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CLINICAL TRIALS (J LANG, SECTION EDITOR)

Fertility Preservation and Breast Cancer

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Abstract

Purpose of Review Breast cancer in young women presents many special challenges in both the treatment and survivorship settings. Considering premenopausal state at diagnosis and the trend to delay motherhood, many young women have questions about options to preserve fertility. The goal of this review is to provide background on how treatment of young women with breast cancer can affect fertility and to describe available fertility preservation techniques as well as the role of healthcare providers in addressing these issues.

Recent Findings Cancer therapies have various gonadal toxicity risks that should be discussed prior to initiation of systemic therapy. The development and advances of various fertility preservation techniques provide choices for patients to consider, and a multidisciplinary approach is key to the informed decision-making process. *BRCA* mutation carriers may face unique circumstances including loss of fertility due to risk-reducing salpingo-oophorectomy which is frequently recommended as well as concerns about passing on deleterious genetic mutations to their offspring. Pregnancy after breast cancer does not appear to increase risk of breast cancer recurrence; however, timing pregnancy can be challenging particularly for women on long-term endocrine treatment for their cancer.

Summary Oncofertility care represents a vital component of the management of young women diagnosed with breast cancer. A variety of approaches are available to improve fertility prospects for these women, and strategies to further advance this field are strongly desired by both patients and providers.

Keywords Fertility preservation · Young women · Breast cancer · Survivorship · BRCA carrier · Pregnancy

Introduction

Breast cancer affects over 12,000 women under age 40 in the USA each year. Although breast cancer is the leading cause of cancer-related deaths in this age group, the majority of these individuals will experience long-term survival [1]. Young women with breast cancer may be diagnosed during significant periods of life including education, career development, and starting a family. The majority of breast cancer cases in young women are found by self-detection and are generally characterized by a more advanced stage [2]. Breast cancers diagnosed in young women also tend to present with more aggressive pathologic features including higher grade and hormone receptor (HR)–negative and HER2-positive subtypes [3–5]. As a result, aggressive systemic therapy including chemotherapy and/or prolonged endocrine therapy are often recommended and improve prospects for long-term survival. These treatments may impact future fertility, an important survivorship concern for many young women with breast cancer.

There has been a trend toward delayed motherhood, and concerns surrounding infertility occur in over half of young women diagnosed with breast cancer [2, 6]. These concerns can potentially impact treatment decisions, and subsequently outcomes [2, 7]. Oncofertility counseling is an integral yet often omitted component of cancer management for young patients. Various treatment guidelines support discussion of fertility risk and appropriate referrals as soon as possible after diagnosis and prior to starting cancer treatment [8, 9••, 10, 11]. Improving provider knowledge in the area of oncofertility should lead to better guideline adherence and patient care. Here, we discuss the effects of breast cancer treatment on fertility, options for improving prospects for future fertility, and some of the specific challenges related to fertility and breast cancer.

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Systemic Treatment of Breast Cancer and Risks to Fertility in Premenopausal Woman

While young age alone is not an indication for chemotherapy in the setting of early-stage breast cancer [12], young women with breast cancer often receive cytotoxic chemotherapy based on their tumor pathology and cancer stage at diagnosis. Standard chemotherapy regimens used in breast cancer can induce temporary ovarian failure, early menopause, and infertility. The risk of chemotherapy-induced menopause and infertility is influenced by the type of chemotherapy, dosage, and patient's age.

