

## Letter to the Editor

### THE LINK BETWEEN OVARIAN CANCER AND INFERTILITY DRUGS

Dear Editor,

In a recent article, Jeremic *et al.* [1] have addressed the problem of infertility therapy related to ovarian cancer development. It is well known that ovarian cancer is among the most frequent cancers in the Western world. Recently, a large array of researches have dealt with the development of ovarian cancer after infertility treatment, with inconsistent conclusions. The medical expertise as well as the public require a clear stand on this issue. A review from 2004 [2] emphasized that induction of ovulation is not linked to a higher risk of ovarian cancer development. Furthermore, it is stated that infertility therapy may confer protection for those patients who conceive. We completely disagree with these stands. In our report published ten years ago [3] we presented a strong relation between induction of ovulation and epithelial ovarian cancer. Since this report, we have had three more such cases. Our study was supported by an investigation carried out by Polish researchers [4]. According to a recent review [5] there is a direct influence of ovulatory drugs on the development of ovarian cancer. In our experience, in infertility patients induction of ovulation needs to be achieved with as minimal a dosage of medication as possible. The up-to-date approach to infertility patients recommends short courses of ovulation induction and patients undergoing this procedure should be aware that there is an increased risk of ovarian cancer development following treatment.

Yours sincerely,

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## Authors' Reply

To the Editor

We thank Drs. Terzic and Arsenovic for their comments on our article that raised many questions.

It is well known that infertile patients who receive ovulation stimulating drugs may be at particularly high risk for carcinoma. That association has a biologic base, given that "incessant ovulation" and excessive gonadotropin levels during the reproductive years appear to be likely explanations for a number of the recognized risk factors for ovarian cancer [2]. It was observed that reproductive hormones can lead to generation of malignant ovarian tumors. The majority of previous studies have observed the elevated risk for ovarian cancer associated with the usage of ovarian drug stimulation. That opinion has been supported by the fact that the GnRh receivers have been found in the tissues of almost 80% of epithelial tumors and in numerous cancer cell lines as EFO-21 [1].

However the association between fertility drugs and ovarian cancer is still controversial. Some authors do not share the same opinion about the relationship between stimulation drugs and cancer, leading to scrutiny regarding the methodologies of the previous studies.

A large retrospective cohort study among women treated for infertility at five specialized practices, approved by the institutional review boards at the collaborating centers as well as the National Cancer Institute, included detailed medical abstraction records and extended follow-up. The study found that infertile women had a higher risk of ovarian cancer than the general population, but pointed out the importance of accounting for characteristics of patients in estimating drug effects. Compared with other infertile patients, the authors concluded that use of either clomiphene or gonadotropins had no adverse effect on ovarian cancer risk. Thus the results of this study do not confirm a strong connection between ovulation stimulating drugs and ovarian cancer. Of course it could not rule out the possibility that certain subgroups of users might experience some slight elevation in risk, showing the need for continued monitoring of long-term effects [2].

Although it has been suggested that controlled ovarian stimulation may initiate ovarian cancer, some recent studies postulate a protective effect if fertility treatments result in successful pregnancy [3].

Thus, in the future we need prospective studies with high numbers of events, long and complete follow-up and information on the other predictors of ovarian cancer in order to get concrete data on the influence of ovulation-stimulating drugs on cancer.

Sincerely yours,

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