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[Intervention Review]

Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility

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ABSTRACT

Background

The use of assisted reproductive techniques is increasing, but the possible link between fertility drugs and ovarian cancer remains controversial.

Objectives

To evaluate the risk of ovarian cancer in women treated with ovulation stimulating drugs for subfertility.

Search methods

We searched for published and unpublished observational studies from 1990 to February 2013. The following databases were used: the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register, Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 1, MEDLINE (to February week 4 2013), EMBASE (to 2013 week 09) and databases of conference abstracts. We also scanned reference lists of retrieved articles. The search was not restricted by language of publication.

Selection criteria

We searched for randomised controlled trials (RCTs) and non-randomised studies, and case series including more than 30 participants, reporting on women with exposure to ovarian stimulating drugs for treatment of subfertility and histologically confirmed borderline or invasive ovarian cancer.

Data collection and analysis

At least two review authors independently conducted eligibility and 'Risk of bias' assessment, and extracted data. We grouped studies based on the fertility drug used for two outcomes: borderline ovarian tumours and invasive ovarian cancer. We expressed findings as adjusted odds ratio (OR), risk ratio (RR), hazard ratio (HR) or crude OR if adjusted values were not reported and standardised incidence ratio (SIR) where reported. We conducted no meta-analyses due to expected methodological and clinical heterogeneity.

Main results

We included 11 case-control studies and 14 cohort studies, which included a total of 182,972 women.

Seven cohort studies showed no evidence of an increased risk of invasive ovarian cancer in subfertile women treated with any drug compared with untreated subfertile women. Seven case-control studies showed no evidence of an increased risk, compared with control women of a similar age. Two cohort studies reported an increased incidence of invasive ovarian cancer in subfertile women treated with

any fertility drug compared with the general population. One of these reported a SIR of 5.0 (95% confidence interval (CI) 1.0 to 15), based on three cancer cases, and a decreased risk when cancer cases diagnosed within one year of treatment were excluded from the analysis(SIR 1.67, 95% CI 0.02 to 9.27). The other cohort study reported an OR of 2.09 (95% CI 1.39 to 3.12), based on 26 cases.

For borderline ovarian tumours, exposure to any fertility drug was associated with a two to three-fold increased risk in two case-control studies. One case-control study reported an OR of 28 (95% CI 1.5 to 516), which was based on only four cases. In one cohort study, there was more than a two-fold increase in the incidence of borderline tumours compared with the general population (SIR 2.6, 95% CI 1.4 to 4.6) and in another the risk of a borderline ovarian tumour was HR 4.23 (95% CI 1.25 to 14.33) for subfertile women treated with in vitro fertilisation (IVF) compared with a non-IVF treated group with more than one year of follow-up.

There was no evidence of an increased risk in women exposed to clomiphene alone or clomiphene plus gonadotrophin, compared with unexposed women. One case-control study reported an increased risk in users of human menopausal gonadotrophin (HMG)(OR 9.4, 95% CI 1.7 to 52). However, this estimate is based on only six cases with a history of HMG use.

Authors' conclusions

We found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. There may be an increased risk of borderline ovarian tumours in subfertile women treated with IVF. Studies showing an increase in the risk of ovarian cancer had a high overall risk of bias, due to retrospective study design, lack of accounting for potential confounding and estimates based on a small number of cases. More studies at low risk of bias are needed.

PLAIN LANGUAGE SUMMARY

Is there an increased risk of ovarian cancer in women treated with drugs for subfertility?

Drugs to stimulate ovulation have been widely used for various types of subfertility since the early 1960s and their use has increased in recent years. Subfertile women are commonly exposed to these agents, which may be administered at high doses for long periods of time during treatment for subfertility. There is uncertainty about the safety of these drugs and the potential risk of causing cancers associated with their use.

Overall, based on 25 studies, which included a total of 182,972 women, we found no evidence that the risk of ovarian cancer was increased in women treated with fertility drugs, compared with subfertile women untreated with fertility drugs, or women in the general population.

Five of the 25 studies showed an increase in the risk of ovarian cancer, but these studies were of low methodological quality and therefore the results are too unreliable to conclude that there is a definitive risk of cancer while on treatment for subfertility.

More research studies, which are of high quality, are needed to determine whether there is an increased risk of ovarian cancer in women treated with fertility drugs.