Standard chemotherapy regimens utilized in early-stage breast cancer include anthracyclines, alkylating agents, taxanes, platinum drugs, and fluoropyrimidines. Although exact mechanisms of ovarian toxicity are not completely elucidated, depletion of the primordial follicle pool has been demonstrated with most of these agents. Doxorubicin and alkylating agents cause double-strand DNA breaks leading to apoptosis of primordial follicles [13, 14]. Doxorubicin is also associated with ovarian vascular and stromal damage [13]. Taxanes and platinum agents can deplete primordial follicles, although taxanes do not cause direct vascular damage [15–17]. Capecitabine, an oral pro-drug form of 5-fluorouracil (5-FU), appears to have a low risk for gonadotoxicity [18–20]. Treatment-induced amenorrhea does not necessarily indicate infertility in an individual patient, but may be helpful for estimating comparative gonadal toxicity of various regimens and among different patient groups. Increasing patient age has been associated with higher rates of chemotherapy-induced amenorrhea (CIA), including irreversible menopause, likely due to reduced ovarian reserve [21]. CIA occurs in about 68% of premenopausal woman $\geq$40 years of age with 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel, while about 27% of those <40 years of age experience CIA with these treatments [22]. Higher rates of amenorrhea have also been observed with longer duration of chemotherapy [23•].

Evaluation of ovarian reserve prior to chemotherapy is an attractive option to help counsel patients on future risk. Anti-Mullerian hormone (AMH) has surfaced as a promising marker of ovarian reserve due to its stability throughout the menstrual cycle, and it is unaffected by hormonal therapy [24]. AMH levels are lower in breast cancer survivors compared to that in controls [25, 26]. Studies have demonstrated the value of pre-chemotherapy AMH levels in predicting magnitude of impact on ovarian function as well as rate of recovery [27–29]. Pregnancy can occur even in the setting of low AMH, and neither baseline nor post-chemotherapy AMH levels are clearly associated with rate of spontaneous pregnancy [30]. Although AMH levels may provide helpful information for reproductive discussions prior to chemotherapy, no measure of ovarian reserve or ovarian function has been shown to equate to fertility.

Compared to chemotherapy, endocrine therapy for breast cancer appears to have little direct ovarian toxicity. The greatest challenge with endocrine treatment with respect to fertility is the duration of treatment. A variety of endocrine treatment regimens are used in premenopausal women. The selective estrogen receptor modulator tamoxifen has been associated with menstrual changes including amenorrhea; however, this finding has not been consistent across all studies [19, 31, 32]. Tamoxifen-associated amenorrhea does not necessarily correlate with the development of ovarian failure. The duration of endocrine therapy can present a challenge to fertility. Traditionally, tamoxifen had been recommended for 5 years and recent data have demonstrated further reduction in breast cancer recurrence and mortality with extending tamoxifen therapy for up to 10 years [33, 34]. With adjuvant endocrine therapy lasting as long as 10 years, optimal endocrine therapy may necessitate a delay in childbearing attempts, in turn affecting fertility risk by the age factor. Increasingly, aromatase inhibitors are being used in combination with ovarian function suppression in premenopausal women. The addition of ovarian function suppression (OFS) to either an aromatase inhibitor or tamoxifen improves recurrence risk over tamoxifen alone [35]. While reversible ovarian ablation can be achieved with the use of GnRH agonists, some patients will choose a permanent means via oophorectomy, which eliminates the possibility of pregnancy without the use of assisted reproductive technology.

Fertility-Preserving Techniques

Fertility preservation (FP) advances provide patients with options to optimize their reproductive potential in the setting of planned cancer-directed therapy. It is beneficial for providers to be familiar with these procedures so they can effectively advise patients regarding how these may fit into their treatment plan (Table 1).

Cryopreservation of embryos and oocytes are well-established FP techniques and are believed to have the most dependable pregnancy rate data in both oncologic and non-oncologic settings [9••, 11]. A woman's age at the time of oocyte collection and transfer is a determinant of success [36]. In a retrospective observational study including 1582 patient-couples who underwent in vitro fertilization, the cumulative live birth rate declined with increasing age, with rates of 30.0% and 37.2% for women age 26–30 and 31–35, respectively, compared to rates of 16.3% and 2.4% for those age 36–40 and 40–42, respectively [37]. For cancer patients wishing to preserve fertility, early referral to a fertility specialist is important, regardless of whether or not cytotoxic chemotherapy is planned.

