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FERTILITY ISSUES AND BREAST CANCER (J JERUSS, SECTION EDITOR)

Oocyte Donation, Gestational Carriers, and Adoption for Breast Cancer Survivors

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Abstract

Purpose of Review The purpose of this review is to describe and compare the use of oocyte donation, gestational carriers, and adoption for family building specifically in women with a history of breast cancer.

Recent Findings Oocyte donation is an effective and safe option for women whose exposure to gonadotoxic cancer therapy has resulted in primary ovarian insufficiency, or for women with a familial cancer syndrome who are concerned about genetic risk to their offspring. A gestational carrier may also be considered—with or without oocyte donation—depending on the patient's acceptance of ovarian stimulation and pregnancy in the context of prior breast cancer or ongoing endocrine therapy. Lastly, adoption is a frequently considered option for family building by many breast cancer survivors.

Summary Assisted reproductive technology and adoption offer breast cancer survivors the opportunity to expand their families despite the challenges that the diagnosis may pose.

Keywords Oocyte donation · Gestational carriers · Adoption · Breast cancer

Introduction

Four to 10% of women with breast cancer in the USA are under 40 years of age, and of these patients, over half desire future fertility at the time of their diagnosis [1, 2]. The diagnosis of breast cancer may therefore trigger anxieties not only about treatment and surveillance but also about how these processes may affect reproductive prospects. Prior studies have found that 73% of young breast cancer patients expressed concern about the possibility of becoming infertile, and 29% reported that their concern influenced treatment decisions [3••].

Breast cancer treatment has many implications for fertility in young women. First, many chemotherapeutic agents commonly used for breast cancer treatment may induce primary ovarian insufficiency (POI), which is defined as premature depletion of the pool of primordial follicles (i.e., ovarian reserve) and loss of ovarian function [4]. For example, a standard course of cyclophosphamide adds approximately 10 years to ovarian reproductive age [5]. Though some women may experience resumption of menses and fertility, others experience permanent POI. In addition, many adjuvant therapies are contraindicated during pregnancy, potentially resulting in a delay in childbearing [6]. This is especially important given recent recommendations to consider extending adjuvant anti-hormonal therapy from 5 to 10 years in women with hormone receptor-positive breast cancers [7]. For women with familial cancer syndromes such as hereditary breast and ovarian cancer syndrome (HBOC), concerns about fertility may be further complicated by recommendations for risk-reducing oophorectomy as early as 35 years, limiting their window for childbearing [8]. They may also wish to ensure that they do not pass on genetic risk to their children [9].

While fertility preservation prior to or during treatment is paramount, women who are actively hoping to expand their families may also benefit from other strategies. The aim of this review is to describe options including oocyte donation, gestational carrier, and adoption, as well as to highlight ways in

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which a diagnosis of breast cancer may raise special considerations for these processes.

Oocyte Donation

In vitro fertilization (IVF) with oocyte donation is an assisted reproductive technology in which a third-party donor undergoes ovarian stimulation to yield oocytes, which can then be fertilized. The resulting embryo is transferred into the patient in the hopes of achieving pregnancy. The sperm used to fertilize the oocyte may be from a donor or from the patient's partner. In the general population, oocyte donation accounts for 14% of all IVF cycles and is commonly used for women with POI. The cumulative live birth rate is as high as 60%, making this an extremely effective treatment option [10]. This is in contrast to autologous IVF, in which the patient herself undergoes ovarian stimulation, which has a much lower success rate among women with POI [11].

Oocyte donation circumvents the issue of POI in women who have undergone treatment with gonadotoxic agents. In a retrospective cohort study of 142 women who had been treated and cured of cancer, including breast cancer ($n = 30$), there was no significant difference in live birth rate from those seen in a non-cancer control group after using donor oocytes (39.4% versus 40.2%) [12]. Though this study did not specify the average number of cycles needed to achieve delivery, there was also no significant difference in live birth rate after the first cycle (41.8% versus 36.9%). Subanalysis by the type of malignancy revealed similar results. Another study found that while there was a significant difference in live birth rate for women with a history of cancer when using autologous oocytes (24.7% versus 47.7%, $p < 0.01$), there was no difference when using donor oocytes (60.4% versus 64.5%) [13•]. For those who value the experience of being pregnant and delivering an infant, donor oocytes are an effective treatment option for women with iatrogenic POI from antineoplastic therapies.

For women with a familial cancer syndrome, use of donor oocytes has the potential to decrease the risk of passing the condition on to offspring—assuming the egg donors themselves do not carry a similar gene mutation. The American Society for Reproductive Medicine (ASRM) guidelines for oocyte donor screening note that potential donors with significant familial diseases should undergo genetic screening, though testing for particular diseases or carrier states is not mandated [14]. In a retrospective study of oocyte donors at a single university fertility center over 12 years, none of the 1303 participants was screened for familial cancer syndromes after consultation with a genetic counselor [15]. While it may not be possible to eliminate the risk of a donor carrying a gene for a familial cancer syndrome, many women may perceive this risk to be lower given that egg donors do not have a *known* genetic defect. An alternative means of reducing genetic risk to offspring is to undergo autologous IVF with preimplantation genetic testing for monogenic disorders (PGT-M), in which the embryo is biopsied prior to transfer in order to identify whether or not it carries the genetic defect. For some women who are unable or unwilling to undergo autologous IVF with PGT-M, oocyte donation may be a more favorable approach.

