

CANCER RISK ASSOCIATED WITH THE USE OF FERTILITY DRUGS FOR OVULATION INDUCTION

VICTORIA
FERTILITY



C·E·N·T·R·E

Drugs used to superovulate the ovary and enhance fertility are amongst the fastest growing group of drugs in the world. Recent projections suggest that by the year 2025 over six million women aged between 15 and 44 will be diagnosed with some form of infertility.

We the public are becoming increasingly aware and also somewhat suspicious of new drugs on the market. Expensive and slick advertising by drug manufacturers make incredible claims about fantastic therapeutic effects with minimal side effects. The public confidence has been shattered a number of times recently. Take for example the anti-inflammatory drug Vioxx. It certainly did seem to be the answer to many forms of pain control – however now we are hearing about increased risks of cardiovascular events and the drug has been taken from the market.

Over the years, some clinical studies have suggested that there may be a link between ovulation inducing medications and risk of various cancers. These studies have all been retrospective (historical) and have mainly been observational. What has been more confusing is that some studies have suggested an increased association with cancer, and some a decreased incidence of cancer.

It is sometimes very difficult to draw conclusions. There are so many other factors which may influence the risk of cancer – genetics, diet, pregnancy, abortion, age at first breast feeding, smoking, alcohol, exercise, body weight and so on.

OVARIAN CANCER

There have been a number of clinical reports expressing concern about a potential link between the use of fertility drugs and the risk of ovarian cancer.

The drug which has been most written about has been clomiphene. It has been suggested that the use of clomiphene for 12 or more cycles may increase the risk of some forms of ovarian cancer. The majority of these ovarian cancers were in the borderline group. Borderline ovarian tumours are somewhat in a grey zone in between frankly malignant tumours and benign tumours. They are certainly not good news but the prognosis is far better than with the more aggressively malignant ovarian cancers.

More recent studies have focused on looking at risk in women using fertility drugs for in vitro fertilization. An Australian study recently looked at 32,000 women referred to 10 IVF clinics. During a follow up period close to 10 years, 13 ovarian cancers were identified. Not all the women who were referred received fertility drugs. Interestingly this study suggested that there was no higher risk for cancer for women who went through an in vitro fertilization cycle as compared to those who did not. What they did notice however is that women with unexplained infertility were at significantly increased risk of ovarian cancer compared with the general population.

Within the subgroup there was no difference in risk between women who used fertility drugs and women who did not.

Another large study has been reported from the Netherlands. Over 25,000 women treated for infertility were followed for 6 years. Seventeen cancers developed. These results showed no difference in risk between women who were treated with fertility drugs and those who were not.

Based on the available evidence there does not seem to be a conclusive link between the use of fertility drugs and ovarian cancer. There does however seem to be an increased risk of ovarian cancer in women with sub fertility who never achieve a pregnancy. (whether they have been exposed to fertility drugs or not)

Personally I feel that there are a subset of women (i.e. those who receive fertility treatments such as in vitro fertilization) but never achieve a pregnancy who may be at increased risk – and should be followed very carefully throughout life for a increased risk for ovarian cancer. Although screening for ovarian cancer has been very controversial, the best options would include a 6 monthly or yearly pelvic ultrasound to measure ovarian volume and blood flow, along with a blood test to measure certain proteins which can be produced by early ovarian cancers (CA125, CA19/9). A further option for such patients would be prophylactic oophorectomy (removing of the ovaries) when they reach menopause. This is a day-care procedure, relatively non-invasive, and may be beneficial to this subgroup.

BREAST CANCER

The epidemiology of breast cancer has been extensively studied with most investigations supporting the idea of an important role for hormonal therapy. I think most readers are aware of the potential link between hormone replacement therapy after menopause and the incidence of breast cancer. Unfortunately, some irresponsible reporting in the media has perhaps fueled the controversy about this.

There have been several studies suggesting a link between fertility drugs and breast cancer. However, the results are conflicting – some studies have suggested a potential increase in risk and others have suggested a decrease in risk. The use of clomiphene for more than a year has been significantly associated with a decreased risk of breast cancer. This is not that much of a surprise in that it is known clomiphene has antiestrogenic properties.

Because breast cancer is so common (the incidence in North America is approximately 1 in 9 women) and because there are so many variables associated with its risk, I doubt that in our lifetime we will ever know the answer. However at this stage there is no clear evidence that there is an increased risk of breast cancer related to the use of fertility drugs.

ENDOMETRIAL CANCER (UTERINE CANCER)

There are not many good studies available which have looked at this issue. It is however known that the drug tamoxifen which has been used extensively in the

treatment of breast cancer over the past 30 years does carry with it a slightly increased risk of endometrial cancer. Because tamoxifen has similar properties to the fertility drug clomiphene a concern has been raised that women who use clomiphene for long periods of time may be at increased risk for endometrial cancer.

Within the subgroup of women seeking fertility treatment there are many who have an ovulatory dysfunction. In other words, these women do not ovulate regularly on their own. Such women independently have an increased risk of endometrial cancer due to an imbalance between their estrogen and progesterone levels.

So in summary, we do not know the answer here. It is possible that there may be a slight risk, though the subject has not been well studied.

MELANOMA

For many years it has been felt that melanoma risk may be related to circulating hormone levels. Observational studies done many years ago suggested that melanoma risk may be increased by pregnancy. The obvious assumption made suggested that increased circulating levels of female hormones may be responsible. It was also speculated that the immune system changes that occur in pregnancy could also decrease the body's natural defences against fighting this particular cancer.

It has been suggested that women with underlying hormone abnormalities may be at increased risk for melanoma. However the available evidence does not allow us to draw any conclusions regarding an association between melanoma and the use of fertility drugs.

CERVICAL CANCER

Although cervical cancer is not generally regarded as being a hormonally related tumour there does seem to be an increased risk of cervical cancer associated with the use of oral contraceptives and increasing parity (number of children). The only well conducted studies have suggested that there is a reduced risk of cervical cancer associated with the use of clomiphene.

THYROID CANCER

There is no doubt that thyroid cancer is much more common amongst women. This has led to the notion that perhaps it is a hormonally sensitive tumour. There is also been some speculation that there is an increase risk of thyroid cancer in women suffering from sub fertility. The association between thyroid cancer and the use of fertility drugs is unknown.

COLON CANCER

There is only ever been one good study looking at the relationship between colon cancer and fertility drugs – and this found no relationship.

CONCLUSIONS

In summary, the results so far are reassuring. From my personal perspective I think that it would appear there may be a small subgroup of women at increased risk for ovarian cancer. Specifically these are women who have received more than 6 to 12 of cycles of either superovulation or in vitro fertilization and yet never achieved a pregnancy. This group may be at slightly increased risk for ovarian cancer as they get older – and I think deserve to be followed very closely. I would advise such women to discuss their risks with their gynaecologist and choose a follow up program with which they are comfortable. This may consist of yearly ultrasounds, and blood tests, or more aggressively removing ovaries at around the time of menopause.