Fertility Preservation and Pregnancy in Women With and Without *BRCA* Mutation–Positive Breast Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the difficulties in fertility preservation for women with *BRCA* positive/negative breast cancer.
2. Cite some of the effective methods for preserving fertility.
3. Describe the utilization of aromatase inhibitors as ovarian stimulants to reduce estrogen exposure in women with breast cancer attempting fertility preservation via embryo or oocyte cryopreservation.

CME

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ABSTRACT

Women with breast cancer face many challenges when considering fertility preservation. Delayed referral results in the limitation of fertility preservation options because most established methods, such as embryo and oocyte cryopreservation, require several weeks to complete. Women with *BRCA* mutations, on the other hand, may be more aware of fertility issues and motivated to see fertility preservation specialists earlier. Fear of exposure to estrogen limits access to fertility preservation via embryo or oocyte cryopreservation; however, the use of aromatase inhibitors as ovarian stimulants reduces such concern. Ovarian cryopreservation can be used when there is insufficient time to perform ovarian stimulation because this technique does not require hormonal stimulation, but there are safety concerns both in women with *BRCA*

mutations and in patients with hormone receptor–positive disease as well. There does not seem to be a proven ovarian suppression strategy to preserve fertility in women with breast cancer. Pregnancy appears to be safe for breast cancer survivors but studies specific for women with *BRCA* mutations are lacking. Women with *BRCA* mutations may elect to use preimplantation genetic diagnosis during in vitro fertilization to avoid transmitting the mutation, but there may be psychosocial difficulties in entertaining this option. Overall, the last decade has brought many options for women with breast cancer considering fertility preservation, but numerous challenges remain. The presence of *BRCA* mutations further contributes to these challenges. *The Oncologist* 2012;17:1409–1417

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INTRODUCTION

A breast cancer diagnosis in a young woman poses unique challenges in management, one of which is fertility preservation (FP). This article presents current evidence on the safety of pregnancy in women with breast cancer with and without *BRCA* mutations and discusses FP options for those patients, highlighting the use of potentially safer stimulation protocols such as those with aromatase inhibitors. Specific management issues regarding FP as well as the use of preimplantation genetic diagnosis (PGD) technology to avoid the transmission of *BRCA* mutations to offspring are also discussed.

SAFETY OF PREGNANCY BEFORE AND AFTER BREAST CANCER: DO *BRCA* MUTATIONS CONFER ADDITIONAL RISK?

Until now, no study has shown a negative impact of subsequent conception on breast cancer survivors' prognoses, particularly their risk for recurrence or death [1]. Additionally, some studies have suggested a survival advantage among those women who conceived following a breast cancer diagnosis and treatment [2]. As recently reported, in women aged <35 years presenting with early-stage breast cancer, a pregnancy subsequent to cancer therapy resulted in a 77% lower probability of death [3]. It has been suggested that at least some (but not all) of the studies that show a benefit or no effect of pregnancy on survival outcomes may be biased by the "healthy mother effect," that is, women who become pregnant after breast cancer are likely to be healthier and less likely to develop a recurrence than women who do not become pregnant [4]. Nevertheless, the findings are consistent across all studies and strongly suggest that the observations are clinically relevant. In a recent comprehensive literature review, the Endocrine Working Group of the Breast International Group–North American Breast Cancer Group concluded that, overall, the available data support pregnancy and breast feeding after breast cancer as safe and feasible for women at low risk for recurrence [5]. In that report, clinical and preclinical data were reviewed and a plausible biological explanation was proposed for the surprising protective effect of pregnancy after breast cancer—the induction of apoptosis of endocrine-responsive breast tumor cells by high levels of estrogen, progesterone, and human chorionic gonadotropin (hCG), similar to those presenting during pregnancy—which may also partially explain the known protective effect of an early term pregnancy in parous women against the occurrence of breast cancer later in life [5–7].

Furthermore, it has been shown that conceptions occurring as early as 6 months following an initial diagnosis of localized breast cancer confer a nonsignificant survival advantage, and if these women waited for 24 months, their survival outcome was significantly better (hazard ratio, 0.48; 95% confidence interval [CI], 0.27–0.83) [8]. The authors of that report concluded that the current medical advice given to women to wait for 2 years before attempting pregnancy is not supported by their data.