Table 1 Fertility preservation options

Method	Description	Advantages	Disadvantages
Embryo cryopreservation	• Ovarian stimulation, egg harvesting, in vitro fertilization, freezing of embryos • Gold standard for fertility preservation	• High pregnancy rate • Random-start protocols allow for more timely initiation of cancer therapy	• Not applicable for prepubertal females • Requires ovarian stimulation thus possible treatment delay • Theoretical concern with hormonal stimulation in women with hormone-sensitive cancers • Requires male partner or sperm donation • High cost
Oocyte cryopreservation	• Ovarian stimulation, egg harvesting, and freezing of mature eggs for in vitro fertilization and implantation after cancer treatment • Considered FP standard	• Option for those without partner (no immediate need for sperm)	• Not applicable for prepubertal females • Requires ovarian stimulation thus possible treatment delay • Theoretical concern with hormonal stimulation in women with hormone-positive cancers
Ovarian tissue cryopreservation	• Surgical harvesting of ovarian tissue followed by freezing • Considered experimental	• Only available option for prepubertal females • No hormonal stimulation needed • No delay in chemotherapy start • Allows natural pregnancy after autotransplantation • Ovarian stimulation not required • No need for sperm donation	• Historical low success rate • Not widely available • Potential risk of re-introduction of malignant cells • Tissue not appropriate for transplant if high risk of ovarian metastases • Risk of ovarian failure after removing ovarian volume • Safety and ethical issues following xenotransplantation
Ovarian suppression with GnRH analogue	• Administration of GnRHa during chemotherapy • Increasingly accepted as standard option to reduce ovarian failure risk in women with breast cancer • Use in other cancer types under investigation	• Inexpensive, easy to perform, widely available • No surgery required • Ovarian function preservation can be achieved • Chance of spontaneous pregnancy	• Data on ovarian function preservation stronger than data regarding fertility

For breast cancer patients requiring timely treatment of their malignancy, there is a desire to avoid delays in treatment. Embryo/oocyte cryopreservation requires ovarian stimulation and oocyte retrieval, which are ideally completed prior to initiation of systemic treatment. In addition, those with hormone-sensitive disease may have concerns about the risks of hormonal stimulation given for oocyte collection. Recent advances can help to mitigate these concerns for women with breast cancer. Random-start stimulation protocols, in which a patient is stimulated at the desired time point regardless of menstrual cycle phase, have similar efficacy compared to conventional protocols and allow women to begin cancer treatment within 2–3 weeks [38]. Protocols utilizing an anti-estrogen medication such as tamoxifen or the aromatase inhibitor letrozole for controlled ovarian hyperstimulation (COH) have shown adequate oocyte yield and decreased estrogen levels compared to standard methods [39, 40]. Letrozole is preferred due to its effect of lower peak estradiol levels and known teratogenicity of tamoxifen [40, 41]. Furthermore, available data support the safety of these protocols, including for women with estrogen receptor (ER)–positive breast cancer and those carrying *BRCA* mutations [42–44].

The available literature on success rates of embryo/oocyte cryopreservation in women with breast cancer is surprisingly limited. Oktay et al. reported on pregnancy outcomes among 131 women with early-stage breast cancer who underwent ovarian stimulation with concurrent letrozole and cryopreserved embryos prior to receiving chemotherapy. A total of 40 embryo transfer attempts among 30 women were carried out with an overall live birth rate comparable to infertile women of similar age undergoing in vitro fertilization (45.0% vs 38.2%; $p = 0.02$). [45]. These results support the role of embryo/oocyte cryopreservation in young women with breast cancer; however, patients need to understand that success is not guaranteed.

