Review Article

BREAST CANCER IN YOUNG WOMEN AND ITS IMPACT ON REPRODUCTIVE FUNCTION

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Breast cancer is the most common cancer in women in developed countries. Chemotherapy for breast cancer is likely to negatively impact on reproductive function.We review current treatment; effects on reproductive function; breastfeeding and management of menopausal symptoms following breast cancer.

Key words: Breast Cancer, Fertility, Pregnancy, Menopause.

BREAST cancer is the most common cancer in women in developed countries, and 12% breast cancer occur in women between 20-34 yrs. Survival from breast cancer has significantly improved, and potential late effects of treatment and the impact on quality of life have become increasingly important. Young women constitute a minority of breast cancer patients, but commonly have distinct concerns and issues compared with older women, including queries regarding fertility, contraception and pregnancy. Reproductive medicine specialists and gynecologists commonly see these women either shortly after initial diagnosis or following adjuvant therapy and should be aware of current management of breast cancer, the options for women at increased genetic risk, the prognosis of patients with early stage breast cancer and how adjuvant systemic treatments may impact reproductive function. In particular, the potential impact of fertility treatments on hormone receptor positive breast cancer needs to be considered and discussed. The reproductive medicine specialist and gynecologist should be aware of current protocols for counseling, surveillance and management of women who carry genetic mutations which may increase their risk for breast, endometrial and ovarian cancer. The incidence of breast cancer by age is shown in *Table* 1.

Approximately 2% of breast cancer occurs in young woman between 20-34 years of age and 11% between 35-44 years.

BREAST CANCER SUSCEPTIBILITY GENE CARRIERS

Hereditary breast cancer accounts for 5-10% of all breast carcinomas and most are attributed to autosomal dominant germline mutations in breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) . The likelihood of a BRCA mutation is higher in women with breast cancer under the age of 45 with a strong family history of breast and/or ovarian cancer. Although there is some variability between different series, there are population-based studies that have demonstrated BRCA1 and BRCA2 mutations in 9% of women under 40. In the study of Loman *et al*. [1], the subset of women with a strong family history of breast or breast/ovarian cancer had almost a 40% risk of carrying a BRCA1 or BRCA2 mutation. There are also a number of other less common breast cancer susceptibility genes and syndromes that are beyond the scope of this review. Women with BRCA gene mutations tend to develop breast cancer at a younger age and are at greater risk of bilateral breast cancer at presentation as well as increased risk of subsequently developing a contralateral breast cancer. BRCA 1 mutation carriers have a 50-80-% lifetime risk of breast cancer and a risk of 40-60% risk of ovarian cancer, with the median age

Table 1. Incidence of breast cancer by age

Age	Annual incidences/100000 women
<20	0.1
20-24	1.4
25-29	8.1
30-34	24.8
35-39	58.4
40-44	116.1
45-49	198.5

at diagnosis in the mid 40s. The breast cancer risk is similar in BRCA2 mutation carriers, but the lifetime risks of Ovarian Cancer is ~15% and tend to occur in post-menopausal women in their 60s. For BRCA mutation carriers diagnosed with breast cancer, the risk of a recurrence or a new primary in the ipsilatereral breast in women who have breast conserving surgery is estimated to be as high as 20-50% at 10 years, and the lifetime risk for a contra lateral second primary cancer is ~ 40-60% in women diagnosed with breast cancer under 40 years [2].

The management of women with BRCA mutation is complex, requires a multi-disciplinary team approach and includes counseling about cancer risk, surveillance options and discussion of risk reducing surgery including prophylactic mastectomy and or oophorectomy. Prophylactic mastectomy is very effective and reduces the risk of breast cancer by over 90% [3,4].

Prophylactic bilateral salpingo-oophorectomy (BSO) significantly reduces the risk of both ovarian and breast cancer in BRCA1/2 carriers [5] BSO reduces the risk of ovarian cancers by 85 - 90% and reduces the risk of breast cancer by 50% [6]. The reduction in the risk of breast cancer even in women with BRCA1 – associated Breast cancer which is commonly ER-ve may seem counterintuitive, but there is growing evidence to suggest that many ER-ve breast cancers evolve from ER+ve precursors [7]. Risk reduction following BSO may differ for BRCA1/2 carriers. Case-control studies suggest that prophylactic oophorectomy may result in greater reduction in breast cancer risk in BRCA1 carriers who undergo surgery before 40years of age, compared with BRCA2 carriers [8]. Both ovaries and fallopian tubes should be removed since both area at increased risk for malignant transformation [9]. There is growing evidence to suggest that most BRCA-related 'ovarian cancers' actually arise in the fimbrial end of the fallopian tube which probably explains why transvaginal ultrasound screening for ovarian cancer does not appear to be effective screening modality [10]. Hysterectomy at the time of BSO is controversial, and the additional morbidity needs to be taken into account and weighed against the potential risks of combined HT for the management of menopausal symptoms and bone protection.