Although the aforementioned studies are highly reassuring for breast cancer survivors in general, there is no specific information on whether or not pregnancy is safe following a

breast cancer diagnosis in women with *BRCA* mutations. Nevertheless, there is some information on the impact of pregnancy on the risk for breast cancer in that population. Parity and number of children appear to be protective against developing breast cancer in carriers of *BRCA1* and *BRCA2* mutations in most large studies [8–11]. However, results have been contradictory, particularly in women with *BRCA2* mutations [11], but also those with *BRCA1* mutations [12]. It has been claimed that this inconsistency of results among various studies could be dependent on the analytical approach used. Results of studies using a similar analytic approach, that is, the weighted Cox regression analysis of affected and unaffected *BRCA1* and *BRCA2* mutation carriers of all ages, by gene and by age, have consistently shown a lower breast cancer risk associated with parity in women carriers of *BRCA1* and *BRCA2* mutations. This analytic model allows all mutation carriers with complete data to be included in the analysis, in contrast to other models using matched pairs, an approach that only allows cases if a matched pair is found [13].

Finally, reassuring to women with *BRCA* mutations, a case–control study in 1,380 matched pairs of women with *BRCA1* and *BRCA2* mutations did not find an adverse effect of fertility treatment on the risk for developing breast cancer, compared with controls (odds ratio, 1.21; 95% CI, 0.81–1.82). Those authors cautioned, however, that given the small sizes of the exposed subgroups, confirmatory studies were needed [14].

IMPACT OF BREAST CANCER TREATMENT ON FERTILITY

Although an exhaustive review of the literature on the impact of chemotherapy agents on ovarian function is not within the scope of this article and has been done elsewhere [15], a brief update can be found in the supplemental online Appendix A (see also Fig. 1). Because recent research suggested that *BRCA* mutation carriers may have a lower ovarian reserve [16, 17] and because deficient DNA repair may also make oocytes more susceptible to DNA-damaging agents (Appendix A), *BRCA* mutation carriers may be more susceptible to chemotherapy-induced ovarian reserve loss.

PRACTICAL POINTS WHEN COUNSELING WOMEN WITH BREAST CANCER ON FP

When deciding whether or not a candidate needs FP at all, several factors other than the impact of chemotherapy on ovarian reserve must also be considered. These include age, the delay necessary for the treatment to be completed, and the desired family size. Given this complexity, there cannot be a "one-size-fits-all" approach to FP [15]. Women are born with a set number of oocytes according to the current understanding, and this reserve of oocytes is continually depleted with age. The rate of depletion appears to accelerate after the age of 37 years [18]; mirroring this change, pregnancy rates and assisted reproduction success rates also decline more sharply past the age of 37 years. Fertility is significantly diminished in the early 40s and is practically abolished by the age of 46 years [19]. As discussed in Appendix A, gonadotoxic chemotherapeutic agents

Figure 1. Impact of breast cancer chemotherapy on different stages of follicle growth. Based on molecular studies in our laboratory, alkylating agents such as cyclophosphamide and topoisomerase inhibitors such as doxorubicin affect primordial follicle reserve, which results in the shortening of the reproductive life span. These agents are toxic against the nonproliferating population of primordial follicles because they induce apoptotic cell death via induction of breaks in double-strand DNA. The impact of taxanes on the primordial follicle population is unclear from clinical observations and molecular studies are awaited. Regardless of the type of agent, all chemotherapeutics are capable of damaging developing follicles because their granulosa cells are proliferating, and causing at least temporary amenorrhea. Because new follicles will develop from an undamaged primordial follicle population within 3–6 months, this amenorrhea is temporary for non-DNA-damaging agents and hence should not affect future fertility. Antimetabolites such as methotrexate appear to only affect the developing population and hence cause transient amenorrhea without altering ovarian reserve.

Abbreviation: FSH, follicle-stimulating hormone.

Figure 2. Chemotherapy-induced decline in follicle reserve. Our quantitative histological analysis revealed that the primordial ovarian follicle density of chemotherapy-exposed females with a mean age of 26.7 years was similar to that of females of 36.5 years of age with no prior exposure. This suggests that chemotherapy exposure may advance "ovarian age" by nearly a decade. Adapted from Oktay O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. *Cancer* 2007;110:2222-2229, with permission.

such as cyclophosphamide, and potentially doxorubicin, may result in a significant diminishing of ovarian reserve. Based on our histological analysis of primordial follicle density from chemotherapy-exposed and unexposed women, we estimated that combination chemotherapy regimens such as cyclophosphamide and doxorubicin (AC) may result in at least the loss of 10 years worth of oocyte reserve. Specifically, we found that

the mean primordial follicle density of chemotherapy-exposed females with the mean age of 26–27 years was similar to that of those aged 36–37 years with no prior exposure (Fig. 2) [20].

