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CONDITIONS & TREATMENTS: OVULATION INDUCTION

Ovulation is the release of a mature egg from the ovary. Normally this occurs approximately every 28 days. The time from the start of the period to ovulation is variable; however it is usually 14 days from ovulation to the next period. Anovulation is the absence of ovulation. Anovulation is frequently corrected with fertility drugs and called ovulation induction. Ovulation induction is also performed in patients who are ovulatory to increase the chance of pregnancy. Most pregnancies occur in three cycles of a particular therapy.

Commonly prescribed drugs include: clomiphene citrate, human chorionic gonadotropin, follicle stimulating hormone and human menopausal gonadotropin.

Clomiphene citrate (CC) is often used to correct ovulatory disturbances. Approximately 80% of individuals will ovulate and approximately 40% will achieve a pregnancy using CC. CC is usually started at a dose of 50 - 100 mg daily by mouth on days 3 to 5 of the cycle and continued for 5 days. Ovulation usually occurs a week after the last dose of CC, from days 12 through 21 of the cycle. The total cycle may be as long as 35 days. Documentation of ovulation may be confirmed with a day 21 progesterone blood test, basal body temperature chart or a urine ovulation predictor kit. If ovulation is not achieved, the dose is increased by 50 mg increments usually to a maximum dose of 150 mg daily.

The side effects of CC include:

- Hot flashes (10%),
- Abdominal discomfort (5%),
- Nausea and vomiting (2.2%),
- Headache (1.3%),
- Visual symptoms (1.5%),
- Mood swings

The risks of CC include multiple pregnancy, ovarian cysts, torsion (twisting of the ovary), and ovarian hyperstimulation syndrome. An increased risk of ovarian cancer has been debated and the data are conflicting, however it is recommended to minimize the number of cycles to those necessary.

Baseline ultrasound or pelvic exam should be performed in consecutive cycles to avoid large cyst formation. Visual symptoms usually resolve within two weeks. CC should be discontinued if visual symptoms occur and an alternative therapy utilized. The multiple pregnancy rate is approximately 5%, almost entirely twins; however, rare cases of higher order multiples have been reported. Once ovulation has been achieved, higher doses of CC do not appear to have any beneficial effects. One should reassess therapy after 3 ovulatory cycles if no conception occurs. The pregnancy rate with additional cycles is low, although the ovulatory rate remains high.

CC may alter the quality of the lining of the uterus and the cervical mucous. CC may make the lining of the uterus thin. If this occurs the chance of pregnancy is low. This may be corrected by adjusting the dosage of CC or using FSH in subsequent cycles. CC may make cervical mucous thick and impermeable to sperm. Intrauterine insemination of sperm bypasses the cervical mucous and may increase the chance of pregnancy.

Human chorionic gonadotropin (hCG) is often added to CC or FSH cycles. HCG causes the ovary to release an egg and help time inseminations. Ovulation usually occurs 36-72 hours after hCG is given. HCG will cause pregnancy tests to be falsely positive.

Follicle stimulating hormone (FSH) is the hormone that stimulates eggs to mature in the ovary. Recombinant FSH is manufactured in the laboratory. These products do not contain Luteinizing hormone (LH), a hormone that helps regulate the menstrual cycle and egg production (ovulation). Human menopausal gonadotropin (hMG) contains equal parts of FSH and LH that are derived from the urine of menopausal women. FSH may be used in women who can not make their own FSH, who failed CC or to increase the chance of pregnancy in ovulatory women. FSH treatment requires careful monitoring. Risks include a multiple pregnancy rate of 20-30% and ovarian hyperstimulation syndrome rate of 1%. An increased risk of ovarian cancer has been debated and the data are conflicting; however, it is recommended to minimize the number of cycles to those necessary.

FSH is usually begun on the third day of the cycle by either subcutaneous or intramuscular injection. The daily dose is adjusted after monitoring with ultrasound and estradiol blood tests. The injections usually last 7-12 days, but may take longer if the ovaries are slow to respond. Once a mature egg is identified on ultrasound ovulation is triggered with hCG or LH. The cycle may be cancelled if too few or too many eggs develop.

GnRH agonists and antagonists are synthetic hormones that are administered by injection to control the release of LH. GnRH analogues are used to prevent the spontaneous release of an egg.

Side Effects of Medications - there are many types of gonadotropins used alone or in combination for ovulation induction. During the use of these drugs careful monitoring is required to minimize the risk of side effects, discussed below.

Ovarian Hyperstimulation (OHSS) - occurring in 1 to 5 percent of cycles, the chance of OHSS is increased in women with polycystic ovarian syndrome and in conception cycles. When severe, it can result in blood clots, kidney damage, ovarian twisting (torsion), and chest and abdominal fluid collections. In severe cases, hospitalization is required for monitoring, but the condition is transient, lasting only a week or so. Occasionally, drawing fluid out of the chest or abdominal cavity helps. The best prevention is to not give hCG to induce ovulation at the end of an overly vigorous stimulation cycle.

Multiple Gestation - up to 20 percent of pregnancies resulting from gonadotropins are multiple, in contrast to a rate of 1 to 2 percent in the general population. While most of these pregnancies are twins, a significant percentage are triplets or higher. High order multiple gestation pregnancy is associated with increased risk of pregnancy loss, premature delivery, infant abnormalities, handicap due to the consequences of very premature delivery, pregnancy induced hypertension, gestational diabetes, hemorrhage, and other significant maternal complications.

Ectopic (Tubal) Pregnancies - while ectopic pregnancies occur 1 to 2 percent of the time, in gonadotropin cycles the rate is slightly increased at 1 to 3 percent. These can be treated with medicine or surgery. Combined tubal and intrauterine pregnancies (heterotropic pregnancies) occasionally occur with hMG and need to be treated with surgery.

Birth Defects - the rate of birth defects after gonadotropin cycles is no higher than in the general population, at 2 to 3 percent. Furthermore, these children are developmentally no different than their peers.

Adnexal Torsion (Ovarian Twisting) - less than 1 percent of the time, the stimulated ovary can twist on itself, cutting off its own blood supply. Surgery is required to untwist or even remove it.

Gonadotropins and Ovarian Cancer - the risk of ovarian cancer seems, in part, to be related to the number of times a woman ovulates. Infertility increases this risk; birth control pill use decreases it. Controversial data exists that associate ovulation stimulation drugs, like gonadotropins, with the risk of future ovarian cancer. While research is underway to help clarify this issue, the careful use of gonadotropins is still reasonable, especially considering that pregnancy and breast feeding reduce cancer risk.