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COMMENT & RESPONSE

Breast Cancer Risk After Ovarian Stimulation for In Vitro Fertilization

To the Editor The study by Dr van den Belt-Dusebout and colleagues[1] investigated a debated aspect of reproductive medicine: breast cancer risk following ovarian stimulation for in vitro fertilization (IVF).[2-5] The authors concluded that "these findings are consistent with absence of a significant increase in long-term risk of breast cancer among IVF-treated women."[1] However, some important points should be discussed.

For approximately 23% of women, subfertility diagnosis and number of IVF cycles were collected using a questionnaire because medical records were not available. This high rate threatens the reliability of results. It is not possible to compare a detailed report of official medical records with data deriving from subjective memory of treatments received many years before. This may be a strong bias, because reproductive medicine, IVF strategies, and the pharmacological protocols have changed rapidly in the last decades.

Dates of diagnosis and histology were reported but unfortunately not disease staging. It would be interesting to investigate if ovarian stimulation with the use of IVF techniques can promote the occurrence of biologically different types of breast cancer, as in the case of tamoxifen-related endometrial cancer, a neoplasia with better prognostic profile and outcome.

Also, the authors reported that breast cancer risk decreased with more IVF cycles (≥7 compared with 1-2). They suggested as potential explanations that women treated with more IVF cycles received more human chorionic gonadotropin or had longer periods of down-regulation with low estradiol and progesterone levels, or that the women requiring more IVF cycles were inherently different. It is difficult to provide a definitive conclusion because the clinical outcomes of IVF cycles were not reported. The decreased risk among women treated with many IVF cycles also could be related to the improvement of ovarian function after repeated endocrine stimulations. Infertility and infertility-related nulliparity must be considered as risk factors for breast cancer, and prolonged treatment of anovulatory or poor ovulatory cycles could be one approach for restoring normal ovarian activity and reducing breast cancer risk.

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In Reply Dr Tomao and colleagues are concerned that our results may be biased because, for 23% of the study population, information on subfertility diagnosis and number of IVF cycles was obtained from a self-administered questionnaire when medical records were not available. We felt confident using questionnaire data for subfertility diagnosis to limit the amount of missing data because de Boer and colleagues[1] reported that in the same study population, the validity of self-reported subfertility causes was satisfactory.

For the most frequent subfertility diagnoses, tubal and male subfertility (50% of all diagnoses), measures of agreement (using the κ statistic) were 0.79 for self-report vs 0.71 for medical record review. Also, adjustment for subfertility diagnosis did not change the risk estimates for the association between IVF and breast cancer. Because the most important reason for missing medical record data was that medical record abstraction could not be performed (in 3 of 12 clinics),[2,3] the

absent data are likely missing at random. When comparing questionnaire and medical record information regarding number of IVF cycles among women with both sources (n = 9769 [51%]), 80% of women were classified into the same category. Therefore, it is unlikely that using self-reported subfertility diagnosis and number of cycles for 23% would have biased the results.

Tomao and colleagues suggest that it would be interesting to investigate whether ovarian stimulation for IVF can promote the occurrence of biologically different types of breast cancer, as in the case of tamoxifen-related endometrial cancer. We agree this would be interesting; however, because IVF treatment was not associated with increased risk of breast cancer, we considered it less relevant to examine whether IVF treatment was associated with breast cancer type. To investigate whether exposure to many IVF cycles could be associated with decreased risk of specific breast cancer types, larger numbers of women with breast cancer would be needed.

We agree that the decreased breast cancer risk in women treated with many IVF cycles (≥7 compared with 1-2) might also be associated with the improvement of ovarian function after repeated endocrine stimulations, or there could be other possible explanations. In the analyses, we adjusted for parity and age at first birth as clinical outcomes of IVF, which were the only confounding factors. Other clinical outcomes (ie, cancelled cycles, ovarian hyperstimulation syndrome, poor response to first IVF cycle, and duration of gestation <24 weeks) did not influence the results. However, we did not have measures of estradiol and progesterone levels to draw definitive conclusions.

In our study, infertility and infertility-related nulliparity were not associated with increased risk of breast cancer. We think that anovulatory or poor ovulatory cycles should be treated to restore normal ovarian activity if women wish to have a child or are hindered by their irregular ovulatory cycles, regardless of a potential reduction of breast cancer risk.

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Colorectal Cancer Screening

To the Editor To inform the recently updated guidelines from the US Preventive Services Task Force (USPSTF) on colorectal cancer (CRC) screening,[1] Dr Lin and colleagues conducted a meta-analysis of randomized trials of different screening interventions, including flexible sigmoidoscopy.[2] Unfortunately, the authors pooled different age groups in the Norwegian Colorectal Cancer Prevention Trial (NORCCAP)[3] to calculate the summary mortality estimate for flexible sigmoidoscopy screening. Methodologically, we do not think this approach is correct because pooling the age groups introduced confounding by age.

In NORCCAP, individuals aged 55 to 64 years were randomized to screening or usual care in a 1:3 ratio, and individuals aged 50 to 54 years were randomized in a 1:5.4 ratio. The mean age was well balanced within each age group. However, owing to uneven randomization ratios, individuals in the usual care group were, on average, younger than those in the screening group (mean age, 56.1 years in the usual care group and 56.9 years in the screening group). As a result, a valid summary estimate of the trial data has to take this imbalance into account.

To understand why this is necessary, consider both age groups (50-54 years and 55-64 years) separately. The relative risk (RR) for CRC mortality in the group aged 50 to 54 years was 0.74 (95% CI, 0.40-1.35), and the RR in the group aged 55 to 64 years was 0.73 (95% CI, 0.55-0.97).[3] However, when the 2 age groups were pooled, the crude RR for CRC mortality was 0.80 (95% CI, 0.62-1.04).[2]

Lin and colleagues acknowledged that they used crude rates in their meta-analysis, but in doing so, the summary estimate for the effectiveness of flexible sigmoidoscopy screening on CRC mortality was incorrect. To avoid introducing confounding by age, the 2 age groups in NORCCAP should have been analyzed as separate trials. This approach does not have a serious effect on the result reported in the meta-analysis because NORCCAP was a relatively small trial compared with some of the other trials.

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