In addition, by measuring circulating levels of anti-Müllerian hormone (AMH), the current best biochemical marker of ovarian reserve, which is produced by the cohort of growing follicles in the ovaries [21], we found, in a preliminary analysis, that chemotherapy-treated breast cancer patients also presented with significantly lower AMH levels ($n = 68$; age, 35.4 ± 0.7 years; AMH, 0.7 ± 0.2 mg/mL) than those of a control group of women matched for age ($n = 67$; age, 34.6 ± 0.7 years; AMH, 2.4 ± 0.3 ng/mL). Though these two groups were similar in age, the AMH levels of the chemotherapy-treated group were consistent with those found in women a decade older [22]. Our results are also supported by published AMH values from postchemotherapy-treated breast cancer patients and age-matched controls, indicating that there is an ~10-year advancement in "ovarian age" subsequent to breast cancer chemotherapy [23]. Based on this, for example, if a 30-year-old woman receives AC therapy, her reserve may be reduced and become comparable with that of a 40-year-old female immediately after treatment. She would resume her menstruation because she has not depleted her reserve and would deceptively appear as if unaffected by such treatment. If, for example, she has to receive tamoxifen for 5 years, her ovarian reserve would be comparable with that of a 45-year-old woman by the time that treatment was completed, and hence severely depleted. In such a case scenario, she would still benefit from FP even though, at age 30, the initial age of diagnosis, the risk for permanent amenorrhea is misleadingly low. FP may be indicated even in younger

women, especially in those who wish to build a larger family, because by the time one or two pregnancies are achieved, age-related decline in ovarian reserve may compound the chemotherapy-induced damage to the ovarian reserve. It is therefore highly critical that candidates are thoroughly evaluated by a team experienced in FP [24, 25] (Fig. 3).

AN INDIVIDUALIZED APPROACH TO CHOOSING THE APPROPRIATE FP PROCEDURE

The main principle in FP counseling is to guide the candidate to the least experimental and most successful method when sufficient time is available. Embryo cryopreservation is the most established and successful FP method, and hence is offered as the first choice in women who have a partner and sufficient time. When a partner is not available, oocyte cryopreservation can be considered instead, but it is still considered investigational. Though, overall, pregnancy rates with oocyte cryopreservation are lower than those with embryo freezing, recent research indicates that this gap may be closing [26–28]. Both procedures require ovarian stimulation, which may take ~2 weeks to complete. In either case, ovarian-stimulating drugs significantly increase estrogen levels, which is not desirable in most breast cancer patients. Egg retrieval is also possible without hormone stimulation in a natural cycle, but this procedure has a very low yield of oocytes and embryos [29]. Immature oocytes can also be retrieved without waiting for the necessary 2 weeks for oocyte maturation, but this procedure requires further in vitro maturation in the laboratory, which is not as efficient as working with mature oocytes from stimulated cycles and is only available in a small number of clinics worldwide [30]. In addition, we have shown that ovarian stimulation can be initiated at various times during the menstrual cycle, and even after ovulation in emergency cases, and still a significant number of oocytes and embryos can be obtained for cryopreservation [31, 32]. This is consistent with our recently improved understanding of ovarian physiology, which indicates that there are multiple waves of follicle recruitment during each menstrual cycle [33].

To reduce estrogen exposure and yet be able to obtain a large number of oocytes, we developed ovarian-stimulation protocols using aromatase inhibitors (see next section). Ovarian tissue cryopreservation, on the other hand, is a more experimental technique that does not require ovarian stimulation and can be accomplished within a short period. An advantage of ovarian cryopreservation for subsequent transplantation is that it can restore ovarian hormonal function, though the latter may not always be desirable in women with advanced stage breast cancer [34, 35]. Ovarian cryopreservation is considered the most experimental of all three cryopreservation procedures discussed. This is because, since the performance of the first transplantation of frozen ovarian tissue in 1999 by us [36], there have been <20 live births from an unknown number of attempts [37]. In contrast, there have been >1,000 live births with oocyte cryopreservation [38]. Ovarian cryopreservation is typically offered when there is insufficient time to perform ovarian stimulation and when the candidate also desires future resumption of ovarian endocrine function.

