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RE: Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status

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We read the article by Lambertini et al. with great interest (1). This case–control study showed that, at a median follow-up of 7.2 years for women with a history of estrogen receptor (ER)–positive or ER-negative breast cancer (BC), there was no difference in disease-free survival between women who became pregnant and those who did not. Overall survival (OS) of the ER-positive patients was unaffected by pregnancy (hazard ratio [HR] = 0.84, 95% confidence interval [CI] = 0.60 to 1.18, $P = .32$), but, surprisingly, ER-negative patients who became pregnant had a longer median survival than those who did not (HR = 0.57, 95% CI = 0.36 to 0.90, $P = .01$). While these results appear reassuring to the many young BC survivors who so desperately wish to become pregnant, we are concerned about a possible source of bias that would be almost impossible to eliminate in a retrospective study of this nature.

That bias is the unknown number of women who underwent tests to exclude subclinical metastatic disease prior to attempting pregnancy. As women who are found to have metastatic disease as part of a prepregnancy evaluation would presumably choose to forgo pregnancy and restaging tests are not the standard of care for asymptomatic BC survivors, this would automatically give the pregnancy cohort a prognostic advantage.

To what extent might this affect the study results? In our PYNK cohort (2) (unpublished data), approximately 10% of the women restaged prior to attempting pregnancy were found to have occult metastatic disease. Let us assume conservatively that in the study by Lambertini et al. 50% of the 210 women who either completed their pregnancy or had a spontaneous abortion underwent restaging tests, but 10% of these women would have been excluded from the pregnancy cohort due to the discovery of metastatic disease. Based on these assumptions, 12 additional hypothetical women destined to relapse and die of metastatic disease need to be added to the 333 women in the pregnant cohort in order to compare it with the 874 women in the nonpregnant cohort (who would not have had restaging tests).

Without access to the raw data, we are unable to calculate the impact this might have on the hazard ratios for recurrence and death in the current study, particularly for the ER-positive patients. Of greater concern, however, is the fact that in the ongoing international prospective POSITIVE study (3), any restaging will be done prior to study enrollment. As to date that study has only recruited approximately one-third of its target of 500 women, we strongly urge the principal investigators to modify the protocol. We suggest adding a pre-enrollment phase to the study, in which patients being considered for POSITIVE are registered prior to their restaging tests and followed for recurrence and survival regardless of whether they ultimately participate in the full study.

References

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