Editorial Commentary

Pregnancy wishes after breast cancer—an unsettled conflict solved?

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Breast cancer is the most common type of cancer also in women of premenopausal age (1). After surgery and possible radiotherapy and (neo)adjuvant chemotherapy, the patients with estrogen receptor-positive early-stage breast cancer are almost always treated with 5–10 years of adjuvant endocrine therapy. With all these treatment modalities, the 5-year relative survival rate of premenopausal women now exceeds 90% in developed countries, although young age itself is one of the established adverse prognostic factors (2,3). Due to excellent outcomes in the earliest stages of invasive breast cancer, both the therapy de-escalation and ways to improve post-diagnostic quality of life have gained much attention during the recent years.

As more women are having breast cancer in their 30's or early 40's, the possibility to become pregnant after early-stage breast cancer diagnosis is not an uncommon topic of discussion in the appointments of breast oncologists. The impact of adjuvant endocrine therapies on prognosis is substantial and there is a clear correlation between the low adherence to endocrine therapy and the increased risk of breast cancer relapse (4-7). Again, all adjuvant endocrine therapies are embryotoxic. Although previous retrospective data suggest that pregnancy after a breast cancer diagnosis does not associate with worse outcomes, there has been a lack of prospective studies if it is safe to temporarily discontinue adjuvant endocrine therapy to attempt pregnancy (8,9).

In the POSITIVE trial (10), a prospective single-group study covering 516 women under 43-year-old with early-stage hormone receptor-positive breast cancer, the research questions were clear: (I) is a temporary break in adjuvant endocrine therapy to attempt pregnancy associated with adverse breast cancer-related outcomes; and (II) what are the pregnancy and birth rates in these women. The interruption in endocrine therapy was allowed after receiving previously 18–30 months of the adjuvant endocrine therapy, the break lasting up to 2 years. According to the reported results, 85% of the patients indeed were resuming their endocrine treatment, most usually tamoxifen, after the interruption. In this trial at least 3-month washout period from endocrine therapy was required before attempting pregnancy. Although patients with stage I to III were allowed to participate in the study, it is worth to note that 93% of women finally enrolled had stage I–II disease of generally good prognosis.

Also, the main results were rather unambiguous. The interruption of the endocrine therapy was safe: the 3-year incidence of breast cancer events was 8.9% in the treatment-interruption group and 9.2% in the external control cohort. Of the 44 observed breast cancer events in the treatment-interruption patients, half were distant recurrences, which are still considered almost always as non-curable. The

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median follow-up was only 3.4 years at the time of data cut-off, while most of the recurrences in hormone receptor-positive breast cancer are diagnosed after several years post-diagnosis. There will be 10-year follow-up in this trial, which will later show the effect of the endocrine therapy discontinuation on these, often biologically diverse diseases compared to early recurrences.

The results were consistent in all other pre-specified subgroups, but for some reason the 3-year cumulative incidence of breast cancer events was over two-fold in the patients treated with mastectomy (12.7%), compared with the patients who underwent breast-conserving surgery (5.7%). This observation was not discussed in the article, nor in the accompanying editorial (11), but it may be related to larger or more multifocal tumors in the mastectomy-treated group, which patients could carry a higher risk of recurrence and would in theory be more vulnerable to interruptions in the endocrine therapy.

The potential loss of fertility is frequently a distressing factor for young women with breast cancer, although several methods have been developed to improve pregnancy rates in these women (12). Thus, it was consoling that 74.0% of the patients with the pregnancy status available became pregnant during the trial, especially considering that ovarian-suppressing adjuvant chemotherapy was administered to 62% of the participants. Two-thirds of the pregnancies occurred even during the first year after the endocrine therapy interruption. Forty-three point three percent of the women had used assisted reproductive technology and the rate of the birth defects (2.2%) is in line with the general population.

Already these short-term results are relieving for this enlarging subgroup of young breast cancer patients, but long-term follow-up is still crucial. The current paper focused on the primary, very down-to-earth objectives of the POSITIVE study. There will be a great interest for the translational research endpoints, which will compare e.g., the ovarian function and ovarian reserve, the tissue samples from endometrial biopsies and circulating tumor DNA levels to the clinical endpoints. Results from these translational analyses have potential to yield novel knowledge on the women with highest risk of recurrence during the endocrine therapy interruption and to predict who would have the highest need for assisted reproductive technologies. Meanwhile, physicians can already incorporate these positive results to their discussions with patients. Implementation to clinical guidelines will very likely follow soon.

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References

1. International Agency for Research on Cancer. Cancer today. Accessed August 8th 2023. Available online: https://gco.iarc.fr
2. Thomas A, Rhoads A, Pinkerton E, et al. Incidence and Survival Among Young Women With Stage I-III Breast Cancer: SEER 2000-2015. JNCI Cancer Spectr 2019;3:pkz040.
3. Taylor C, McGale P, Probert J, et al. Breast cancer mortality in 500 000 women with early invasive breast cancer diagnosed in England, 1993-2015: population based observational cohort study. BMJ 2023;381:e074684.
4. Tamoxifen for early breast cancer. Cochrane Database Syst Rev 2001;(1):CD000486.

5. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. J Clin Oncol 2016;34:1689-701.
6. Francis PA, Pagani O, Fleming GF, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med 2018;379:122-37.
7. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011;126:529-37.
8. Lambertini M, Blondeaux E, Bruzzone M, et al. Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis. J Clin Oncol 2021;39:3293-305.
9. Anderson RA, Lambertini M, Hall PS, et al. Survival after breast cancer in women with a subsequent live birth: Influence of age at diagnosis and interval to subsequent pregnancy. Eur J Cancer 2022;173:113-22.
10. Partridge AH, Niman SM, Ruggeri M, et al. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. N Engl J Med 2023;388:1645-56.
11. Giordano SH. POSITIVE Results for Breast Cancer Survivors Who Desire Pregnancy. N Engl J Med 2023;388:1709-10.
12. Waks AG, Partridge AH. Fertility Preservation in Patients With Breast Cancer: Necessity, Methods, and Safety. J Natl Compr Canc Netw 2016;14:355-63.

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