

# Fertility Drugs and Ovarian Cancer

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**Summary:** A systematic review of reports on association of ovarian cancer and fertility drug use was conducted through MEDLINE search. It revealed case reports and studies where at least 95 cases of ovarian cancer were found to be associated with use of different fertility drugs. Of them in 75 cases, authors have published the names of fertility drugs which were used. In 74% cases Clomiphene Citrate (CC) either alone or in combination with human menopausal gonadotrophin (HMG), was implicated.

## Introduction

In recent years there is a surge of case reports and studies on possible carcinogenic effect of fertility drugs on ovary in world literature. They are dispersed and till date no such attempt is made to address this important subject in its totality. In the light of rapid and tremendous growth of invitro technology and menstrual cycle manipulation it seemed essential to sum up all the reports on such association to perceive the implication and impact of possible overuse of fertility drugs.

## Material & Methods

A systematic review of reports in MEDLINE (1967 – 1997) was performed in June-July 1997 on fertility drugs and ovarian cancer. Most of the reports were collected from journals and additional reports were perused from the reference lists of retrieved articles.

## Results

Atleast 95 cases of ovarian cancer could be identified in 15 publications. Majority of publications were case reports (80%, n = 12). They reported as many as 40 cases of ovarian cancer (epithelial 14, granulosa 14, borderline 11 and malignant teratoma 1). Only 3 publications (20%) were studies. Nature of studies were as follows: case control 1, cohort 1 and meta analysis 1. Other 2 cohort studies correlated ovarian cancer with infertile women and not with fertility drugs and were excluded from the present paper. Three study reports described 55 cases of ovarian cancer (epithelial 33 and borderline 22).

Clomiphene (2[p-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine) citrate (CC) and human menopausal gonadotrophin (HMG) are the two fertility drugs implicated in these reports. Meta analysis of 12 US case control studies does not mention the names of drug used in causing or in association with their reported 20 ovarian cancer cases. Amongst the remaining cases, 35 had exposure to CC only while 19 had exposure to HMG only. In 20 cases both CC and HMG were used and in a single case CC and tamoxifen were used. Thus, 25.3% cases were exposed to HMG alone and in 74% cases to CC, either alone or in combination with HMG.

## Discussion

In these papers no causality could be established and only association is shown. Balasch and Barri (1993) aptly pointed out that establishment of causal relation needs very large prospective case control study with carefully selected control group. This is because prevalence of ovarian cancer is low, minority of infertile couple take fertility drugs and aetiology of ovarian cancer is multifactorial. But Whittemore (1993), commenting on criticisms published in response to such studies, has opined that such publications should prompt attempts by individuals affiliated with, sponsored by or sympathetic with professional fertility societies to evaluate and, if possible, to discredit the findings.

Persistent stimulation of the ovary by gonadotrophins may have direct and indirect carcinogenic effect as evident from a number of in vivo and in vitro studies. But, the carcinogenesis and mutagenesis due to CC in ovary is

not yet studied. It is astonishing that when about 74% of ovarian cancer was associated with CC not a single toxicity study of CC was found. At least animal experiments with the help of molecular biology can establish safety of CC in this respect. While there are so many proponents of very large case control studies no such suggestion was found to conduct safety study of CC.

Though no causality could be established it seems that an individual approach rather than a 'blanket' approach is necessary. Injudicious and unsupervised use of CC especially for longer period than one year must strongly be discouraged.

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### References

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- 2 Whittemore A S. Hum. Reproduction; 8: 999; 1993.