No link between fertility drugs and breast, ovarian and uterine cancers

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There is "little evidence" that the use of conventional fertility hormones used for ovarian stimulation in the treatment of infertility increases the long-term risk of breast and gynecological cancers, according to the results of a substantial 30-year follow-up study. However, the extended use of clomiphene citrate was associated with a higher risk of breast cancer among women who had used the fertility drug for 12 cycles or more. Gonadotrophins, more commonly used for ovarian stimulation today, were not generally associated with any increased risk, except in a sub-group of women who remained childless after treatment.

Results of the study, which was in part funded by the National Institutes of Health of the USA, are presented today at the Annual Meeting of ESHRE by Dr Humberto Scoccia from the University of Illinois at Chicago, USA. Dr Louise Brinton of the US National Cancer Institute was principal investigator.(1)

The study was a retrospective investigation involving 12,193 women treated for infertility between 1965 and 1988 at five US sites. Follow-up lasted until 2010, with evaluation based on questionnaire and linkage to US death and cancer registries. A total of 9,892 women were successfully followed for cancer outcomes.

As background to the study Dr Scoccia explained that fertility drugs are known to increase levels of the principal female hormones estradiol and progesterone, both of which have been implicated in the pathogenesis of breast, ovarian and uterine cancers. Drugs to stimulate the ovaries for

ovulation induction and IVF have included clomiphene and fertility hormones derived from human subjects - human menopausal gonadotrophins, hMG, and follicle stimulating hormone, FSH. Both hMG and FSH were not introduced into widespread use until the very early 1980s - and until then clomiphene was the most commonly used agent.(2)

"Despite the biologic plausibility, results of studies of fertility drugs and breast and gynecological cancers present a mixed picture, with some showing increases in risk, others decreases, and still others showing no substantial associations," said Dr Scoccia. "However, most of these studies had small numbers with relatively short follow-up periods, and were unable to control for other cancer predictors - including the indications for drug usage, such as anovulation or endometriosis, which could independently affect cancer risk. Many questions remain unresolved."

Over the 30 years of follow-up 749 breast, 119 endometrial (uterine) and 85 ovarian cancers were identified in the 9,892 subjects. The "ever use" of clomiphene - which included approximately 40% of the cohort - was not associated with any increased breast cancer risk, except when subjects had used the drug in 12 or more treatment cycles. In such cases clomiphene use was associated with a significant hazard ratio of invasive breast cancer of 1.69 (95% CI 1.16-2.45). This risk remained relatively unchanged after adjustment for causes of infertility and multiple breast cancer predictors. Clomiphene use was not significantly associated with either endometrial (HR 1.41, 95% CI 0.98-2.04) or ovarian (HR 1.34, 95% CI 0.86-2.07) cancers, even when multiple exposure cycles were involved.

Only 10% of the cohort had been treated with gonadotrophins (hMG and FSH) - usually in combination with clomiphene - and there was no association with cancer risk identified, except in those who remained

childless (HR 1.98; 95% CI, 1.04–3.60). "Given that the majority of our women who received gonadotrophins also received clomiphene," said Dr Scoccia, "it is likely that the increased risk among nulligravid women reflects an effect on risk of their infertility rather than that of drug usage."

In making further comment, he said that the study's findings do not support "a strong relationship" between the use of fertility drugs (mainly clomiphene citrate) and breast, uterine and ovarian cancers. He described the results as "generally reassuring", noting that this study had considerably more statistical power than previous efforts. However, despite the long follow-up of this study he urged continuous monitoring because of the "relatively young age of our study population and the later peak incidence of most of these cancers". It is also likely that the proportion of patients using gonadotrophins for ovarian stimulation - particularly in IVF - increased substantially after the mid-1980s.

More information: Notes

1. Several reports from this study have been published during its long follow-up period, but this is the first summary of findings at three reproductive cancer sites (breast, ovary and endometrium) during that 30-year follow-up. The previous publications used varying exposure classification schemes but this study presents all results in one place with standardised exposure categories to allow comparisons across all three cancer sites. This summary information has not been presented or published previously.

2. Clomiphene citrate is defined as a selective estrogen receptor modulator chemically similar to tamoxifen. Despite the substantial use of gonadotrophins for ovarian stimulation today, clomiphene is still in widespread use, particularly as a first-line of treatment to induce ovulation for natural conception or insemination. A recent Cochrane

review (albeit including several older studies) found that the use of clomiphene along with gonadotropins leads to similar pregnancy rates as those occurring after the use of gonadotrophins alone. A recent "opinion" from the American Society for Reproductive Medicine (ASRM) described clomiphene as "an effective first-line treatment for the majority of women with anovulatory infertility".

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