EFFECTS OF BREAST CANCER TREATMENT ON REPRODUCTIVE FUNCTION

Around 2.7% of breast cancers occur in women of peak reproductive age (25-35 years) [11]. The growing tendency in developed countries for delayed childbearing may increase breast cancer risk and also increases the number of women who have not yet started or completed there families when breast cancer is diagnosed. In addition to possibly having an inferior outcome compared with older women as discussed above .Young breast cancer patients may face dilemmas regarding fertility, pregnancy and contraception and report having difficulty obtaining information in these areas [12].

Breast cancer is likely to have a negative impact on reproductive function for a number of reasons. First, from the toxic effect of chemotherapy on ovarian follicles, secondly from the advice commonly given to patients to delay pregnancy for at least 2 years following a diagnosis of breast cancer and thirdly because endocrine therapy commonly continues for at least 5 years, after which fertility is likely to be reduced due to age-related decline. In addition, ovarian ablation or bilateral oophorectomy may be advised for some younger women with HR +ve cancers or as risk-reducing surgery in BRCA1/2 gene mutation carriers as discussed earlier.

OVARIAN FUNCTION FOLLOWING CHEMOTHERAPY FOR BREAST CANCER

Ovarian dysfunction following chemotherapy for breast cancer is related to patient age, to ovarian function at the time of treatment and to the specific agents used, particularly the dose of alkylating agents such as cyclophosphamide [13]. Common effects of chemotherapy on ovarian function include temporary amenorrhea due to loss of the developing cohort of ovarian follicles or permanent amenorrhea due to loss of remaining follicles [14,15]. Chemotherapy causes depletion of the primordial follicle pool in a drug – and dose – dependent manner [16]. Prevalence rates of temporary regimens, patients' characteristics and outcome measure used. For those who do resume normal menstrual cycles, ovarian damage due to chemotherapy can still be identified. There is a marked follicular depletion [17], fertility is impaired and the mean age at menopause is reduced [18].

Amenorrhea rates following combination chemotherapy consisting of cyclophosphamide + methotrexate + 5 –fluorouracil (CMF regimen) range from 21 to 71% in women aged <40 years, and from 40-100% in older women [19] although this combination is now rarely used. In most series, anthracycline-based adjuvant chemotherapy regimens appear to have a lower incidence of amenorrhea, which is probably due to the lower cumulative cyclophosphamide dose administered compared with that given in the CMF regimen.

The impact of taxanes on the incidence of amenorrhea is uncertain with conflicting results. Some studies suggest no additional effect [20] whereas others report that the rates of amenorrhea may be increased [21], but there is insufficient data to comment on the impact of different

schedules of paclitaxel (e.g. weekly, dose dense or three-weekly dosing) on the rate of amenorrhoea.

As a rule of thumb, chemotherapy for breast cancer appears to add about 10 years to ovarian age in terms of reproductive function. Unfortunately, many young women are not fully aware or well informed of the potential adverse reproductive effects of chemotherapy on fertility or fail to understand the possible consequences of treatment while making treatment decisions shortly after the diagnosis of breast cancer [22].

ENDOCRINE THERAPY AND REPRODUCTIVE FUNCTION

Around 60% of pre-menopausal breast cancer patients will have HR +ve cancers and will be given endocrine therapy either alone (in selected patients) or more commonly chemotherapy followed by endocrine therapy. Endocrine therapy regimens vary according to patient and tumor characteristics. But may include tamoxifen or ovarian suppression or ablation or both.