Figure 3. Approach to candidate for fertility preservation (FP). We use a three-tier approach—triage, physician evaluation, and supportive care—to facilitate and streamline the evaluation of the candidate for FP.

In summary, everything being equal, the recommended FP procedures are, in order of preference, embryo, oocyte, and ovarian tissue cryopreservation. Overall FP options for women with breast cancer are summarized in Figure 4.

VALUE OF EARLY REFERRAL FOR FP

Early referral for FP allows women with breast cancer a wider choice of options, as already discussed. In a recent study, we investigated whether or not early referral before breast surgery resulted in better FP cycle outcomes, using embryo or oocyte cryopreservation in 93 women with a mean age of 35.2 ± 4.4 years [39]. That study is summarized in the supplemental online Appendix B. We concluded that FP referral before breast surgery enables earlier initiation of cryopreservation cycles and chemotherapy and, when appropriate, multiple FP cycles. Women who can undergo multiple cycles may have an advantage in FP because of a larger number of oocytes or embryos cryopreserved [39, 40].

There is some difference for women who carry *BRCA* mutations and for those with a family history of breast cancer in terms of referral patterns. We recently analyzed the determinants of access to FP in 314 women with breast cancer. We found that, overall, there was a trend toward earlier referral to FP in women with breast cancer. It also appeared that women with a family history of breast cancer tended to be referred earlier. The latter observation could be a result of the increased awareness of *BRCA* mutation carriers because other family members might have had similar experiences or possibly because a looming risk-reducing salpingo-oophorectomy (RRSO) made FP a more urgent issue.

In summary, early referral for FP may improve the likelihood of success. Health care providers, including primary care physicians, interventional radiologists, and breast surgeons, involved in the early stages of diagnosis should become more proactive to facilitate early referrals.

OVARIAN STIMULATION PROTOCOLS WITH AROMATASE INHIBITORS

In women diagnosed with breast cancer, there is usually sufficient time to undergo ovarian stimulation for the purpose of FP

Figure 4. An individualized strategy for FP in breast cancer patients. Depending on the availability of time, patient's age, whether or not adjuvant chemotherapy and/or tamoxifen treatment is planned, and the candidate's preference in future family size, the FP strategy will vary.

Abbreviations: FP, fertility preservation; FSH, follicle-stimulating hormone.

by embryo or oocyte cryopreservation, especially if adjuvant instead of neoadjuvant chemotherapy is planned. After the initial diagnosis, it takes at least 3–4 weeks to schedule breast surgery, and typically, chemotherapy is initiated 5–6 weeks after breast surgery. This, in theory, provides sufficient time to undergo ovarian stimulation for embryo or oocyte cryopreservation, especially if patients are referred early in the process [39]. A significant concern in performing ovarian stimulation in women with breast cancer is exposure to high levels of estrogen. Historically, ovarian stimulation was avoided in women with breast cancer for the same reason, and hence embryo or oocyte cryopreservation was rarely offered. Tamoxifen, an estrogen agonist–antagonist, is also an ovarian stimulant. Because of this concern, we originally developed an ovarian stimulation protocol using tamoxifen [29]. Subsequently, we used aromatase inhibitors along with standard injectable follicle-stimulating hormone (FSH) to suppress the estrogen rise resulting from ovarian stimulation. Aromatase inhibitors, when used in premenopausal women, also act as ovarian stimulants, and have been used to induce ovulation induction in infertile women [41]. In the first trial, we compared ovarian stimulation with tamoxifen versus letrozole and found that letrozole stimulation resulted in larger number of oocytes and embryos while being associated with lower estrogen levels [42]. As a result, ovarian stimulation with aromatase inhibitors became our first choice for ovarian stimulation with breast cancer. We also found that letrozole but not anastrozole causes ovarian stimulation along with suppression of estrogen levels at or close to natural cycle levels during a cryopreservation cycle [42–44]. Anastrozole did not suppress estrogen pro-