Ovarian tissue cryopreservation (OTC) is an evolving technique and while still considered experimental may be considered standard in the near future [9••, 46]. Success with OTC has been reported including small studies with live-birth rates of up to 33% [47, 48]. Advantages of this method include its ability to be performed without ovarian stimulation. Potential disadvantages include requirement of specialized facility with expertise and necessity of two separate procedures (collection of ovarian tissue to be cryopreserved and future autotransplantation of tissue). A literature review of ovarian tissue cryopreservation in women with breast cancer included 16 cases of ovarian transplants with 14 pregnancies and 11 births [49•]. Two cases of breast cancer recurrence were reported in these patients. While concern exists regarding risk of re-introduction of malignant tissue, other studies have shown reassuring findings with no indication of sufficient numbers of malignant cells in ovarian tissue to cause cancer recurrence after ovarian tissue transplantation [50].

The role of gonadotropin-releasing hormone analogues (GnRHa) for ovarian function protection during chemotherapy has been outlined in the ASCO guidelines with discussion of seven randomized trials in this setting [9••]. While the value of this approach in non-breast cancer malignancies remains under investigation, its role for reducing ovarian failure risk in premenopausal women with breast cancer is now well-established. The POEMS trial investigated the 2-year ovarian failure rate among premenopausal women with early-stage ER-negative breast cancer who were randomized to receive chemotherapy with or without the GnRHa goserelin and also described pregnancy outcomes. The goserelin group had a lower ovarian failure rate compared to the chemotherapy-alone group (8% vs 22%, OR 0.30; 95% CI 0.09–0.97; p = 0.04) [51]. There were more pregnancies in the goserelin group compared to the chemotherapy-alone group (5-year cumulative incidence = 23.1%, 95% CI 15.3–31.9%; and 12.2%, 95% CI 6.8–19.2%, respectively; OR 2.34; 95% CI 1.07–5.11; p = 0.03) [52•]. The phase 3 PROMISE-GIM6 trial provides data regarding GnRHa for ovarian protection in ER-positive breast cancer. This study randomized 281 women with early-stage breast cancer, 80% of whom had ER-positive disease, to receive chemotherapy with or without concurrent triptorelin. Similar to the POEMS, this study demonstrated a significant reduction in the rate of early menopause in the GnRHa plus chemotherapy group compared to the chemotherapy-alone group (8.9% vs 25.9%, OR 0.28, 95% CI 0.14–0.59; p < 0.001) [53]. The results of a meta-analysis of 5 trials (PROMISE-GUM6, POEMS/SWOG S0230, Anglo Celtic Group OPTION, GBG-37 ZORO) in which young women with early-stage breast cancer were randomized to receive chemotherapy alone or with concurrent GnRHa support the efficacy and safety of this approach. Outcomes were reported for 873 women, median age 38 years; the GnRHa group had lower rates of premature ovarian insufficiency compared to controls (14.1% vs 30.9%, adjusted OR 0.38, 95% CI 0.26–0.57; p < 0.001). More pregnancies (37 vs 20 patients, IRR 1.83, 95% CI 1.06–3.15; p = 0.030) were seen in the GnRHa groups with the pregnancy benefit being more apparent among those with ER-negative disease [54].

The safety of ovarian function suppression during chemotherapy in young breast cancer patients has been demonstrated in various studies [43, 52•, 54, 55]. In POEMS, women who received goserelin with chemotherapy had a nonstatistically significant improvement in DFS (HR 0.55, 95% CI 0.27–1.10; p = 0.09) and OS (HR 0.45, 95% CI 0.19–1.04; p = 0.06) [52•]. Results from PROMISE-GIM6 showed no difference in DFS between the GnRHa group and the control group (HR 1.17, 95% CI 0.72–1.92; p = 0.52), including among those women with ER-positive disease (HR 0.96, 95% CI 0.55–1.70; p = 0.19) [55]. In the meta-analysis, there were no significant differences between the GnRHa and control groups in DFS (adjusted HR 1.01, 95% CI 0.72–1.42; p = 0.999) or OS (adjusted HR 0.67, 95% CI 0.42–1.06; p = 0.083). These data have led multiple groups to recommend consideration of ovarian suppression with GnRHa in young women with breast cancer who wish to reduce the chance of premature ovarian failure associated with cytotoxic therapy [9••, 11]. It is important to note that use of assisted reproductive technology and ovarian suppression with a GnRHa during chemotherapy are not mutually exclusive. Considering all methods are imperfect, offering multiple options may improve outcomes for patients desiring future fertility.

