

Not all patients will be using all of the medications or procedures described here.

CLOMIPHENE CITRATE (Serophene, Clomid)

Clomiphene citrate is a synthetic, oral medication that acts on the pituitary gland to stimulate the production of hormones that can then stimulate the ovary to produce follicles. Clomiphene both stimulates and inhibits the reproductive hormone system. On the whole, the effect is to stimulate the output of the pituitary hormone FSH which, in turn, stimulates the ovary follicles leading to ovulation of one or more eggs. Since clomiphene also inhibits estrogen action, it occasionally produces side effects that limit its usefulness.

Clomiphene is taken in pill form by mouth, so it is convenient and painless and it is a relatively inexpensive medication. Consequently, it is the drug of choice for patients who do not ovulate at all (anovulation) or infrequently (oligo-ovulation). The success rate for ovulation is over 80%. The success rate for pregnancy is less because many other factors affect pregnancy rates. The starting dose is 50 mg daily (one tablet) for 5 days (typically cycle days 5-9 or 3-7). If ovulation does not occur with 150 mg, then higher doses usually do not work either. Nevertheless, because the medication is inexpensive and easy to administer, some physicians will try doses as high as 250 mg for as many as 10 days.

Clomiphene also induces multiple ovulations in women who ovulate naturally on their own. This technique called Controlled Ovarian Hyperstimulation (COH) is a common treatment for unexplained infertility. Usually, we use doses of at least 100 mg daily to purposely induce multiple follicular development. Clomiphene is less commonly used for COH because of the anti-estrogen side effects which many believe lowers the pregnancy rates.

Clomiphene is also used for the Clomiphene Challenge Test (CCT, see separate handout). The CCT is a stimulation test to measure the fertility potential of a woman. The CCT requires clomiphene 100 mg daily on cycle days 5-9. A blood sample for estradiol and FSH is collected on cycle day 2-5 (ideal is day 3) and another blood sample for FSH is obtained on cycle day 10. Elevated levels of FSH indicate subfertility for the woman.

SIDE EFFECTS

Clomiphene, a partial anti-estrogen, may cause symptoms of estrogen deprivation such as hot flashes and headaches (10% of patients). Other possible symptoms (which occur in 6% or less of patients) include:

- Visual-blurring, spots or flashes
- Nausea and vomiting
- Abnormal uterine bleeding
- Abdominal or pelvic pain, weight gain
- Breast discomfort

Other side effects, including allergic reactions, have been reported but with an incidence of less than 1%

MISCARRIAGE, STILLBIRTH, AND FETAL CONGENITAL MALFORMATIONS (BIRTH DEFECTS)

The risk of miscarriage or stillbirth does not appear to be related to the use of clomiphene. The incidence of miscarriage in clinical trials was approximately 20% and the risk for stillbirth was 1%. Clomiphene is considered pregnancy Category X. Its use is contraindicated in women who are already pregnant. Studies in rats and mice have shown a dose-related increase in some types of malformations and an increase in mortality. Studies in human beings do not support an association between clomiphene and congenital defects.

HUMAN CHORIONIC GONADOTROPINS, HCG (Ovidrel, Profasi, Pregnyl)

Chorionic gonadotropins are injectable medications containing the hormone HCG which is normally produced by the placenta during pregnancy. Chorionic gonadotropins are produced by isolating and purifying these hormones from the urine of pregnant human women or by using recombinant DNA technology. There are small amounts of urinary proteins contained in the preparations. There are no known cases of disease being transmitted of one person to another through these medications.

HCG is used primarily to trigger ovulation (maturation and eventual release of the egg) in women attempting pregnancy. It is also used to help support a potential or existing pregnancy by augmenting progesterone production from the ovary after ovulation (corpus luteum) and to support follicle growth during ovulation induction.