duction during the 2 weeks of ovarian stimulation probably because of its lower efficiency in inhibiting aromatase activity and slower action in premenopausal women [43, 44]. Letrozole–FSH stimulation resulted in numbers of oocytes and embryos comparable with those obtained with standard in vitro fertilization (IVF) cycles [43]. We also determined the impact of ovarian stimulation on relapse-free survival times. In that study, we followed 79 women who underwent ovarian stimulation and embryo or oocyte cryopreservation with the letrozole–FSH protocol for a mean of 23.4 months (range, 7.5–63.6 months). They were then compared with 136 similar women with breast cancer who did not elect to undergo ovarian stimulation and who were followed up for a mean of 33.05 months (range, 4.5–63.6 months) [45]. Prognostic differences between the treatment and control groups were adjusted for using Adjuvant Online! (<http://www.adjuvantonline.com>). We found no differences in relapse-free survival rates between the two groups, and the hazard ratio for recurrence after ovarian stimulation with letrozole and gonadotropins was 0.56 (95% CI, 0.17–1.9). Our extended follow-up indicates that the same pattern holds [46]. Thus, ovarian stimulation with letrozole appears to be an effective and relatively safe approach in women with breast cancer, pending long-term follow-up. Our preliminary data on pregnancy outcomes also indicate that the procedure results in pregnancy rates comparable with those seen with standard IVF treatments [46].

In the initial letrozole protocol, the final maturity of oocytes was triggered with hCG, as is the case for standard ovarian-stimulation cycles. Use of hCG has two disadvantages. First, it causes a false-positive pregnancy test and cre-

ates confusion when a required pregnancy test is performed prior to initiation of chemotherapy. Second, it further stimulates the ovaries and may increase estrogen levels after egg retrieval. In our initial protocol, we discontinued letrozole treatment on the day of hCG administration and resumed it 2 days later (on the day of oocyte retrieval) to keep estrogen levels suppressed in the luteal phase. In a recent modification of the protocol, we used 1 mg leuprolide acetate, a gonadotropin-releasing hormone (GnRH) analog, for the oocyte maturity trigger [47]. GnRH analogs cause an initial surge in FSH and luteinizing hormone (LH) levels before causing pituitary suppression, and as a result can be used as ovulation-triggering or oocyte-maturation agents. Because of subsequent suppression, however, estrogen levels drop sharply, thereby reducing estrogen exposure. In that nonrandomized sequential prospective study, the first 47 women received hCG whereas the next 27 received a GnRH analog as a trigger. We found that the estradiol concentration dropped more significantly in the GnRH analog group ($p = .013$) and the incidence of ovarian hyperstimulation was lower. More interestingly, GnRH analog trigger resulted in a higher number of mature oocytes and embryos. Hence, the letrozole-FSH protocol (also named Controlled Ovarian Hyperstimulation Treatment with Letrozole Supplementation Study [COST-LESS]) has now been modified to incorporate a GnRH analog injection, further reducing estrogen exposure in the setting of breast cancer [47]. Moreover, because of the ovarian suppression that follows a GnRH analog trigger, we no longer have to administer letrozole after oocyte retrieval to prevent a secondary rise in estrogen levels (Fig. 5).

OVARIAN RESERVE IN WOMEN WITH *BRCA* MUTATIONS

During COST-LESS cycles, we observed that some women with *BRCA* mutations did not sufficiently respond to ovarian stimulation, which is usually described as low ovarian response and denotes reduced ovarian reserve. We subsequently studied this in 126 women with breast cancer by using letrozole and gonadotropins for the purpose of FP by embryo or oocyte cryopreservation. Of the 82 women who met the inclusion criteria, 47 (57%) had undergone *BRCA* testing and 14 had a *BRCA* mutation, of which two were of clinically undetermined significance. Those two patients were not included in the *BRCA* mutation-positive cohort for analysis because it was unclear whether they had true mutations or polymorphisms. In *BRCA* mutation-positive patients, a low response to ovarian stimulation occurred significantly more frequently than in patients without *BRCA* mutations (33.3% vs. 3.3%; $p = .014$) and than in women not tested for their *BRCA* status (2.9%; $p = .012$). All *BRCA* mutation-positive patients presenting with a low response to ovarian stimulation and requiring higher doses of gonadotropins for their stimulation treatment had *BRCA1* mutations, and a low response was not encountered in women who were only positive for a *BRCA2* mutation. Compared with controls, *BRCA1* mutation-positive, but not *BRCA2* mutation-positive, women produced lower numbers of eggs—7.4 (95% CI, 3.1–17.7) versus 12.4 (95% CI, 10.8–14.2) ($p = .025$)—