The use of donor oocytes may also be appealing for breast cancer patients who are hesitant to undergo ovarian stimulation for autologous IVF. Injectable gonadotropins, which are the most common method of ovarian stimulation, may result in estrogen levels up to 20 times the levels seen in natural cycles [16]. There is concern that supra-physiologic levels of estrogen may stimulate hormone receptors in malignant cells among women with hormone-responsive breast cancer. Even for those with hormone-receptor negative tumors, estrogen is thought to potentially have an indirect mitogenic effect. Despite these concerns, there is little evidence that ovarian stimulation increases the risk of breast cancer recurrence [17]. In addition, the aromatase inhibitor letrozole has been used as an adjunct during ovarian stimulation and results in significantly lower circulating estrogen levels [18]. Though the evidence on ovarian stimulation is overall reassuring, oocyte donation offers an alternative to patients and their oncologists who may remain hesitant to pursue autologous IVF.

Importantly, women with a history of cancer may be at higher risk of certain adverse maternal and perinatal outcomes after becoming pregnant using donor oocytes. In a prospective study of donor oocyte outcomes, there was a fivefold increased risk of preeclampsia and threefold increased risk of preterm birth in women with a history of cancer when compared to women without a history of cancer [19]. While the risks of assisted reproductive technology in this patient population must be acknowledged, for many women, the experience of pregnancy and childbirth is highly valuable. Use of donor oocytes offers women with a history of breast cancer an effective way to achieve pregnancy.

Gestational Carrier

A gestational carrier is a woman who carries a pregnancy and delivers a baby for another individual or couple, known as the intended parent or parents. The primary advantage of a gestational carrier over adoption is the ability to have a genetically related child, since the gestational carrier can carry a pregnancy created with gametes derived from one or both intended parents. Gestational carriers were involved in 3% of assisted reproduction cycles in the USA in 2016, a significant increase from 1% in 1999, and 2.5% in 2013 [20•, 21]. Good success rates have been reported for IVF cycles involving gestational carriers [22]. According to national registry data collected by

the Society for Assisted Reproductive Technology (SART) in 2013, the live birth rate per embryo transfer was 42% for cycles using oocytes from the intended mother [20•].

For female patients who have diminished ovarian reserve, POI, or a desire to avoid ovarian stimulation, donor oocytes may be used in conjunction with a gestational carrier. In the same study of national data from 2013, the live birth rate for gestational carriers using donor oocytes was 61%, which was significantly higher than those using oocytes from the intended mother [23]. Especially for patients with known infertility, utilizing both a gestational carrier and donated oocytes may maximize the chances of having a child [24].

The incidence of gestational carrier use among cancer survivors is not known, as SART does not collect information on the indication for using a gestational carrier. In a series of 333 gestational carrier cycles in Canada, only one patient reported breast cancer as the indication for using a gestational carrier. In small studies of cancer survivors who underwent fertility preservation, about 40% of the patients who returned for their cryopreserved specimens chose to use a gestational carrier [25–28]. Small sample sizes in these reports make it difficult to interpret success rates; however, about 30–40% of non-donor embryo transfers in gestational carriers in these studies did result in live birth [29, 30].

Women with breast cancer may consider using a gestational carrier due to concerns that pregnancy may worsen cancer outcomes or recurrence risk, or to avoid delays in conception necessitated by cancer therapy. Moreover, repeated IVF failure, advanced maternal age, or other medical comorbidities can be indications for gestational carrier use that are independent of cancer history.

Many women with a history of estrogen-sensitive tumors are concerned about implications of pregnancy on breast cancer. It was once thought that the high levels of ovarian hormones, prolactin, and placental lactogens might result in exposure of mammary glands to stimulation leading to cancer recurrence [31]. However, there is little evidence that pregnancy worsens cancer outcomes or increases the risk of disease recurrence [32]. In fact, some studies show that pregnancy after breast cancer may improve survival regardless of estrogen receptor status. A meta-analysis found that there was a 41% reduced risk of death in women who became pregnant after breast cancer [33]. This may partially reflect a "healthy mother bias," in which women who are healthier tend to have children and thus be overrepresented in these studies. There are no studies that have been able to fully adjust for this bias, though one meta-analysis did perform a subanalysis of only women with low risk characteristics and controls matched on prognostic factors [34]. In this study, the hazard ratio for death was 0.51 in women who had children. Overall, the data is reassuring that pregnancy after breast cancer is at least safe, if not beneficial. However, some women remain hesitant to pursue pregnancy, and among women who reported not wanting biological children, 36% cited fear of recurrence as the primary reason [3••]. For those women, a gestational carrier may be seen as a safer alternative.