BRCA Mutation Carriers

BRCA 1 and *2* are tumor suppressor genes known to play an essential role in DNA repair and recombination, cell cycle checkpoint activation, and transcription [56]. Deleterious mutations in *BRCA 1* and *2* genes carry an associated risk of carcinogenesis, most notably breast and ovarian cancer, as well as fallopian tube, pancreatic, stomach, skin, and prostate cancer [57]. Early-onset characteristic of these cancers presents a particular challenge to this group of young women with respect to future fertility. Guidelines recommend risk-reducing salpingo-oophorectomy between ages 35 and 45 years, after childbearing is completed, in *BRCA* mutation carriers [58, 59]. This prophylactic surgery is associated with reduced risks of ovarian and breast cancer, as well as a beneficial effect on mortality in this population [60] and also complicates any plans for pregnancy.

The relationship between *BRCA* mutations and ovarian function has been studied. There is evidence of accelerated menopause in *BRCA* mutation carriers [61, 62]. Lin et al. demonstrated that *BRCA* mutation carriers went through menopause a median of 3–4 years earlier than noncarriers, and had a significant fourfold increased HR for early menopause after

adjusting for variables known to affect age at menopause (parity, smoking, OCP use) [63] suggesting the possibility of reduced ovarian reserve in this population. Phillips and colleagues showed that *BRCA1* carriers had, on average, 25% (95% CI 5–41%; p = 0.02) lower AMH concentrations than noncarriers and were more likely to have AMH concentrations in the lowest quartile for age (OR 1.84, 95% CI 1.11–303; p = 0.02) [64]. A retrospective study by Son et al. including 52 *BRCA* mutation carriers and 263 noncarriers demonstrated significantly lower AMH levels in the *BRCA* cohort than those without a mutation (2.60 vs 3.85 ng/ml, 32% reduction; p = 0.004) [65]. Encouragingly, most studies have not identified significant differences in actual fertility outcomes between carriers and noncarriers [61, 66–68], and some literature exists showing higher parity in *BRCA* carriers [69, 70].

Considering potentially lower ovarian reserve and deficient DNA repair mechanisms, it is possible that cancer therapies may have more dramatic impact on the pool of follicles in *BRCA* mutation carriers. However, rates of CIA appear to be similar in these patients compared to noncarriers [71]. Fertility-preserving treatments, including COH for oocyte collection, have not been associated with increased risk of breast or gynecologic cancers, including in *BRCA* mutation carriers [72, 73]. In a prospective, controlled study evaluating risk of breast cancer recurrence among women undergoing COH with letrozole, no significant difference was observed between fertility preservation (n = 26) and control groups in the 47 women with *BRCA* mutations (p = 0.57), similar to what was observed in non-*BRCA* carriers [43]. While safety concerns with COH do not appear to be greater among *BRCA* carriers than noncarriers, some studies have shown decreased ovarian response to stimulation in *BRCA* mutation carriers [74••, 75, 76]. Oktay et al. demonstrated significantly higher rates of low ovarian response in *BRCA* mutation carriers compared to noncarriers (33% vs 3.3%; p = 0.014), and this was fully accounted for by *BRCA1* mutation carriers who produced lower number of eggs compared to controls (7.4 (95% CI 3.1–17.7) vs 12.4 (95% CI 10.8–14.2); p = 0.025) [76].