Tamoxifen

Tamoxifen is a mixed estrogen agonist and antagonist, which commonly induces hot flushes, night sweats, vaginal discharge, itching or dryness [23]. Tamoxifen may also stimulate ovulation [24] and is licensed in UK for the treatment of anovulatory infertility. It is important that younger women realize that tamoxifen is not a contraceptive and carries a risk of stimulating multiple ovulations and hence multiple pregnancy.

Tamoxifen has a similar chemical structure to diethylstilbestrol. Concern that tamoxifen may be teratogenic arose from animal studies showing increased genital tract malformations [25]. However, there is relatively little human evidence that tamoxifen is teratogenic. There have been four reports of craniofacial abnormalities associated with tamoxifen use in the first trimester. No fetal abnormalities were seen in the offspring of 85 women who became pregnant while taking prophylactic tamoxifen for the prevention of breast cancer. However, there are no long-term data from children exposed to tamoxifen during development. This is important because the effects of diethylstilbestrol only became evident in later life.

Assessment of fertility following breast cancer treatment

Lack of prospective studies with current chemotherapeutic regimens makes it difficult to predict their impact on future fertility. Most studies have used amenorrhoea or menstrual irregularity as an end point, but these do not reliably relate to fertility. Recent studies have assessed the impact of chemotherapy on ovarian function using composite measures derived from assisted reproductive technology (ART) studies. Ovarian reserve testing (ORT) includes timed (Day 2-5 of the menstrual cycle) Follicle-stimulating hormone (FSH) and Luteinizing hormone, estradiol, inhibin B and anti-Mullerian hormone (AMH) in combination with ovarian antral follicle count determined at transvaginal ultrasound. Declining ovarian reserve is reflected in lower circulating levels of estradiol, inhibin B and AMH produced by the granulosa cells of the ovarian follicle and reduced number of antral follicles. These tests appear to predict the outcome in ART [26] and control levels have been published in a healthy and subfertile population [27]. ORT has not been shown to reliably predict earlier age at menopause [28]. The validity of ORT following chemotherapy for breast cancer is not yet established, and this battery of tests is not commonly available in clinical practice. ORT following chemotherapy suggests that it does not reliably predict the response to ovarian stimulation [28]. Prospective studies in breast cancer patients indicate that ovarian reserve declines during chemotherapy, with regimens containing taxanes in addition to cyclophosphamide showing increased gonadotoxicity. Gonadotrophin suppression with endocrine therapy resulted in expected falls in estradiol ($P<0.05$) and inhibin B ($P<0.001$) levels, but also resulted in a delayed fall in AMH level after 6 months ($P<0.0001$). A fall in AMH may precede other changes in ORT following breast cancer chemotherapy [29].

Preservation of fertility in breast cancer patients

Breast cancer patients who have not started or completed their families may wish to consider available options to try and increase the chance of successful pregnancy following chemotherapy. Currently, there are no treatments, which are guaranteed to preserve fertility. For women with breast cancer, the issue of fertility preservation is more complex than in other cancers with concerns that fertility preservation strategies and /or subsequent pregnancy may increase the risk of cancer recurrence, particularly in women with hormone-receptor positive disease [18]. The potential risks and benefits of treatment should be considered on an individual basis (*Table* 2). In evaluating patient options, a critical factor is whether the patient has a fertile male partner with whom she is planning a family. For single women, the options are currently very limited.

Fertility preservation options can be divided into those, which aim to reduce the impact of chemotherapy on ovarian function, those which aim to remove and preserve ovarian tissue before starting chemotherapy and those, which aim to produce mature oocytes or fertilized embryos for future use. Sonmezer and Oktay (2006) have proposed an

Table 2. Advantages and disadvantages of fertility-preserving strategies

Option	Advantage	Disadvantage
Potential fertility preserving strategies		
1. IVF and embryo cryopreservation	Relatively effective in achieving pregnancy	Require a male partner and embryos legally owned by both partners. Likely to increase circulating Estrogen levels which may impact on prognosis of ER positive breast cancer. In gene mutation, carriers may transmit increased cancer risk offspring.
2. Ovarian stimulation and oocyte cryopreservation	Does not require a male partner	Very few successful pregnancies. Likely to increase circulating estrogen levels which may impact on prognosis of ER positive breast cancer. In gene mutation, carriers may transmit increased cancer risk to offspring.
3. Ovarian tissue Cryop-reservation and xeno-transplantation micrometastases	Does not require a male partner. Does not require Ovarian Stimulation and increased Estradiol level. Unlikely to delay Chemotherapy.	Very few successful pregnancies. May reimplant Ovarian tissue affected by Surgical procedure.
4 . Ovarian suppression with GnRH agonists	Does not require a male partner. Simple to administer unlikely to delay	Efficacy in fertility preservation not confirmed. Side effects unknown.

algorithm to aid decisions regarding fertility preservation based on cancer treatment choices and age that may be a useful tool in clinical practice [30].

