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FERTILITY CENTER
Pathway to Parenthood

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CLOMIPHENE CITRATE
(SEROPHENE, CLOMID)

Clomiphene citrate (Clomid, Serophene) is the most popular agent used for inducing ovulation, and in the 1980's, was also the most widely used method for COH in preparation for In Vitro Fertilization (IVF). Clomiphene citrate is a synthetic hormone that deceives the hypothalamus into thinking that the body's estrogen level is too low. In response, the hypothalamus releases GnRH (gonadotropin-releasing hormone), which in turn prompts the pituitary gland to release an exaggerated amount of FSH (follicle-stimulating hormone). As happens in nature, the increased secretion of FSH stimulates development of the follicles, ultimately resulting in ovulation. The growing follicles secrete estrogen into the bloodstream, thus closing the feedback circle that the hypothalamus initiated in response to the anti-estrogen properties of Clomiphene.

Administration of Clomiphene citrate enhances the normal cyclical pattern of follicular development and ovulation. If initiated as early as day 2 or day 3 of the menstrual cycle, it usually induces ovulation on day 13 or 14 of a regular 28-day cycle. If administered later, such as on day 5, ovulation could occur as late as day 16 or 17, and the length of the cycle may be extended. If the woman does not stimulate appropriately on the original dosage of Clomiphene, the dosage may be increased to achieve optimal stimulation. Frequently, hCG is administered to the patient once ultrasound examinations and hormonal evaluations confirm optimal follicular development. In such cases, ovulation will usually occur about 38 hours later.

Two major advantages of Clomiphene are its relatively low cost and the fact that it can be taken orally instead of by injection. A distinct disadvantage is that when administered alone, it does not stimulate the growth and maturation of as many follicles as do alternative therapies such as gonadotropins alone or in combination with Clomiphene; accordingly, fewer eggs can be retrieved. Another disadvantage is that clomiphene has an anti-estrogenic effect on the cervical mucus production, which can be profound and thereby limit the penetrability of the sperm through the female reproductive tract (see below).

Safety and Side Effects of Clomiphene: The side effects associated with Clomiphene are related to the follicular development the drug has stimulated. When administered alone, a luteal-phase defect

(deficiency in progesterone production following ovulation) may result if the follicles do not develop properly. This would hinder implantation by preventing the endometrium (uterine lining) from responding optimally to the progesterone produced by the corpus luteum. Clomiphene may also interfere with the nurturing effect estrogen must have on the developing endometrium. In addition, traces of Clomiphene that might linger in the woman's circulatory system for many weeks may inhibit the normal function of enzymes produced by the developing follicular cells. Too high a dose of Clomiphene may cause follicles to grow too rapidly, producing large fluid-filled collections known as cysts. This may lead to tenderness and swelling of the ovaries, visual disturbances, and hot flashes similar to those at menopause.

The progressive build-up of Clomiphene in the body over a period of three (3) or more consecutive months of treatment compounds its anti-estrogenic properties and effects and leads to: a) a reduction in the quality of the cervical mucus, with negative implications for the capacitation and transportation of the sperm and b) a profound thinning of the uterine lining (endometrium), which seriously compromises embryo implantation. These two effects probably explain why prolonged usage of Clomiphene (i.e. for three (3) or more back-to-back cycles of treatment) without allowing for at least one month's break before re-initiating therapy, seriously compromises fertility, and results in a significant increase in the risk of early spontaneous abortion. Unless allowance is made for such a break in therapy, each additional, consecutive Clomiphene treatment cycle will inevitably result in a progressive decline in pregnancy potential and/ or reproductive performance. In fact if administered for more than six (6) consecutive back-to back cycles (without allowing for at least one (1) resting cycle), a progressive escalation in Clomiphene anti-estrogenic effects will convert this fertility agent into a “relative contraceptive.” Fortunately, the cessation of Clomiphene treatment for only one (1) month is sufficient to completely reverse such highly undesirable side-effects.

It has been observed that few women over 40 years respond well to Clomiphene. In spite of the fact that they appear to ovulate on Clomiphene treatment, they frequently develop poor mucus and a poor endometrial lining from the inception of Clomiphene administration. We accordingly believe that Clomiphene treatment is relatively contraindicated in women over the age of 40.

Some studies have suggested that Clomiphene citrate has caused birth defects or a higher miscarriage rate in laboratory animals and could, therefore, potentially threaten human offspring. We, however, believe that when Clomiphene is taken under proper supervision, these risks should not be of major significance.

The fear that Clomiphene might cause birth defects arises from the fact that its inner structure, or nucleus, is very similar to that of the hormone DES, which is known to have caused significant birth defects when administered to pregnant women. Although it is theoretically possible that Clomiphene might cause such defects; birth statistics do not indicate an increased birth-defect rate after stimulation with the drug. The laboratory studies mentioned above should not be ignored, however, but should be heeded as a guide to safe, prudent administration of fertility drugs. We caution that Clomiphene citrate should be taken only when it is absolutely certain that the woman is not pregnant. (The appearance of a menstrual period does not provide adequate certainty because more than 10% of women might bleed

during early pregnancy. Assessment by a physician, or even a home pregnancy test, provides greater assurance that a pregnancy does not exist.)

The administration of Clomiphene as a fertility agent over a series of months might also promote ovulatory problems. It has been observed that in one out of five cases where Clomiphene is administered, the egg remains trapped in the follicle after ovulation. Therefore, the practice of physicians saying to patients, "Here's some Clomiphene-take some each month and call me if you miss your period," should be deplored. If Clomiphene citrate is taken under proper supervision and the woman has previously determined that she is not pregnant, its safety is beyond question. The use of clomiphene in patients undergoing IVF is limited at best, primarily because of the significant anti-estrogenic effect discussed above.

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This handout is intended as an aid to provide patients with general information. As science is rapidly evolving, some new information may not be presented here. It is not intended to replace or define evaluation and treatment by a physician.