Data regarding ovarian tissue cryopreservation (OTC) in *BRCA* carriers is scarce, and there is a case report of one birth after transplantation of ovarian tissue in a breast cancer patient with *BRCA2* mutation [77]. Since OTC highly depends on ovarian reserve and RRBSO is recommended at a fairly young age in *BRCA* mutation carriers, candidates for OTC may be only very young patients (<35) who have a higher number of primordial follicles and if oocyte cryopreservation after COH cannot be done. A potential challenge is how to address frozen ovarian tissue with malignant potential given the high risk for ovarian cancer among *BRCA* carriers [78].

Preimplantation genetic diagnosis (PGD) represents an option at the time of embryo transfer for *BRCA* mutation carriers who wish to avoid transmission of predisposition for hereditary breast and ovarian cancer. This process requires in vitro fertilization, culturing of embryos and testing for the *BRCA* mutation prior to transfer [79]. Studies have found that *BRCA* carriers have positive attitudes regarding this approach, although relatively few will actually pursue this option [80, 81]. PGD is fraught with potential emotional and ethical issues, as *BRCA* mutations are not associated with lethality or a definite diagnosis of future cancer in carriers. This may create distressful situations for both patients and providers when deciding how to manage otherwise normal embryos [79, 82, 83].

A survey study of physicians exploring attitudes and practice showed a difference in FP recommendations for *BRCA* carriers. GnRHas were less commonly proposed during chemotherapy (74% vs 81%; p = 0.001) and 42% of providers were in agreement or neutral that ovarian stimulation should not be considered safe in breast cancer patients with *BRCA* mutations [84]. The challenges facing young *BRCA* mutation carriers in regards to fertility are certainly complex, and more education and research are warranted in this area.

Pregnancy After Breast Cancer Diagnosis

Even with progress in the field of fertility preservation, pregnancy rates after cancer treatment are lower than in the general population. Breast cancer survivors are among the least likely cancer survivors to have post-cancer pregnancy [85]. In one study, pregnancy rate after treatment for breast cancer was on average 40% lower than in the general population, and women with ER-positive breast cancer were nearly 4 times less likely to become pregnant compared to women with ER-negative breast cancer [86].

For those women who successfully pursue pregnancy following breast cancer treatment, studies evaluating disease-related outcomes are encouraging regarding the safety of pregnancy after breast cancer [87, 88••]. Azim and colleagues conducted a retrospective cohort study including 333 pregnant and 874 nonpregnant breast cancer survivors. They found no difference in DFS between those who became pregnant after breast cancer diagnosis and the nonpregnant group (H 0.84, 95% CI 0.66–1.06; p = 0.14); in fact, those with pregnancy had an improved OS (HR 0.72, 95% CI 0.54–0.97; p = 0.03) with no interaction according to hormone receptor status [89]. A recent study including over 1200 women with *BRCA* mutations demonstrated success in becoming pregnant in nearly 20% of patients and no difference in DFS (HR 0.87, 95% CI 0.61–1.23; p = 0.41) or OS (HR 0.88, 95% CI 0.50–1.56; p = 0.66) between those who became pregnant and those who did not after more than 8 years of follow-up [90].

While data support the safety of pregnancy after breast cancer diagnosis, it is important to keep in mind that not all women with early-stage breast cancer will be cured and recurrence in the setting of pregnancy or while raising young children remains a real risk. Providers must be prepared to have