The mechanism of action of GnRH agonists in preserving ovarian function are not fully understood, but may include interruption of FSH receptors, up-regulation of intra-gonadal antiapoptic molecules such as sphingosine-1-phosphate or by protection of undifferentiated germ line stem cells [31]. Embryo cryopreservation is a standard, widely available treatment for infertility that may be used in breast cancer patients who have a male partner or who have access to donor sperm. Although success rates with frozen embryos are somewhat reduced, these women can undergo ovarian stimulation, oocyte harvesting followed by IVF and embryo freezing for attempted pregnancy when breast cancer treatment is completed. Advantages of this strategy are the relatively high success rates. Disadvantages include the need for ovarian stimulation (and subsequent high estradiol levels), cost (variable), possible delays in commencing adjuvant treatment [13] and the risk of cancelled cycles. Strategies to avoid high estrogen levels include 'natural cycle' IVF, albeit with very low pregnancy rates [24]. Ovarian stimulation protocols using the Aromatase Inhibitor letrozole, together with gonadotrophin treatment (FSH), resulted in significantly lower peak estradiol levels than tamoxifen alone or plus FSH, and 44% reduction in the amount of gonadotrophin needed but similar length of stimulation and number of embryos obtained. Fertilization rates were similar to conventional ovarian stimulation protocols and 81% completed their IVF cycles within 8 weeks of surgery [14,15]. Short term follow-up (around 1 year) is reassuring that this intervention does not appear to affect breast cancer prognosis [32] but long-term data are not yet available. In patients with potentially fatal disease, the issue of what to do with the embryos if the patient dies prior to their use should be addressed.

For those who do not have a male partner, oocyte cryopreservation may be considered. However, success rates with this method are three to four times lower than that seen with embryo cryopreservation, at ~20% at best [18]. Further, it is possible that reimplanted ovarian tissue may harbour breast cancer micrometastases that may increase recurrence risk, although this is more a theoretical risk and there are no supportive clinical data. Women who carry a pathogenic BRCA1 or 2-gene mutation have a 50% risk of transmitting this mutation to their offspring. Recent advances in pre-implantantation genetic diagnosis have allowed the selection of unaffected embryos during IVF protocols in these women [33].

Ovum donation is another option and has the benefit of using fresh ova from a donor (with higher success rates than frozen ova). This may be particularly appealing to women who do not, at the time of diagnosis, have a partner with whom they are considering having child. For BRCA1 or 2

mutation carriers, there is a potential benefit that the child will not inherit their gene mutation. There is no required delay in cancer treatment as this process would occur after cancer treatment is completed, however, similar to IVF, the recipient of the ova may require hormonal stimulation (to prepare the endometrium for embryo transfer) and subsequent increase estradiol levels. The recipient will incur not only the cost for her own stimulation and transfer but also the costs for the ovarian stimulation and collection of the ova from the donor and other medical costs including counseling. Also, the patient will usually need to find the oocyte donor herself.

Pregnancy following breast cancer

Less than 10% of women previously diagnosed with breast cancer subsequently become pregnant. This is around half the pregnancy rates seen in an age-matched group who have not had breast cancer [34]. Of these pregnancies, between 14 and 44% are terminated (24). Relatively few studies have addressed the impact of pregnancy following breast cancer [34].

The use of adjuvant chemotherapy does not appear to affect the outcome of pregnancy in women who become pregnant at least 6 months after diagnosis, with more women having a successful live birth than having an abortion or miscarriage [34]. Moreover, pregnancy does not appear to adversely affect prognosis following a prior history of breast cancer. The overall survival rates at 5 and 10 years were found to be better with for women who subsequently conceived in a Western Australian population study [34] than has been reported in similar cohorts [35,36]. This apparent survival benefit is probably due to a 'healthy mother effect' suggesting that breast cancer survivors who subsequently conceive are a self – selecting group of women with better prognosis. Retrospective case controlled studies report that subsequent live birth does not adversely affect prognosis [37,38]. The little available information appears to show no increase in the incidence of prematurity, stillbirth or congenital malformations in their babies. Small series following these children are also reassuring [39], but little is known about the long – term impact of chemotherapy or endocrine therapy on offspring [40]. The largest reported series included 84 children who were exposed to a variety of chemotherapy agents in uterus and followed for a median of 18 years. Reassuringly, no adverse sequelae were documented although the numbers are relatively small [41].