and had as many as 38.3 times the odds ratio for a low response (95% CI, 4.1–353.4; $p = .001$) [16]. Moreover, recent work indicated that women with *BRCA* mutations may experience menopause earlier [17, 48]. Although these findings require further confirmation, these data indicate that some women with *BRCA* mutations may have a lower egg reserve and can experience earlier menopause. Whether or not this has an effect on the fertility potential of women with *BRCA* mutations is another question that needs to be answered. In a recent study based on a survey of 2,254 women with *BRCA* mutations in comparison with 764 controls, a history of fertility problems and fertility medication use as well as the mean parity were similar. Those authors concluded that larger studies with age-stratified analyses are needed to definitely answer this question, and if there is a difference in fertility it would most likely be toward the limits of their reproductive life [49]. Consistent with this observation and hypothesis, we found that all *BRCA* mutation-positive women who responded poorly to fertility medications were aged >33 years [16]. Taking these observations together with the data indicating earlier menopause in *BRCA* carriers [17, 48], some women with *BRCA* mutations may have a reproductive life span that is 2–4 years shorter than that of the general population.

OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION: RECENT PROGRESS AND THE ISSUES SPECIFIC TO *BRCA* CARRIERS

The current state of ovarian tissue cryopreservation and transplantation as well as potential future options for using such tissue are discussed in the supplemental online Appendix C and reviewed in Figure 6. Because RRSO is recommended in young women with *BRCA* mutations at the completion of childbearing or by age 40, FP by ovarian cryopreservation is commonly brought into discussion. Although an ovary cryopreserved from a *BRCA* mutation carrier age ≥ 40 years may pose a significant risk for ovarian cancer if transplanted later, theoretically this risk may be lower if the ovary is cryopreserved at a younger age, and regardless of the age, the tissue is transplanted. With this approach, at least in theory, *BRCA* carriers may be able to “suspend” their risk for ovarian cancer until they are ready for childbearing. To minimize concerns regarding the development of ovarian cancer, another approach is to transplant ovaries s.c., as we have previously described [50, 51]. In our previous work, we showed that ovarian cortical strips transplanted s.c. in the forearm or lower abdomen can produce estrogen and result in follicle development. We were also able to retrieve oocytes from these s.c. transplants and generate embryos. This technique may be preferable in women with *BRCA* mutations because it allows closer monitoring of the tissue. Another theoretical advantage of ovarian transplants to the s.c. space in the forearm is that the antecubital vein becomes the ovarian vein and the immediate ovarian output of tumor markers can be monitored by simple phlebotomy [51]. Nevertheless, no *BRCA* mutation-positive woman has undergone ovarian transplantation yet, and hence the efficacy and safety of these approaches need to be tested in future studies.

Figure 5. Controlled Ovarian Stimulation with Letrozole Supplementation Study (COST-LESS) protocol. The aromatase inhibitor letrozole is initiated on the second day of the menstrual cycle, 2 days ahead of starting follicle-stimulating hormone (FSH) stimulation. Gonadotropin-releasing hormone (GnRH) antagonists are added later, when a lead follicle reaches 13 mm in size, to prevent spontaneous ovulation ahead of oocyte retrieval. In the current modification of the protocol, a GnRH analog trigger (1 mg, s.c.) is used to initiate the oocyte maturation process, and oocyte retrieval is performed 35 hours later just prior to ovulation. GnRH analog trigger causes ovarian suppression immediately after oocyte retrieval, further minimizing estrogen exposure in the luteal phase.

Figure 6. Potential future strategies to use cryopreserved ovarian tissue when ovarian transplantation is not considered safe. When ovarian cryopreservation is the only available option for fertility preservation but the future transplantation of ovarian tissue is not considered safe, such as with ovarian metastasis or a high risk for ovarian cancer development in women with *BRCA* mutations, experimental strategies such as in vitro follicle growth and xenografting may become available to mature oocytes ex vivo in the future. These options are currently theoretical in the clinical setting.