honest discussions with patients regarding prognosis and recurrence risk so that patients and their partners can make informed decisions regarding family planning. Another important question that arises for those choosing to pursue pregnancy is the optimal timing of attempting to conceive. Although studies in this space are limited, one study reported that women who conceived within 12 months of diagnosis had a trend toward inferior survival outcomes (HR 1.4, 95% CI 0.8–2.7) although this finding has not been corroborated in other studies [89, 91]. Often a 2-year waiting period is recommended to reduce the possibility of an aggressive early recurrence in the setting of pregnancy. The question of timing is particularly relevant and challenging for women with HR-positive breast cancer given the important role for endocrine therapy for at least 5 and up to 10 years and that pregnancy should be avoided while taking endocrine therapy. A survey study in young women with HR-positive early breast cancer showed 37% were interested in a clinical study of endocrine therapy interruption to allow pregnancy, with younger patients (≤30 years) expressing higher interest (57%). In those treated >30 months, 83% of younger patients were interested in such a study compared to 14% of older women. The POSITIVE study (IBCSG 48-14/BIG 8-13) is designed to explore pregnancy outcomes and safety of a temporary pause in endocrine treatment in young women with HR-positive early-stage breast cancer who desire pregnancy. Women enrolled in this trial who have completed between 18 and 30 months of endocrine therapy may interrupt endocrine therapy for up to 2 years for attempts to conceive [92]. While results from that study are awaited, pregnancy timing remains an individualized discussion taking into account patient characteristics, family planning preferences, and risk of recurrence.

Multidisciplinary Approach to Fertility Care

Studies have shown high reproductive concerns yet relatively low referral rates to fertility specialists in female adolescent and young adult cancer patients [93, 94]. Oncofertility care is best delivered with a multidisciplinary approach. Medical oncologists, surgeons, radiation oncologists, genetics counselors, and reproductive endocrinologists should all be prepared to discuss these concerns with patients. Web-based resources may also be a means to disseminate information regarding cancer and fertility. Stark et al. evaluated a web-based survivorship plan intervention focusing on components of reproductive health (including hot flashes, sexual health, contraception, and fertility-related concerns). Among young breast cancer survivors surveyed, fertility-related concerns were reported by 50%. Healthcare providers who also participated in the study reported confidence in discussing reproductive issues, yet fertility care represented the area they felt least confident to address with patients [95]. The recognition and discussion of fertility concerns is important to address at the time of initial cancer diagnosis as these may impact treatment decisions. In a prospective multicenter cohort study which surveyed women ≤40 years of age diagnosed with early-stage breast cancer, 68% reported discussion of fertility issues prior to therapy and 51% had fertility concerns. As a result of fertility concern, 1% omitted chemotherapy, 2% elected for one chemotherapy regimen versus another, 3% deferred endocrine therapy, and 11% contemplated shorter duration of endocrine therapy (<5 years) [96]. In another study in premenopausal women diagnosed with early-stage breast cancer who were recommended tamoxifen, fertility concerns were associated with non-initiation (OR = 5.04, 95% CI 2.29–11.07; p = 0.009) and early discontinuation (HR = 1.78, 95% CI 1.09–3.38; p = 0.001) of tamoxifen [7].

Barriers to fertility care encompass both internal and external factors, and can be identified on the level of patient, healthcare provider, institution, and public health system. Patients' attitudes, fear of supposed risks with FP (including delay to treatment, negative impact on a hormone receptor-positive breast cancer, pregnancy consequences), relationship status, parity, health beliefs, and health literacy may contribute to whether or not they choose to explore FP. Factors on the level of the clinician include their FP knowledge, values, attitude regarding FP priority, skills, and perception of patient's wishes for children. The doctor-patient relationship can also have an impact depending on the level of comfort in having these conversations. External factors include the availability of services, organization of care, relationship between specialists, and financial resources [97•, 98, 99]. Access to a fertility specialist may be dependent on geographic and institutional resources, as well as knowledge regarding how to initiate FP referral. In a global survey designed to assess oncofertility experiences in different regions, barriers to FP care were reported in 93% with the most common related to financial issues (62%), then religious or cultural limitations (61%) and finally lack of specialists (24%) [100]. A study conducted with 24 providers involved in oncofertility care identified barriers to FP care including lack of written information, absence of FP discussion at multidisciplinary meetings, difficulty arranging appointments, and lack of staff resources to support professionals [101]. Strategies to help improve discussion and access to FP include educational programs and resources for both clinicians and patients, development and implementation of institutional policies/metrics and guidelines, discussion at multidisciplinary meetings, collaboration between oncology and fertility specialists, role of dedicated personnel such as oncofertility nurse coordinators, and optimization of the electronic medical record to facilitate appropriate referrals.

