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## **Patient Fact Sheet**

# **Infertility, Fertility Drugs, and Ovarian Cancer**

Many couples faced with infertility are treated with ovulation induction medications, often referred to as fertility drugs. These medications (such as clomiphene citrate) may help a patient to ovulate who previously was not ovulating or, when given empirically, may induce one or two more follicles to be produced each cycle than the customary one. The second class of fertility drugs (gonadotropins) are usually given as some form of an injection and will induce the timed release of multiple eggs in one cycle. These medications are commonly combined with intrauterine inseminations (IUI) or with in vitro fertilization. There has been some concern about the possible increased risk of ovarian cancer after treatment with medications that stimulate ovulation from the ovaries. Most well-designed studies show no increase in risk, while others have shown a slight increased risk in ovarian cancer after fertility treatment. This information packet will attempt to address these issues.

It is important to understand several facts about ovarian cancer. The overall risk of developing ovarian cancer in woman during her lifetime is somewhere between 1-2%. The cause of ovarian cancer is multifactorial. Well-established risk factors include a history of irregular menstrual cycles, a history of untreated infertility, never having children in one's lifetime, early onset of menses, and the late onset of menopause. Conversely, some factors which may be protective include the use of oral contraceptives, late onset of menopause, early onset of menopause, repeated pregnancy, prolonged lactation, and surgical removal of ovaries.

Studies reported in the early 1990s compared the general population, consisting mostly of fertile women, with infertile women who had been given fertility drugs. They suggested an increased risk of ovarian cancer in the infertile group that took fertility drugs. These studies were criticized because using a fertile group of women for comparison is inappropriate. This is because it would not be clear if it were the infertility drugs or the state of infertility to be the risk factor of increasing their chance for ovarian cancer.

One recent article published from the UCLA School of Medicine revealed that the apparent association between fertility drug use and ovarian cancer may actually be because these women were already at higher risk for ovarian cancer because of their infertile status. This study and other recent studies suggest that the use of fertility drugs alone does not increase the risk of ovarian cancer.

Another article suggested an increased risk of ovarian cancer in an infertile group that took clomiphene citrate for 12 cycles or more, compared to a similar infertile group that had never taken clomiphene citrate. There did not appear to be any increased risk between groups of women who took clomiphene citrate for less than 12 cycles. It is our general recommendation that once a patient is ovulatory, a total of three to six cycle of clomiphene citrate should be the maximum therapy before moving on to an alternative therapy.

In the largest case-control study to date, Mosgaard et al. saw no association between fertility medications and ovarian cancer. They did not find an increased risk of ovarian cancer in nulliparous women (who had never been pregnant) when compared to fertile women. Their data suggested that infertility alone may be responsible for the increased risk of ovarian cancer reported in some studies. A recent study of women who underwent IVF in Israel

found no increased risk in breast or ovarian cancer. The meta-analysis by Ness et al. pooled data from eight studies in the U.S., Denmark, Canada, and Australia to review possible relations among infertility, fertility drug use, and the risk of ovarian cancer. Among subfertile women without children, neither any fertility drug use nor more than 12 months of use was associated with ovarian cancer. In those infertile women who developed ovarian cancer, fertility drug use was associated with borderline tumors but not with invasive ovarian cancer.

The most recent studies are reassuring in that fertility drugs probably do not increase the risk of ovarian cancer. However, it is important to understand the question is not completely answered. Currently, there is no recommendation for increased screening for patients who have taken fertility drugs, other than the current practice of annual exams. Birth control pills have been shown to decrease the risk of ovarian cancer, so your doctor may recommend these after your treatment is completed. Future research efforts are directed toward providing long-term follow-up of women who required fertility treatments.

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