DOES OVARIAN SUPPRESSION PROVIDE OVARIAN PROTECTION AGAINST CHEMOTHERAPY?

Much controversy still exists on the use of GnRH analogs aimed at suppressing ovarian function transiently during chemotherapy. This topic is reviewed in the supplemental online Appendix D. In summary, data from randomized studies are still conflicting on the protection of menstrual function, whereas none showed evidence for FP. Studies investigating the effects of ovarian suppression on markers of ovarian reserve do not currently support GnRH analog cotreatment as an effective strategy for female FP. The ongoing Southwest Oncology Group Study, which aimed at investigating GnRH analog cotreatment effects on the rate of ovarian failure at 2 years of follow-up, was expected to help finalize the discussion on the effectiveness of ovarian suppression for FP during chemotherapy. Unfortunately, that trial was prematurely closed because of poor accrual. Although there is consensus that

endocrine therapy given sequentially after chemotherapy is beneficial in women with hormone receptor-positive breast cancer, there is concern about decreasing the efficacy of chemotherapy with concurrent endocrine therapy in patients with hormone-positive breast cancer [52], and additional potential late effects of GnRH analogs in combination with chemotherapy for early breast cancer have been postulated [53].

ALTERNATIVE OPTIONS: EGG DONATION, GESTATIONAL CARRIERS, AND ADOPTION

Cancer survivors who have lost their ovarian reserve as a result of gonadotoxic treatments but who are permitted to carry a pregnancy as well as those who are unable to carry a pregnancy have the possibility of building their families through third-party reproduction, that is, the participation of a third person who donates the gametes or acts as a gestational carrier to the

intended parents. These options are reviewed in the supplemental online Appendix E.

PGD FOR *BRCA* MUTATION CARRIERS

PGD is a technique whereby one to two blastomeres of a developing embryo are removed and subjected to molecular analysis to determine chromosomal or single gene disorders prior to implantation of the embryos during an IVF procedure. There are numerous single gene disorders diagnosed with this approach, and recently *BRCA* mutations were successfully tested [54]. This, however, may create emotional distress among some women because *BRCA* mutations are neither lethal per se nor does their presence guarantee cancer development. Therefore, thorough counseling and psychosocial evaluation are essential [55, 56]. The decision to discard otherwise normal embryos may not always be acceptable from an emotional, religious, or ethical point of view, and PGD for cancer predisposition divides opinion among health care professionals in Europe and in the U.S. [57].

CONCLUSIONS

We summarize the key points in this article in Table 1. Women in general, and particularly women with breast cancer, face many challenges when considering FP [58]. Fear of exposure to estrogen limits access to FP via embryo or oocyte cryopreservation; however, the use of aromatase inhibitors as ovarian stimulants reduces such concerns. *BRCA* mutation carriers may show a lower response to ovarian stimulation but whether or not this impacts their future fertility needs to be further determined. An early oophorectomy can be performed to cryopreserve ovarian tissue from women with *BRCA* mutations before their risk for ovarian cancer increases with age, but the safety of transplanting this tissue back must be determined. Pregnancy appears to be safe for breast cancer survivors, but studies specific for women with *BRCA* mutations are lacking. Women with *BRCA* mutations may elect to use PGD during IVF to avoid transmitting the mutation, but there may be psychosocial difficulties in entertaining this option. Overall, the last decade has brought many options for women with breast cancer considering FP, but numerous challenges remain. The

Table 1. Key points

- Early referral for fertility preservation is essential to ensure success.
- Use of aromatase inhibitors as ovarian stimulants may reduce concerns of estrogen exposure in women with breast cancer attempting fertility preservation via embryo or oocyte cryopreservation.
- Women with *BRCA* mutations may have a lower ovarian reserve.
- Ovarian cryopreservation can be used when there is insufficient time to perform ovarian stimulation, but this technique is still experimental. An early oophorectomy can be performed to cryopreserve ovarian tissue from women with *BRCA* mutations before the risk for ovarian cancer increases with age, but the safety of transplanting this tissue back must be determined.
- Pregnancy appears to be safe for breast cancer survivors, but studies specific for women with *BRCA* mutations are lacking.
- Women with *BRCA* mutations may elect to use preimplantation genetic diagnosis during in vitro fertilization to avoid transmitting the mutation.

presence of *BRCA* mutations further contributes to these challenges.

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