ORIGINAL ARTICLE: INFERTILITY

Impact of tamoxifen therapy on fertility in breast cancer survivors

Lisa M. Shandley, B.A.,[a] Jessica B. Spencer, M.D., M.Sc.,[b] Amy Fothergill, M.P.H.,[c] Ann C. Mertens, Ph.D.,[d] Amita Manatunga, Ph.D.,[e] Elisavet Paplomata, M.D.,[f] and Penelope P. Howards, Ph.D.[c]

[a] School of Medicine; [b] Department of Gynecology and Obstetrics, School of Medicine; [c] Department of Epidemiology, Rollins School of Public Health; [d] Aflac Cancer Center, Department of Pediatrics, School of Medicine; [e] Department of Biostatistics, Rollins School of Public Health; and [f] Winship Cancer Institute, Department of Hematology and Medical Oncology, School of Medicine, Emory University, Atlanta, Georgia

Objective: To determine whether tamoxifen use is associated with decreased ovarian reserve and decreased likelihood of having a child after a breast cancer diagnosis, using data from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women Study.
Design: Population-based cohort study.
Setting: Not applicable.
Patient(s): Three hundred ninety-seven female breast cancer survivors aged 22–45 years whose cancer was diagnosed between ages 20 and 35 years and who were at least 2 years after diagnosis; 108 survivors also participated in a clinic visit.
Intervention(s): None.
Main Outcome Measure(s): Time to first child after cancer diagnosis, clinical measures of ovarian reserve (antimüllerian hormone [AMH] and antral follicle count [AFC]) after cancer.
Result(s): Women who had ever used tamoxifen were substantially less likely to have a child after the breast cancer diagnosis (hazard ratio [HR] 0.29; 95% confidence interval [CI], 0.16, 0.54) than women who had never used tamoxifen. After adjusting for age at diagnosis, exposure to an alkylating agent, and race, the HR was 0.25 (95% CI, 0.14, 0.47). However, after adjusting for potential confounders, women who had used tamoxifen had an estimated geometric mean AMH level 2.47 times higher (95% CI, 1.08, 5.65) than women who had never taken tamoxifen. Antral follicle count was also higher in the tamoxifen group compared with the tamoxifen nonusers when adjusted for the same variables (risk ratio 1.21; 95% CI, 0.84, 1.73).
Conclusion(s): Breast cancer survivors who had used tamoxifen were less likely to have a child after breast cancer diagnosis compared with survivors who never used tamoxifen. However, tamoxifen users did not have decreased ovarian reserve compared with the tamoxifen nonusers. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Breast cancer, cancer survivorship, infertility, ovarian reserve, tamoxifen

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Advances in breast cancer screening, detection, and treatment have led to a 5-year breast cancer survival rate of over 80% (1). As survival rates have improved, there has been an increased focus on the complex issues associated with breast cancer survivorship, including fertility and family planning. According to the Young Women's Breast Cancer Study, 50% of women younger than 40 years expressed concerns about future fertility and the possibility of pregnancy after chemotherapy and radiation treatment (2).

Between 55% and 70% of women aged 30 to 50 years with a breast cancer diagnosis have a malignancy that is responsive to and stimulated by hormones (3). Since the 1980s, it has been the standard of care to treat hormone-sensitive breast cancer with antiestrogen medications (4). Tamoxifen, a selective estrogen receptor modulator, binds to estrogen receptors and inhibits the action of estrogen in breast tissue. It is the first-line agent for premenopausal women diagnosed with early breast cancer (4). Tamoxifen is considered an endocrine disruptor, and thus is thought to be cytostatic rather than cytotoxic (5, 6). When taken daily for the recommended

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Reprint requests: Lisa M. Shandley, B.A., Emory University School of Medicine, 100 Woodruff Circle, Atlanta, Georgia 30322 (E-mail: Lisa.Shandley@emory.edu).

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5 years, tamoxifen has been shown to statistically significantly improve survival in women with early breast cancer who remain premenopausal during treatment, reducing breast cancer mortality at 15 years after diagnosis by about one-third (risk ratio [RR] 0.70; 95% confidence interval [CI], 0.60, 0.80) compared with women who did not take tamoxifen (7). More recent data from the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial found that 10 years of treatment with tamoxifen can further reduce mortality by an additional 30% when compared with 5 years of treatment with tamoxifen (RR 0.71 for 10 years compared with 5 years; 95% CI, 0.58, 0.88) (8).

