Ovarian stimulation for IVF treatment increases risk of borderline ovarian tumors later in life

October 27 2011

Researchers from The Netherlands have found that subfertile women whose ovaries are stimulated into producing extra eggs for in vitro fertilisation (IVF) have an increased risk of ovarian malignancies, in particular borderline ovarian tumours, later in life.

The long-term risk for ovarian malignancies (ovarian cancer and borderline ovarian tumours) is twice as high among women who undergo ovarian stimulation for IVF compared with subfertile women not treated with IVF. This is due to the increased incidence of borderline ovarian tumours, according to the research, published online today (Thursday Oct. 27) in Europe's leading reproductive medicine journal Human Reproduction. In addition, the overall risk for malignant (invasive) ovarian cancer was not significantly increased in this group of subfertile women treated with IVF.

Lead researcher Professor Flora van Leeuwen, Head of the Department of Epidemiology in The Netherlands Cancer Institute, Amsterdam, said: "This study, with 15 years of follow-up, is the first to include a comparison group of subfertile women not treated with IVF. This is particularly important because IVF-treated women are different from the general population due to the fact that difficulty conceiving or never having been pregnant are known risk factors for an increased risk of developing ovarian malignancies. Women who were unable to conceive after one or more years of frequent unprotected sexual intercourse were

considered to be subfertile, and the main causes of subfertility observed in this study population were Fallopian tube problems, male subfertility, unexplained infertility and endometriosis."

The research was based on data from the OMEGA study, which is a large nationwide observational study examining the late-effects of hormone stimulation in women diagnosed with subfertility problems from all 12 IVF clinics in The Netherlands between 1980 and 1995. The study was conducted by Prof van Leeuwen in Amsterdam, Prof Curt Burger in the Obstetrics and Gynaecology Department of Erasmus University Medical Centre, Rotterdam and their colleagues in the other IVF clinics in The Netherlands. The investigators identified 19,146 subfertile women who received at least one IVF ovarian stimulation treatment and 6,006 subfertile women who were not treated with IVF. Data on reproductive factors were derived from a mailed questionnaire and subfertility treatment information was obtained from medical records. The incidence of ovarian malignancies (including borderline ovarian tumours) was assessed by linking these data with Dutch disease registries up to June 2007.

Prof van Leeuwen said: "We found that of the 25,152 subfertile women included in the analysis 77 had ovarian malignancies. Surprisingly, of the 61 women who had ovarian malignancies in the IVF treatment group, 31 had borderline ovarian cancer and 30 had invasive ovarian cancer. This proportion of ovarian borderline tumours was unusually high. Borderline ovarian tumours are tumours with a low malignancy potential, which means that they are not fatal, but would require extensive surgery and cause substantial morbidity."

After adjusting for factors that could confound the results such as age, how many children (if any) the women had already had, and cause of subfertility, the long-term risks for ovarian malignancies and borderline ovarian tumours were significantly elevated in the IVF treatment group

compared with the subfertile group of women not treated with IVF. For ovarian malignancies overall and for borderline ovarian cancer, there was a two- and four-fold higher risk, respectively, in the IVF treatment group compared with the subfertile group not treated with IVF. While the risk of invasive ovarian cancer was slightly increased in the IVF treatment group, this was not statistically significant.

Prof van Leeuwen said: "Our data clearly show that ovarian stimulation for IVF is associated with an increased risk of borderline ovarian tumours and this risk remains elevated up to more than 15 year after the first cycle of treatment."

Ovarian cancer is the eighth most commonly reported cancer, accounting for 3.7% of all female cancer cases. It usually occurs in older patients and it is the leading cause of gynaecological cancer death; more than 140,000 women died from the disease in 2008 worldwide.

"The individual risk of developing ovarian cancer or a borderline ovarian tumour is very low. In The Netherlands the cumulative risk of ovarian malignancies (including borderline ovarian tumours) before the age of 55 is 0.45% in the general population. The results of our analysis suggest this risk increases to about 0.71% for women who undergo IVF, with the increase being due to borderline tumours of the ovary," Prof van Leeuwen said.

"When we compared ovarian malignancy incidence with the general female population, we also found an increased risk of invasive ovarian cancer in the IVF treatment group after 15 years of follow-up. This is a cause of concern because this type of cancer usually requires extensive surgery and chemotherapy and has poor survival rates. However, this increase may be caused by how many children (if any) the women had already had in the IVF treatment group compared with the general female population. More research is needed to examine the risk of

invasive ovarian cancer, especially after a longer follow-up in IVF treated women," she said.

The researchers had expected that the risk of ovarian malignancies would increase with more IVF cycles but this was not observed. They intend to follow up their work by examining this issue further. "The total number of women with ovarian malignancies in this analysis was low (only 77 women), hence the statistical power of the study to investigate risk after many IVF cycles, or risk after long durations of follow-up, was limited," said Prof van Leeuwen. "We are currently expanding our study population to include another 8,800 women who started their IVF ovarian stimulation treatment during the years 1995-2000, with an emphasis on including women who have had three or more treatment cycles, and with 4,200 subfertile women not treated with IVF in the years 1980-2000," she added.

Prof van Leeuwen concluded: "If we find out that women who receive several IVF cycles or large doses of ovarian stimulating drugs are at a greater risk of ovarian cancer, then these women would need to be informed about these risks when continuing IVF treatment and possibly advised to discontinue treatment after three to six cycles (depending on which number of cycles would be associated with the high risk of ovarian malignancies)."

More information: "Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort", by FE van Leeuwen, H Klip, TM Mooij, AMG van de Swaluw, CB Lambalk, M Kortman, JSE Laven, CAM Jansen, FM Helmerhorst, BJ Cohlen, WNP Willemsen, JMJ Smeenk, AHM Simons, F van der Veen, JLH Evers, PA van Dop, NS Macklon and CW Burger. Human Reproduction journal. doi:10.1093/humrep/der322