For women who develop breast cancer during their reproductive years, there are often medical reasons why a pregnancy is not recommended soon after diagnosis. Many oncologists recommend delaying pregnancy for at least 2 years after diagnosis, since the risk of breast cancer recurrence is highest during this time. A longer interval may be appropriate for patients with more advanced disease, such as axillary node involvement. The reason for this delay is that recurrence during pregnancy can be complicated. In addition to the physical and emotional burdens of recurrent cancer, patients and their care teams must decide, depending on the trimester, whether to terminate the pregnancy, plan for early delivery followed by treatment, or treat during the pregnancy, understanding the maternal and fetal effects of chemotherapy [35].

Additionally, most women with estrogen-receptor positive breast cancer are now prescribed endocrine therapies, such as tamoxifen, for up to 10 years after initial treatment due to evidence of reduced cancer recurrence and overall mortality as reported in the ATLAS trial [36]. These hormonal therapies are contraindicated in pregnancy. Prolonged tamoxifen use has been cited as a primary reason for survivors' use of a gestational carrier, in addition to concerns about general safety of pregnancy after cancer [30]. There remains, however, a paucity of data regarding how an interruption in endocrine therapy to achieve pregnancy may alter disease status or recurrence risk. The POSITIVE Trial (Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine-Responsive Breast Cancer) is an ongoing clinical trial to specifically evaluate the effect of interrupting anti-hormonal therapy in order to achieve pregnancy [37].

Adoption

Adoption is an important option for family building in women with a history of breast cancer who are unable to or uninterested in having a biological child. In a survey study of female cancer survivors, 81.6% reported that they would consider adoption, whereas only 40.3% of women without a cancer history responded similarly [38•].

Despite the evidence that cancer survivors are interested in adoption, there are several barriers to this process. To begin, patients themselves often have reservations about adoption. In a survey study examining attitudes toward adoption, 85% of cancer survivors reported having concerns about the process, including preference for a biological child (48%), expense (45%), not being perceived as a good candidate by an adoption agency (41%), and needing more information about the process (39%) [38•]. Several others also noted a desire to physically experience a pregnancy as a potential reason to

not choose adoption. Among those who would consider adoption, 29% were worried about their personal health interfering with their ability to care for a child.

Another barrier, as alluded to by the patient concerns reported above, is that some adoption agencies are reluctant to work with cancer survivors. In an interview study of six large international adoption agencies, three reported asking about a client's cancer history, and all six agencies reported that cancer would be a barrier to adoption [39]. They also mentioned that in many countries other than the USA, cancer is considered a contraindication to adoption, and birth parents may be wary of placing their child with a cancer survivor. Another study of 77 international adoption agencies found that many required a letter stating that the adoptive parent was 5 years cancer-free, and some requested the contact information of oncologists in order to gather additional information [40].

Limited guidance exists for cancer survivors on the adoption process. Among oncology healthcare professionals, 62% reported knowing "a little" about adoption, and only 15% felt that knew "a lot" [39]. Highlighting the lack of institutional support for adoption in cancer survivors, the American Society of Clinical Oncology's guidelines on fertility preservation only briefly mention adoption without providing details or supplemental resources [41].

Despite these barriers, adoption remains an important option for breast cancer survivors hoping to expand their families. Undergoing successful adoption may partially alleviate distress about infertility among cancer survivors. In a study of attitudes toward infertility among female cancer survivors, including 130 with breast cancer, a follow-up interview was performed 10 years after enrollment [42]. Thirteen of the women in the study tried to adopt a child, nine were successful, and an additional six raised informally adopted children. Those who had a biological child reported significantly less distress surrounding infertility when compared to childless participants, while those who adopted reported intermediate distress about infertility.

It is also important to consider the cost of adoption relative to oocyte donation or use of a gestational carrier. The cost of achieving a live birth following oocyte donation is estimated to be roughly $40,000 [43]. A gestational carrier ranges from $60,000 to $125,000 [44]. On the other hand, private adoption agencies may charge $20,000 to $45,000, in addition to a home study fee of up to $4000 [45]. Alternatively, adopting a child from the foster care system is associated with minimal costs, and the federal government may provide monthly reimbursements. For women with a history of breast cancer, these costs must be weighed against their financial capabilities as well as their personal values and desire for a family.

Conclusion

With advancements in cancer treatments and survival rates, young women with breast cancer are increasingly able to prioritize quality-of-life concerns, with special attention to future fertility and childbearing. Unfortunately, the very cancer therapies that save and prolong life also threaten reproductive potential due to ovarian damage. This review is intended to remind patients and providers that autologous IVF is not the only option for women in this situation. Opening the discussion to include oocyte donation, gestational carriers, and adoption may not only increase the likelihood of success but also offer significant psychological relief for patients whose foremost goal is a healthy baby.

Fertility preservation in cancer patients requires a multidisciplinary approach, and the field of oncofertility has emerged to meet the reproductive demands of this growing population of cancer survivors. Oncologists, reproductive endocrinologists, and other reproductive medicine providers, as well as specialists in psychology, counseling, and research, must collaborate to optimize the experience of these patients and help them remain cancer-free while also building a family.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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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