SIDE EFFECTS

Recombinant HCG is given subcutaneously. Urinary HCG may be given as an intramuscular or subcutaneous injection. It is possible to have pain, rash, or swelling at the injection site. When given subcutaneously, urinary HCG may cause more local swelling, redness or irritation. Other possible symptoms include:

- Abdominal or pelvic pain, weight gain
- Breast discomfort
- Nausea and vomiting
- Abnormal uterine bleeding

Other side effects, including allergic reactions, have been reported but with an incidence of less than 1%

MISCARRIAGE, STILLBIRTH, AND FETAL CONGENITAL MALFORMATIONS (BIRTH DEFECTS)

The risk of miscarriage or stillbirth does not appear to be related to the use of Chorionic gonadotropins. Chorionic gonadotropins are considered pregnancy Category X. Combined use of HCG with PMSG (pregnant mare serum gonadotropin) has caused a high incidence of external congenital anomalies in mice. Studies in human beings do not support an association between gonadotropins and congenital defects.



PROGESTERONE **(Crinone, Progesterone-in-oil, Prometrium, Progesterone Suppositories)**

Progesterone is a steroid hormone normally produced by the ovary after ovulation and by the placenta during pregnancy. We use progesterone primarily to induce the menses in anovulatory women and to help support the early pregnancy.

Crinone contains micronized progesterone in an oil and water emulsion called polycarbophil. Progesterone injections contain an oil base (either sesame or peanut oil).

SIDE EFFECTS

Possible symptoms include:

- Abdominal or pelvic pain, cramps
- Abnormal uterine bleeding
- Bloating, weight gain, fluid retention*
- Breast discomfort
- Fatigue, drowsiness, depression
- Nausea and vomiting
- Muscle or joint ache

* Patients who have epilepsy, migraines, asthma, cardiac or renal dysfunction which might be influenced by the use of progesterone require careful observation.

Injectable progesterone can cause pain, rash or swelling at the injection site. Other reported side effects, such as allergic reactions, may be related to the vehicle (for example, peanut oil) and occur with an incidence of less than 5%. Progesterone should not be used in patients with liver problems, undiagnosed vaginal bleeding, or with a history of clotting disorders.

Multiple pregnancy

Studies indicate that approximately 8% of the pregnancies conceived after clomiphene therapy are multiples [Twins 6.9%; Triplets 0.5%; Quadruplets 0.3%; Quintuplets 0.1%; One sextuplet pregnancy has been reported]. The ratio of monozygotic (identical) to dizygotic (fraternal) twins is 1:5

The risk of complications of pregnancy or adverse outcomes is higher with multiple pregnancies than with singleton pregnancies. These include, but are not limited to, preterm delivery, gestational diabetes, hypertensive disorders, and fetal or neonatal death.

Monitoring with blood tests and ultrasounds may allow us to identify those women most likely to have a multiple pregnancy. We increase the risk of multiples if we proceed with insemination or natural coitus in the face of 5 or more mature follicles.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical complication that appears more commonly after the use of fertility medications such as clomiphene (see separate handout). The estimated incidence of this complication after clomiphene treatment is less than 1%. In its severe form, OHSS is characterized by ovarian enlargement, accumulation of fluid in the abdomen (ascites), chest cavity (pleural effusion), or around the heart (pericardial effusion). There are abnormalities in blood chemistries (electrolytes), abnormal function of the liver and/or kidneys, and increased risk for blood clots.

Patients may notice abdominal discomfort, nausea, vomiting, weight gain, decreased urine output, shortness of breath, difficulty breathing, or pelvic pain. Patients have died as a result of complications of OHSS usually due to blood clots but careful active management of this condition should make this risk exceedingly rare.

Despite monitoring with blood tests or ultrasounds, it is not possible to prevent the occasional occurrence of OHSS. However, we can avoid most cases by preventing ovulation when blood and ultrasound information suggests higher risk of OHSS. The risk of OHSS is higher if the patient achieves pregnancy and especially with multiple pregnancy.

Cancer

Some studies have postulated an association between the use of fertility medications, including clomiphene citrate and the subsequent development of epithelial ovarian cancer while other studies have not demonstrated an association. The current consensus is that infertility imparts an increased risk of ovarian cancer and that the stimulation medications probably do not. Future studies may better define the risk, if any, from using ovulation induction medications.

There appears to be no increased risk of breast cancer associated with use of these medications.