Women are commonly recommended to delay pregnancy for at least 2 years following a diagnosis of breast cancer as most recurrences will develop in that time [42]. The optimal time to delay pregnancy following the diagnosis and treatment is unknown and is an important issue for all patients considering pregnancy. The risk of relapse and the time to recurrence is related to many factors including the stage, grade and nodal status as well as the HR status. Saphner *et al.* have reported annual hazard rates of recurrence after primary therapy. These results should be interpreted with caution since chemotherapy regimens have now changed and the number of younger women included is not stated. For the entire group, the risk of recurrence was greatest (13.3%) for the interval between 1 and 2 years after surgery. This risk then decreased consistently, and beyond 5 years averaged about 4.3% per annum in women with HR +ve breast cancer in the Saphner study, but there are some caveats with these figures, as discussed earlier. Patients with HR –ve tumors had a higher hazard of recurrence in years 0-5 which then decreased over time, whereas the hazard of recurrence for women for women with HR +ve cancers was relatively constant in the first 5 years after diagnosis and from years 5 to 12. This highlights the distinct natural history of HR +ve and HR –ve tumors. More recently, we have recognized that there are a number of different sub-types of breast cancer, some of which are more common in younger women and they appear to have a higher risk of relapse in the first 2-3 years after diagnosis. These estimates of recurrences should be considered in decisions regarding subsequent pregnancy. However, there is a little evidence to show benefit to patients in waiting more than 2 years after diagnosis of breast cancer to attempt pregnancy, as long as adjuvant therapy has been completed. In addition, patients need to understand that there is a risk that breast cancer may return and this may affect their ability to care for future offspring. Over 50% (of 126) of breast cancer patients in a population based series in Western Australia conceived within 2 years of diagnosis and this did not seem to adversely affect their survival [34].

In women with BRCA1 or 2 gene mutations, the risks of pregnancy are not well established. Observational studies suggest that BRCA1 mutation carriers who have their first child at 30 years or older may have a reduced personal risk of breast cancer [43]. However, the opposite effect has been observed in BRCA2 mutation carriers where late first pregnancies (over 30 years) are linked with increased risk of breast cancer [44].

Breastfeeding after breast cancer

Following breast cancer treatment women may need advice about their ability and the safety of breast-feeding. Observational data suggest that breastfeeding does not impact on breast cancer prognosis and that infants breastfed by mothers with a history of breast cancer or current cancer do not have an elevated risk of cancer.

All younger women having breast conserving surgery will be advised to also have RT and will then be unlikely to

be able to feed from the treated breast [45]. Women can successfully breastfeed from the other breast after breast cancer if they do not undergo pharmacological suppression of lactation [45], and it is possible to breastfeed exclusively from one breast.

Menopausal symptoms following breast cancer treatment

Menopausal symptoms are a frequent and troublesome side effect of breast cancer therapy in women of all ages. Hot flashes, night sweats, sexual dysfunction, poor sleep and tiredness are common. Vasomotor symptoms, particularly hot flushes, appear to be more severe than in women who have not had breast cancer treatment [46]. Vasomotor symptoms such as hot flashes are the most common side effects [43]. Up to 20% of breast cancer patients consider stopping or actually cease endocrine therapy because of menopausal symptoms, primarily hot flashes, despite its established role in reducing recurrence, Atrophic vaginitis affects many women using endocrine therapy for breast cancer, particularly those using Aromatase Inhibitors [47]. Sexual dysfunction may be related to atrophic vaginitis but also to changes in body image, libido and self-esteem and may be more common in younger women [48].

The recommended duration of initial adjuvant endocrine therapy is 5 years and some patients may benefit from a further 5 year of treatment. With such long term treatment duration, it is critical to address morbidity associated with treatment side effects in an effort to optimize adherence to therapy and quality of life.