Implementation of oncofertility programs has been shown to increase discussion about FP and access to assisted reproductive techniques [102]. These initiatives help advance the field toward compliance with ASCO and NCCN guidelines

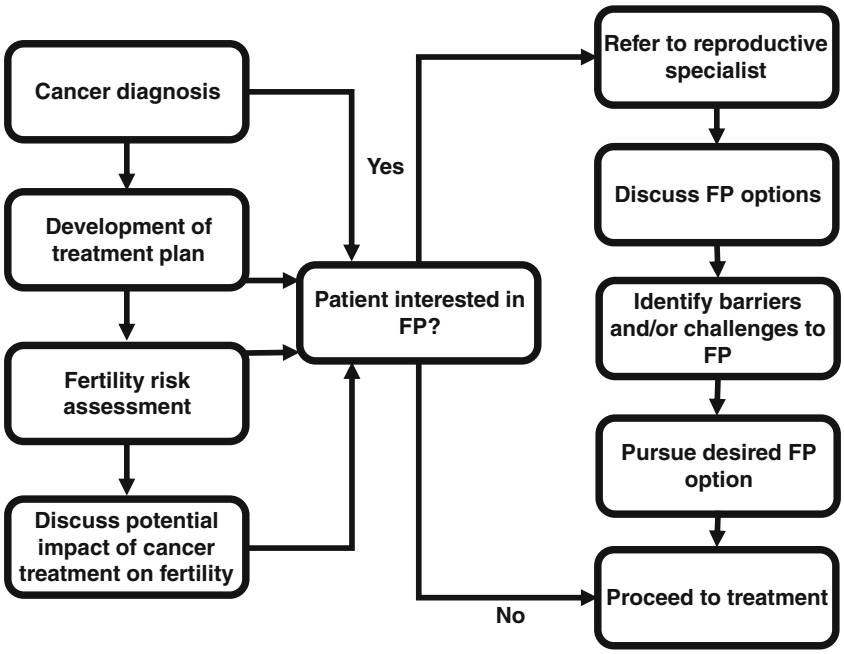

Fig. 1 Fertility care process

recommending that young patients diagnosed with cancer are offered fertility counseling. A retrospective survey study by Leteourneau et al. in over 1000 young women diagnosed with cancer showed lower regret and improved quality of life scores with dual counseling by an oncologist and fertility specialist, as well as with pursuit of FP [94]. Despite these benefits, only 5% reported receiving counseling by a fertility specialist and 4% reported having pursued FP. Fertility consultation with a reproductive specialist enhances patient's understanding of FP options and facilitates the FP decision-making process. While typically referrals to fertility specialists are made following development of the cancer treatment plan, we endorse discussion of potential effects of cancer treatment on fertility as soon as possible after breast cancer diagnosis in young women. These referrals can be offered at the time of initial multidisciplinary appointment scheduling or at any point that an interest in fertility preservation is identified (Fig. 1).

Conclusions

Fertility is an important concern among many young women diagnosed with breast cancer and can impact treatment decisions which may, in turn, potentially alter outcomes for these patients. It is advantageous for healthcare providers to understand reproductive risks of various treatments and available FP options in order to advise patients, make appropriate referrals, and ultimately guide patients in choosing a path that is right for that individual. Coordination of care between oncologists and fertility specialists is valuable to ensure young women have access to important information about fertility as well as FP techniques. This multidisciplinary approach extends to the survivorship setting as women may encounter issues related to fertility and pregnancy following initial treatment; however, interventions to preserve fertility are most successful when applied as early as possible. Reproductive health counseling and coordination of care remains a space for continued research and improvement to help young women achieve family planning goals.

Declarations

Conflict of Interest Erin E Roesch and Halle CF Moore declare that they have no competing interests

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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- •• Of major importance

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