Despite the survival benefit, a recent study found that 13.4% of women decline initiation of tamoxifen and another 15.5% discontinue it earlier than the recommended 5 years (9). The same study found that 35% of women cited concerns about fertility as a factor in their decision to not take tamoxifen, despite a lack of conclusive epidemiologic or experimental evidence regarding tamoxifen's effect on fertility (9). Tamoxifen is more selective than conventional chemotherapies and thus is assumed to be have fewer systemic side effects compared with traditional treatments. Yet, tamoxifen has been shown to induce ovarian cysts (10) and endometrial polyps (11). However, the long-term effects of tamoxifen on fertility remain unknown.

During the past 10 years antimüllerian hormone (AMH) has been used as a clinical marker of fertility that quantifies the number of remaining primordial follicles in the ovaries and has become an accepted, sensitive marker of ovarian reserve (12). Breast cancer survivors exposed to chemotherapy have been shown to have statistically significantly lower AMH levels compared with women unexposed to chemotherapy (13–19). However, it is not clear whether tamoxifen has an additional, independent or possibly even synergistic effect on reducing ovarian reserve beyond the effect of standard chemotherapy for breast cancer. Additionally, no currently published studies investigate the effect of long-term tamoxifen use on later conception and successful pregnancy. The primary objective of this study was to assess how long-term tamoxifen treatment affects rates of childbirth and ovarian reserve in breast cancer survivors.

MATERIALS AND METHODS

Study Population

We used data from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women Study. The FUCHSIA Women Study is a population-based study examining the effect of cancer treatment during the reproductive years on future fertility. Eligible cancer survivors were identified in collaboration with the Georgia Cancer Registry. The eligibility criteria included female sex; a reportable malignant cancer (20) or ductal carcinoma in situ diagnosed between the ages of 20 and 35; cancer diagnosis between 1990 and 2009; age 22 to 45 at the time of enrollment in the study between 2012 and 2013; and at least 2 years since cancer diagnosis at enrollment. The eligible survivors were invited to participate in a detailed telephone interview about their reproductive histories.

The present analysis was restricted to the 397 survivors whose first cancer diagnosis recorded in the Georgia Cancer Registry was breast cancer and who had not had a hysterectomy or bilateral oophorectomy before their cancer diagnosis. A subset of women with a uterus and at least one ovary were invited to participate in a substudy to assess clinical markers of fertility; 108 breast cancer survivors completed a clinic visit. The institutional review boards of Emory University and the Georgia Department of Public Health approved this study.

Procedures

All study participants completed a computer-assisted telephone interview to ascertain demographics, cancer history, menstrual history, desire for children, infertility history, pregnancy history, surgical history, use of medications including hormone medications, and lifestyle.

Information regarding cancer diagnosis and treatment, including treatment with tamoxifen, was abstracted from medical records. All available records from diagnosis to present day or end of treatment were reviewed. Tamoxifen exposure was defined as at least 6 months of ever using tamoxifen. Tamoxifen treatment documented in the medical records was compared with self-reported answers in the interview. Participants with discrepant answers who reported never being exposed to tamoxifen but had clearly documented evidence of tamoxifen use in their medical records were reclassified into the tamoxifen group ($n = 5$). Women who reported taking tamoxifen but whose medical records clearly indicated that tamoxifen was taken for less than 6 months were classified as not taking tamoxifen ($n = 12$). There were 21 women who reported a history of tamoxifen use but whose duration of use could not be confirmed due to incomplete available medical records; these 21 women remained in the tamoxifen group per self-report. There were also 25 women in the group that reported never taking tamoxifen who did not have available medical records to confirm their self-report. Women who took tamoxifen and women with documented hormone receptor status in the medical records were considered to be hormone-receptor positive (ER/PR+).

Clinic visits took place at participating reproductive clinics across the state of Georgia. Clinic visits included a blood draw and a transvaginal ultrasound. Transvaginal ultrasounds were performed by a trained sonographer who measured ovarian volume for each ovary and antral follicle count (AFC, follicle sizes 2–10 mm). Inter-rater reliability of AFC could not be calculated because only one sonographer scanned each participant; however, all ultrasound reports were reviewed by a single reproductive endocrinologist (J.B.S.). Blood was drawn to measure serum AMH. Serum AMH levels were measured in duplicate by an enzyme-linked immunosorbent assay (ELISA) (UltraSensitive AMH/MIS ELISA; Ansh Labs). For participants whose AMH was undetectable by the UltraSensitive assay, samples were measured in duplicate using the Ansh Labs picoAMH ELISA with an assay sensitivity of 0.006 ng/mL.