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Assisted reproductive technology (ART) treatment and risk of ovarian cancer

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Study question:

Is ART treatment associated with risk of ovarian cancer?

Summary answer:

An increased risk of ovarian cancer after ART treatment was mainly apparent during 12 years after treatment initiation and is likely influenced by detection bias.

What is known already:

Ovarian stimulation in ART treatment has been suggested to increase the risk of ovarian cancer. Previous findings are inconsistent and often based on few diagnosed cases, and it has proven difficult to assess potential confounders such as endometriosis in large-scale studies. Nulliparity has been shown to be associated with ovarian cancer, although the causal relation is not clear. Ovarian cancer is often detected at an advanced stage due to a lack of symptoms during the early stages of disease. Latency time from initiated cancer until diagnosis has been estimated to be 30-40 years.

Study design, size, duration:

The Danish National ART-Couple II (DANAC II) cohort includes all women treated with ART at Danish fertility clinics in 1994-2015. Each woman in ART treatment was age-matched with ten women from the background population without a history of ART treatment. The women were followed until first cancer diagnosis, death, migration or end of study December 31st 2015. The cohort consisted of 58,472 women treated with ART and 549,210 women without a history of ART treatment.

Participants/materials, setting, methods:

Multivariable analyses were conducted using cox proportional hazards regression. Having a primary cancer diagnosis other than ovarian cancer was incorporated as a competing risk. Adjustment for confounders included baseline nulliparity, educational level, partnership status, endometriosis and PCOS and time-dependent adjustment for age and treatment year. Analyses were stratified on baseline nulliparity and on cause of infertility. Further, the risk of being diagnosed with ovarian cancer was observed over time in order to detect potential patterns.

Main results and the role of chance:

During follow-up 393 (0.06%) women were diagnosed with ovarian cancer, 64 (0.11%) among ART-treated women and 329 (0.06%) among non-ART women. Women undergoing ART treatment had a higher risk of ovarian cancer than non-ART women (HR 1.20, 95% CI 1.10-1.31). ART treatment was associated with an increased risk of ovarian cancer among parous women (HR 1.34, 95% CI 1.11-1.62) and among nulliparous women (HR 2.38, 95% CI 2.17-2.60) versus (HR 2.03, 95% CI 1.89-2.19). ART treatment due to female factor infertility was associated with an increased risk of ovarian cancer (HR 1.36, 95% CI 1.25-1.48), while ART treatment due to male factor/unexplained infertility was associated with a lower risk (HR 0.87, 95% CI 0.76-1.00). ART treatment was not associated with a long-term increased risk of ovarian cancer which would be expected if caused by ovarian stimulating hormones. The excess risk of ovarian cancer among ART-treated women was highest during the first two years after ART treatment initiation (HR 1.24, 95% CI 1.06-1.45). The excess risk gradually declined and 12 years after ART treatment initiation the risk was similar to the background population (HR 1.05, 95% CI 0.87-1.27). This pattern suggests an influence of detection bias while undergoing ART treatment.

Limitations, reasons for caution:

Although we did not find any indications of harmful effects of ovarian stimulating hormones, it is uncertain to what extent detection bias explains the higher risk among ART-treated women. ART treatment without female factor infertility was not associated with an increased risk of ovarian cancer.

Wider implications of the findings:

Disentangling between the effect of underlying causes of infertility and the ovarian stimulation on the risk of ovarian cancer is a challenge. Further, detection bias should be thoroughly considered prior to drawing conclusions.

Trial registration number:

Not relevant

No
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