INFERTILITY TREATMENT OVERVIEW — Infertility is defined as a couple's inability to become pregnant after one year of unprotected intercourse. In any given year, about 15 percent of couples in North America and Europe who are trying to conceive are infertile.

The fertility of a couple depends upon several factors in both the male and female partner. Among all cases of infertility in developed countries, about 8 percent can be traced to male factors, 37 percent can be traced to female factors, 35 percent can be traced to factors in both the male and female partners, and 5 percent cannot be traced to obvious factors in either partner.

When infertility occurs, the male and female partners are evaluated to determine the cause and best treatment options. If the woman is not ovulating regularly, one treatment option involves taking an oral medication, clomiphene citrate (Clomid or Serophene).

This topic will review the use of clomiphene in the treatment of female infertility. The evaluation of the infertile couple, as well as the causes and treatment of male infertility, are discussed separately.

OVULATION — To understand why and how clomiphene is used, it is important to have a basic understanding of normal ovulation. Normally, a woman's ovaries produce one egg every 24 to 35 days. Ovulation usually occurs about 12 to 14 days before the next menstrual period. A woman's best chance for becoming pregnant occurs around the day of ovulation and one to two days before ovulation. This would be approximately 12 to 14 days after the first day of a 28 day menstrual cycle (day 1 of the menstrual cycle is the first day of bleeding).

Women who are most likely to respond to clomiphene include those with polycystic ovary syndrome (PCOS). Women who are unlikely to respond are those with absent periods and very low estrogen levels due to low body weight or exercise (called "hypothalamic amenorrhea"), or those with high FSH levels, an indicator of ovarian aging (early menopause or "primary ovarian insufficiency").

WHAT IS CLOMIPHENE? — Clomiphene is a weak estrogen-like hormone that acts on the hypothalamus, pituitary gland, and ovary to increase levels of FSH and luteinizing hormone (LH, which is also important in the process of ovulation).

An increased level of these hormones improves the chances of growing an ovarian follicle that can then trigger ovulation. In women who ovulate irregularly, approximately 80 percent who take clomiphene will ovulate, and 30 to 40 percent of all women who take clomiphene become pregnant. These numbers apply to women who have taken up to three cycles of clomiphene.

Pretreatment evaluation — Before any infertility treatment begins, a woman and her partner should undergo an infertility evaluation to be sure that clomiphene is the best treatment. This evaluation may include a complete history and physical examination, a semen
Ovulation induction with clomiphene analysis (for men), blood testing, and other tests depending upon the individual situation.

**Dosing** — Clomiphene is usually started on day five of the menstrual cycle at a dose of 50 mg (one pill) once daily for five days. The first day of bleeding is called cycle day one. If the woman does not have regular menstrual cycles (which is usually the situation), she may be given a course of progestin medication (eg, Provera, medroxyprogesterone acetate) to induce a period.

Ovulation usually occurs around cycle day 16.

The couple is advised to have intercourse every other day for one week, beginning around day 12 (12 days after the menstrual period starts). However, this requires that sperm survival in the upper genital tract is two or more days and in some instances this may not be the case.

Use of an ovulation predictor kit and ultrasounds are not required for women using clomiphene. Progesterone levels will be done to check ovulation on day 23.

If ovulation does not occur during the first month, the clomiphene dose is increased by 50 mg each month until ovulation occurs. There is no benefit of increasing the clomiphene dose if ovulation occurs, even if pregnancy does not occur. Nearly all pregnancies occur within the first six ovulatory cycles while using clomiphene, and there is little benefit of continuing clomiphene treatment after six unsuccessful ovulatory cycles. If this occurs it would suggest the need to evaluate other causes of infertility. Failure to achieve pregnancy when ovulation is occurring is not a “clomid failure.” It usually means that other fertility issues are present, such as tubal or male factor.

**Benefits** — The benefit of clomiphene is that it is relatively inexpensive and can be used before other, more expensive testing (such as hysterosalpingogram or laparoscopy) or infertility treatments (eg, gonadotropin therapy, in vitro fertilization). It does not require monitoring with ultrasound or blood hormone levels, although monitoring may be recommended in some cases. Clomiphene improves the chances of becoming pregnant for most women who ovulate irregularly, and it carries a low risk of dangerous side effects. In addition to anovulation, clomiphene is also administered in conjunction with intra-uterine insemination in unexplained infertility.

**Risks** — Risks of clomiphene therapy include a slightly increased rate of multiple pregnancies; approximately 6 percent of women who use clomiphene have twins, while less than 0.5 percent have triplets or greater. There is a rare risk of the ovaries becoming enlarged, although severe enlargement (known as ovarian hyperstimulation syndrome) is rare.

Common side effects of clomiphene include hot flashes, headaches, abdominal bloating and pain, nausea and vomiting, mood changes, and breast tenderness. Visual symptoms such as blurring, double vision, or seeing spots occur in 1 to 2 percent of women, and usually resolve when treatment stops.

Most studies do not show an increased risk of birth defects, miscarriage, or learning disability in children of women who took clomiphene. There is no increased risk of breast cancer or uterine cancer. There may be a slightly increased risk of ovarian cancer if more than 12 cycles of clomiphene are used.

**INSTRUCTIONS FOR USE:**

If no period for more than 35 days: Obtain a urine pregnancy test. If negative, take Provera 10 mg daily for 10 days. The period will occur within 1 week from the last pill.

**Proceed with instructions below:**

DAY 1: Menstrual flow starts. Make appointment to be checked prior to DAY 5.
DAY 5-9: Clomid once a day at bedtime at dosage prescribed by your doctor.
DAY 12-21: Intercourse every other day.
DAY 23: Have serum progesterone checked at Quest Lab. Use NFRMC if blood draw needs to occur on the weekend. Please bring the lab slip your doctor gave you to that visit.
DAY 35: If no period, obtain a urine pregnancy test.