

Newsletter 2023 – May

Author: Dr Luciana Cacciottola

Long-term risk of ovarian cancer and borderline tumors after assisted reproductive technology

Spaan M, et al J Natl Cancer Inst. 2021 Jun 1;113(6):699-709.

Background

Since the introduction of assisted reproductive technology (ART), concerns have been raised about the possibility of patients being at **increased risk of subsequently developing ovarian tumors**, due either to repeated gonadotropin administration or multiple punctures disrupting the ovarian epithelium. Data have nevertheless yielded inconclusive results over the years.

Two meta-analyses published in 2013 evidenced a correlation between ART and the risk of developing ovarian tumors (1,2). However, this higher prevalence appeared to be associated with **nulliparity and infertility issues**, rather than ART treatment itself. Indeed, no increased risk was observed when set against a population of infertile women not undergoing ART (2), emphasizing the need for **proper comparison models** to reach valid conclusions.

Summary of the paper

A national retrospective cohort study with long-term follow-up was conducted to ascertain the lasting effects of ART on general health, including the risk of developing borderline ovarian tumors (BOTs) and epithelial ovarian cancers (EOCs). A population of 30,625 women undergoing ART (1 to 12 in vitro fertilization [IVF] cycles, mean number 3.3) in the Netherlands between 1995 and 2000 was considered and compared with a population of 9,988 women diagnosed with infertility but not managed by ART. Follow-up for cancer incidence from 1998 to 2018 was ensured using data from the population-based Netherlands Cancer Registry (including 94% of the whole cohort). In total, 158 EOCs and 100 BOTs were encountered during follow-up.

Comparisons with general population. The risk of EOCs was higher in infertile women undergoing ART than in the general Dutch population (standardized incidence ratio [SIR] 1.43, 95% CI = 1.18-1.71). More specifically, it increased significantly in women receiving either 1-2 or more than 7 IVF cycles. ART success rates were also consequential, as nulliparous women had a 2-fold increased risk of developing EOCs compared to those who had had at least one child.

The risk of BOTs was also higher in infertile women than in the general population (SIR 2.2, 95% CI 1.66-2.86, and SIR 1.84, 95% CI = 1.05-2.99) irrespective of the use of ART treatments. However, no clear trend was identified with increasing numbers of IVF cycles. The risk of BOTs was particularly elevated in women with tubal factor infertility compared to other infertility causes.

Comparisons within the cohort. EOCs were found to be more common in infertile women undergoing ART than in infertile women never subjected to ART, with a hazard ratio (HR) of 1.20 (95% CI = 0.7-1.5) adjusted for age and parity. Ovarian hyperstimulation syndrome was not associated to any increase in oncological risk. Within the ART group, the risk of EOCs was lower in women with successful cycles resulting in live births (HR 0.54, 95% CI = 0.34-0.87), confirming the positive impact of parity. Histologically proven endometriosis was linked to a greater risk of non-serous cancer histotypes (HR 1.93, 95% CI = 1.04-3.61).

A higher BOT risk was identified in the group of infertile women who had undergone ART compared to those who had not (HR 1.84, 95% CI = 1.08-3.14), adjusted for age and parity. This was noteworthy especially in case of serous BOTs rather than other histotypes, and in subjects with tubal infertility.



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Other patient characteristics like causes of infertility (male factor, unexplained, endometriosis), response to the first IVF cycle and parity were also analyzed, and none were found to be related to increased incidence of BOTs.

Critical evaluation of the paper

The main study strengths are the **large cohort size and long and complete follow-up** (median: 24 years). However, despite such follow-up, relatively few women actually reached the age of maximum incidence of EOCs, curtailing the number of cases available for analysis. According to existing data, the present study confirms that **ART-treated women are not at increased risk of EOCs compared to non-ART-treated infertile women**. The elevated risk relative to the general population does appear to be due to the higher rate of infertility and nulliparity rather than the effect of ART treatments. By contrast, **the risk of developing BOTs was higher in ART-treated women than in the non-treated infertile group**.

Previously published data evidencing an increased risk compared to the general population (3,4) always considered such findings to be linked to patient characteristics of infertility and low parity. The present results challenge this assumption, leaving ample room for speculation. As **no clear dose-response relationship** was established (number of IVF cycles, response to first IVF cycle), repeated disruption of the ovarian epithelium causing damage does not appear to be the source of this elevated risk. A number of confounding factors may also play a role, including the severity of infertility or type of hormonal treatment, but this raises further questions as to why the risk is not reduced in the event of successful IVF.

Another limitation is the partial overlap of the population of women diagnosed with BOTs and those undergoing ART treatments for infertility. Indeed, subjects found to have ovarian tumors before or during ART treatments were excluded from this study. This may constitute another bias, as pre-existing patient characteristics (like **genetic abnormalities or alterations to the ovarian reserve**) may be responsible for both pathological infertility and BOTs, without one being the cause of the other.

Conclusion

In conclusion, data on the incidence of EOCs after ART treatments are reassuring, as they demonstrate that IVF does not appear to increase the risk. On the other hand, infertility and nulliparity remain key risk factors associated with EOCs. Regarding the relationship between BOTs, infertility and ART treatment, further research is needed to clarify the existence of causal association. This point appears is of crucial importance, as BOTs occurring at reproductive age may hamper fertility and are among the main oncological pathologies requiring feasible and effective fertility preservation strategies.

References:

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