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To interview Ann Partridge or Olivia Pagani, please contact Julia Gunther at julia.gunther@aacr.org or 770-403-7690. For a photo of Partridge, click here. For a photo of Pagani, click here.

Breast Cancer Patients Who Interrupted Endocrine Therapy to Pursue Pregnancy Did Not Experience Worse Short-term Recurrence Rates

Most were able to conceive and more than 60 percent gave birth

SAN ANTONIO – Breast cancer patients who paused their endocrine therapy to try to get pregnant experienced short-term rates of breast cancer recurrence similar to women who did not pause therapy for pregnancy, and many went on to conceive and deliver healthy babies, according to results from the POSITIVE clinical trial presented at the San Antonio Breast Cancer Symposium, held December 6-10, 2022.

While breast cancer is most commonly diagnosed in middle-aged and older women, in the United States, about 5 percent of new diagnoses each year occur in women aged 40 or younger. These younger patients face some unique considerations, including fertility, said the North American study's lead author, Ann Partridge, MD, MPH, vice chair of medical oncology at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School.

"Forty to 60 percent of patients who are diagnosed with breast cancer at age 40 or younger are concerned about their future fertility, especially if the disease occurs before they could decide whether to become a mother or not," she said.

Coauthor Olivia Pagani, MD, who is the international study chair on behalf of the International Breast Cancer Study Group, said only about 5 to 10 percent of younger breast cancer patients go on to become pregnant. While some retrospective studies have shown that pregnancy after cancer is feasible and safe, many women are concerned that breast cancer treatment will make it difficult to conceive or that pregnancy might exacerbate a woman's cancer, explained Pagani, who is also a member of the Swiss Group for Clinical Cancer Research, a faculty member at the Universities of Geneva and Lugano, and a member of the European School of Oncology.

Young women with early-stage hormone receptor (HR)-positive breast cancer are often treated with endocrine therapy, such as ovarian function suppression, aromatase inhibitors, or selective estrogen receptor modulators. To examine the impact of pausing endocrine therapy to pursue pregnancy, researchers designed the single-arm POSITIVE clinical trial (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer). From December 2014 through December 2019, 518 women aged 42 or younger who desired to become pregnant enrolled in the study, opting to pause endocrine therapy for approximately two years to try to get pregnant. Before pausing their treatment, women had completed between 18 and 30 months of adjuvant endocrine therapy.

The study enrolled patients from 116 centers across 20 countries; 23 percent from North America, 61 percent from Europe and 16 percent from Asia/Pacific and Middle East nations. A data safety monitoring committee conducted three interim safety analyses. If more than 46 breast cancer recurrences occurred within approximately three years of average follow-up, the trial would have been suspended. That threshold was not reached.

At a median follow-up of 41 months, 44 participants had experienced a recurrence of breast cancer. The three-year rate of recurrence was 8.9 percent, similar to the 9.2 percent rate in an external control cohort from the SOFT/TEXT trials, which examined adjuvant endocrine therapy in premenopausal women.

Of 497 women followed for pregnancy status, 368 (74 percent) had at least one pregnancy, and 317 (63.8 percent) had at least one live birth, with a total of 365 babies born. These rates of conception and childbirth were on par with or higher than rates in the general public, Pagani said.

Trial participants were strongly recommended to resume endocrine therapy after a pregnancy attempt or success. To date, 76.3 percent have resumed their therapy, the authors said.
Partridge and Pagani said the study provides encouraging guidance to younger women diagnosed with breast cancer who may be hoping to have children. Any such decisions should be made in close consultation with health professionals, they noted.

“The POSITIVE Trial provides important data to support young women with HR-positive early breast cancer who are interested in a pregnancy and taking a break from endocrine therapy to pursue one,” said Partridge, who led the study in North America on behalf of the Alliance for Clinical Trials in Oncology. “Pregnancy after breast cancer is a very personal decision for which, ideally, a woman should take into account not only her desire to carry a pregnancy, but her baseline fertility, prior and current treatment, and any fertility preservation strategy she may have pursued, as well as the underlying risk of cancer recurrence she faces,” Pagani said.

The researchers are continuing to follow the study participants to assess recurrence risk over time. They noted that the short follow-up to date is a limitation of the POSITIVE study, as HR-positive breast cancer can recur many years after an initial diagnosis.

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Abstract

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Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer: Primary Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13)

Presenting Author: Ann Partridge, MD, MPH – Dana-Farber Cancer Institute

Background: Pregnancy after breast cancer (BC) is of substantial importance for many young women at diagnosis and during follow-up. BC treatment including standard endocrine therapy (ET) (5-10 years) may reduce ovarian reserve and the chances of subsequent successful pregnancy, given conception is contraindicated during ET. A temporary interruption of ET to attempt and carry a pregnancy in this population has never been prospectively studied. **Methods:** POSITIVE is a single-arm, prospective, investigator-initiated, international trial evaluating the safety and pregnancy outcomes of interrupting ET for young women with early-stage hormone-receptor-positive (HR+) BC who desire pregnancy. The primary objective is to assess the risk of BC relapse associated with ET interruption for ~2 years to achieve pregnancy. Women ≤42 years with stage I-III HR+ BC who received adjuvant ET (SERM alone, GnRH analogue plus SERM or AI) for 18 to 30 months and wished to interrupt ET to attempt pregnancy were eligible. The primary endpoint is breast cancer free interval (BCFI) defined as the time from enrollment to the first BC event (local, regional, distant recurrence or a new invasive contralateral BC). Planned sample size was 500 patients. Three interim analyses of BCFI were reviewed by the Data Safety Monitoring Committee (DSMC) to assure a 95% chance of stopping the trial early if the annual BCFI event rate exceeded 4%; with primary analysis triggered after 1600 patient years of follow-up (pyfu) and no more than 46 BCFI events defined as the safety threshold. The DSMC recommended continuing the study following each interim analysis. We now report the primary results. **Results:** From 12/2014 to 12/2019, 518 women were enrolled. At enrollment, the median age of participants was 37 years (27-43 years); 75.0% were nulliparous, 93.4% had stage I/II disease, 66.3% node-negative. Median time from BC diagnosis to enrollment was 29 months (IQR: 25-32). Tamoxifen alone was the most prescribed ET (41.7%), followed by tamoxifen+ovarian function suppression (35.7%). 62.0% of participants had received neo/adjuvant chemotherapy. At a median follow-up of 41 months (1638 pyfu), 44 participants had experienced a BCFI event, not exceeding the pre-specified safety threshold of 46 events. The 3-year BCFI failure percent was 8.9% (95% CI: 6.3 to 11.6%), similar to the 9.2% (95% CI: 7.6 to 10.8%) calculated in the comparative external control cohort from the SOFT/TEXT trials (Sun et al, Breast 2020). Of 497 women followed for pregnancy status, 368 (74.0%) had at least one pregnancy, 317 (63.8%) had at least one live birth, with a total of 365 babies born. Based on competing risk analysis, 76.3% of patients resumed ET (half within 26 months), 8.3% had BCFI event/death before ET resumption, and 15.4% had not resumed ET yet. **Conclusions:** The POSITIVE trial demonstrates that for young women with early HR+ BC desiring pregnancy, temporary interruption of ET to attempt pregnancy does not confer a greater short-term risk of recurrence than that observed in a modern historical control group that did not interrupt ET. Most participants have had a live birth. Further follow-up is planned to confirm long-term safety. These results should be considered in counselling BC patients desiring future pregnancy.

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