semen sample may be of poor quality
- The passage of the catheter into the uterus may be technically difficult or impossible
- Even if the insemination is successfully performed, pregnancy may not result
- If a pregnancy is established, it may not develop normally
- Equipment failure, infection, technical problems, human error and/or other unforeseen factors may result in loss or damage to the semen sample