



Reproductive Health Issues for Young Women with Breast Cancer: Emerging Strategies for Difficult Situations

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Young women with breast cancer are a relative minority of breast cancer survivors, with women under 45 years of age representing only approximately 10% of those diagnosed with breast cancer in the US;¹ however, that translates to an estimated 26,000 young women diagnosed annually in the US alone, and thousands more worldwide. Furthermore, the absolute number of young women at risk for breast cancer is growing, positioning breast cancer as an increasingly significant health issue for this population.² While breast cancer at any age can impact one's physical and emotional health and well-being, young women and their loved ones may be more burdened by the disease and associated treatment compared with older women. Fertility, family planning, and pregnancy are unique issues that may be particularly important and difficult to contend with among these patients.

In this issue of *Annals of Surgical Oncology*, Shah et al. add to the growing literature focusing on young women with breast cancer by reviewing fertility preservation strategies and the management of pregnancy-associated breast cancer (PABC), two different clinical situations where patients' reproductive goals may become intertwined with their cancer treatment.³ Shah et al. highlight that fertility may be negatively affected by breast cancer treatment, either through the direct gonadotoxic effects of therapeutics or by the necessity to delay conception until the completion of adjuvant therapy, i.e. several years in the case of endocrine therapy. A general understanding of a woman's infertility risk is critical to effective fertility preservation counseling; however, in practice, making

these estimates can be challenging. For example, in a retrospective study of premenopausal breast cancer patients, the odds ratio of developing chemotherapy-related amenorrhea (CRA) was 10.1 and 39.5 in patients aged 35–39 years and 40–44 years, respectively, compared with patients younger than 35 years.⁴ Given this steep increase in CRA risk over a relatively short time span, discussing average CRA rates is of limited value, and even age-specific estimates lack precision for an individual. Further complicating the prediction of fertility, resumption of menstruation does not necessarily imply fertility, and some studies have shown that post-chemotherapy ovarian reserve may be diminished despite continued menses, possibly more so in BRCA mutation carriers.^{5,6} Biomarkers such as serum anti-Müllerian hormone (AMH) have promise as measures of ovarian reserve, however predictive capabilities have yet to be sufficiently determined and further research is needed.⁷

Strategies for the preservation of fertility in breast cancer patients, as reviewed by Shah et al., include gonadotropin-releasing hormone (GnRH) agonist administration concomitant with chemotherapy, embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation.³ The field of oncofertility has made significant advances in recent years and has managed to address early concerns regarding treatment delay and the use of exogenous hormones, which may have hindered the initial adoption of these procedures for breast cancer patients. Over 50% of young women diagnosed with breast cancer are concerned with future infertility, and international guidelines recommend early discussion and referral of patients interested in fertility preservation to fertility specialists.⁸ Nevertheless, fertility and fertility preservation have been historically under-addressed by providers, and female cancer survivors, especially those with a history of breast cancer, are significantly less likely to have a subsequent pregnancy compared with controls (hazard ratio

0.33, 95% confidence interval 0.27–0.39).⁹ Barriers to the implementation of fertility preservation strategies include inadequate patient–provider communication about infertility risks and resources, inefficient referral pathways, insufficient provider expertise, psychosocial concerns, uncertainty as to the effect on survivorship, and cost.¹⁰ Unaddressed patient fertility concerns may adversely affect not only quality of life but also quantity of life by impacting adherence to treatment recommendations. In a recent survey of young women with newly diagnosed early breast cancer, 26% of women reported that concerns about fertility affected their treatment decisions, either by choosing not to receive chemotherapy, preferring one regimen over another, deciding not to initiate endocrine therapy, or considering a shorter than recommended duration of treatment.⁸ Thus, there are still critical efforts to be made in devising models of care to help providers better address fertility issues, adhere to guidelines, and provide optimal cancer care.

PABC is another unique situation in which the reproductive needs of a young woman with breast cancer introduce challenges to her treatment. While PABC is historically defined as breast cancer occurring during pregnancy or within 1–2 years after a pregnancy, these are two distinct situations and should be considered as such, both clinically and from a research standpoint.¹¹ Shah et al. focus on breast cancer during pregnancy (BCP) rather than a breast cancer arising shortly after a pregnancy (breast cancer post-partum [BCPP]).³ There has been debate around the prognosis of women with PABC, much of which is attributable to the frequent conflation and grouping together of BCP and BCPP. Early case–control studies, and, later, a large 30-study meta-analysis, reported a higher risk of death for PABC.^{12,13} However, overall differences were driven by the inferior survival of BCPP cases. In two large Scandinavian population-based studies, women with BCPP had a higher risk of mortality than women with BCP.^{14, 15} In a more recent effort using a multicentric registry and focusing only on patients with BCP, similar outcomes were observed compared with non-pregnant controls.¹⁶ Taken together, while historically BPC patients may have had a worse prognosis due to diagnostic delay, undertreatment or understaging, contemporary data do not indicate a worse prognosis.

In contrast, as consistently observed in the aforementioned analyses, when separating BPC and BCPP, BCPP seems to confer an inferior prognosis. Moreover, in a recent pooled analysis of nearly 900,000 women from 15 prospective cohorts, parity was associated with an increased risk of breast cancer for more than 20 years after childbirth, peaking at around 5 years.¹⁷ Pregnancy and the postpartum state appear to be influencing breast cancer in different ways. BCP is associated with a high expression of

RANK-L, low number of tumor-infiltrating lymphocytes, and an enrichment of mismatch repair deficiency signatures.^{18–20} Conversely, BCPP may be driven by microenvironmental changes associated with mammary involution, including collagen deposition and cyclooxygenase (COX)-2 activity.²¹ The current management of PABC should follow standard treatment guidelines as closely as possible, with only minor adaptations made for gestational age, teratogenicity, and parental preferences. Efforts are warranted to further study the unique host and disease molecular underpinnings in BCPP in particular.

The treatment of breast cancer in young women is closely linked to female reproduction in a variety of clinical scenarios. Optimal management requires expertise and access, as well as candid communication of goals and risks by patients and providers. Recognizing the need for further understanding, an increasing number of studies are focusing on the medical and psychosocial issues of young women with breast cancer, including prospective trials such as the Young Women's Breast Cancer Study (NCT01468246) in the US, the PREFER study (NCT02895165) in Italy, and the POSITIVE trial (NCT02308085) internationally. The necessity to elucidate and communicate the unique concerns and outcomes among young women has been widely accepted by international professional societies whose efforts have culminated in the establishment of international consensus guidelines for breast cancer in young women.²² Shah and colleagues highlight two complicated situations in which clinicians should not only have the knowledge but also be able to support patients to sometimes make difficult decisions, and potential compromises about their reproductive goals or cancer care.³ Attitudes and practices in this setting are still disparate and continued educational initiatives of multidisciplinary teams are pertinent.²³ Shah et al. as well as *Annals of Surgical Oncology*, are to be commended on their effort to highlight these important issues for young breast cancer patients.

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