Use of estrogen and progestin in breast cancer patients

Estrogen containing HT is the most effective and well studied treatment for menopausal vasomotor symptoms and atrophic vaginitis in healthy postmenopausal women, but the efficacy and safety of HT following breast cancer is contentious. There are two large RCTs investigating the use of HT after diagnosis of early stage breast cancer having contradictory results. The Stockholm and HABITS trials were similar in design, though a goal of the Stockholm protocol was to minimize the use of progestogen combined with estrogen. The HABITS trial was stopped prematurely because it identified a significantly higher risk of recurrence in women taking menopausal HT (relative hazard [RH] =3.3, 95% confidence interval [CI] = 1.5-7.4 at a median follow –up of 2.1 years), whereas at a median follow up of 4.1 years the risk of recurrence was not associated with HT in the Stockholm trial (RH= 0.82, 95% CI=0.35-1.9) [49,50]. HT was not effective in controlling hot flashes in tamoxifen and users in one retrospective study [51]. Long-term use of combined HT has been associated with an increased risk of new breast cancers in some studies [52]. In breast cancer survivors, one RCT reports a 2 to 3 fold increased risk of new primary or recurrent breast cancers in HT users [53]. Further, HT may compromise the effects of endocrine therapy aimed at blocking the effect of estrogen, or reduce its production in ER+ve disease. In addition, combined HT increases breast density, which may compromise the ability of mammography to detect early cancers [54]. Consequently, many women wish to avoid HT following breast cancer. Progestins are also effective for menopausal hot flashes following breast cancer [55], but their safety is not established and their effects may depend on circulating levels of estradiol. Of concern is that the addition of progestin to estrogen for HT appears to increase the risk of a primary breast cancer [56].

Use of estrogen and progestins in BRCA1/2 mutation carriers

Risk-reducing BSO in pre-menopausal BRCA1/2 mutation carriers will induce surgical menopause. There are surprisingly few published studies on the consequences of surgical menopause, but the observational literature suggests that symptoms may be more severe and prolonged following BSO compared with spontaneous menopause. Estrogen containing HT may be of limited efficacy in relieving menopausal symptoms in these younger women [57]. Further the impact of HT on subsequent breast or ovarian cancer risk in these women is poorly understood. One retrospective study [58] was reassuring that the reduction in breast cancer risk associated with BSO is not modified by short-term use of HT. In the absence of other data, a decision model has been developed which allows individualized assessment of the impact of prophylactic BSO, bilateral prophylactic mastectomy and HT use on life expectancy in BRCA1/2. Users should be guided by patient symptoms and issues around quality of life, in the absence of clearer information about relative risks [59].

CONCLUSION

Increasing numbers of breast cancer survivors are presenting to reproductive medicine specialists and their gynecologists with symptoms secondary to breast cancer treatments and queries regarding ongoing issues around fertility and menopause. Many of these will be younger women who prefer greater involvement in treatment decision-making and their needs for information may differ from older women. In general, patients who are better informed experience greater emotional, social and physical well being, better clinical outcomes, quality of life and satisfaction with care. Timing of information is important. Fertility discussion needs to be prioritized and considered soon after diagnosis and before chemotherapy.

Interventions such as IVF or ovarian tissue freezing should be discussed in detail in relation to patient's personal and medical circumstances. Predicting fertility following chemotherapy for breast cancer remains problematic, and more sensitive indices of ovarian function as well as longitudinal data regarding subsequent infertility, pregnancy and pregnancy outcome are needed in order to better inform women about the consequences of chemotherapy and the likelihood of a subsequent pregnancy. Current evidence suggests that pregnancy does not appear to be detrimental following breast cancer, but individualized counseling regarding prognosis and risk relapse based on their age and pathological features of the cancer is required before patients can make informed decisions regarding future childbearing.

The management of menopausal symptoms following breast cancer is a particular challenge. There is a growing literature on safe and effective non-hormonal treatments for hot flushes. However, other common menopausal symptoms such as vaginal dryness and sexual dysfunction should not be overlooked and are likely to require additional management. There is a growing recognition of the importance of developing a 'survivorship care plan' to coordinate care of women and a prior history of breast cancer and to address and prevent the long-term side effects and consequences of adjuvant therapies. This is best done by a multidisciplinary team, of which the reproductive medicine specialist and gynecologists are integral members.

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