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

Surgical Risk Reduction, Breast Cancer and Childbearing

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Abstract

Purpose of Review Young women who carry a genetic predisposition to breast cancer need to balance surgical and nonsurgical risk reducing options with childbearing. In this review, we explore how women make decisions without the benefit of official guidelines and in the context of frequently contradictory strategies.

Recent Findings Women of reproductive age with known BRCA mutations receive incomplete and conflicting advice regarding the urgency and timing of risk reducing mastectomy (RRM). Those who prioritize RRM achieve highly effective prevention and thereby avoid not only a diagnosis of breast cancer but also adjuvant therapies which limit future childbearing. All reconstructive options are available and high levels of satisfaction are reported. Those who delay prophylactic mastectomy can pursue nonsurgical breast and ovarian risk reduction strategies such as tamoxifen and oral contraception, yet these delay child bearing. Women who prioritize child bearing maintain the ability to breast feed but have limited screening options during pregnancy and lactation.

Summary Prioritization and timing of risk reduction and childbearing in young BRCA positive women is challenging. Elucidating these challenges enables clinicians to better counsel these women.

Keywords BRCA mutation · Risk reducing mastectomy · Breast cancer · Childbearing · Breast reconstruction

Introduction

Women of childbearing age who have a genetic predisposition to breast and ovarian cancer face multiple difficult choices and conflicts, and their complex decision making process is often confounded by time pressure. In a society where women increasingly delay childbearing due to higher education and establishing a career, they must confront such realities as undergoing oophorectomy before age 40 and an average age of breast cancer diagnosis as young as 40. In the absence of official recommendations about risk reducing mastectomy (RRM) for high risk women in general, younger women not only need to consider whether to have this surgery but also when to pursue it relative to childbearing. In this review, we will examine nonsurgical options for prevention, factors that influence decision making for risk reducing surgery and its timing, high-risk surveillance during pregnancy and lactation, efficacy of RRM, reconstructive techniques, patient satisfaction with their choices, and impact of risk reducing surgery on fertility.

Decision Making for High Risk Women

The decision making as to whether and when an individual from a known or suspected BRCA positive family undergoes genetic testing is discussed earlier in this series. Women of child-bearing age who do pursue genetic testing and are found to have a deleterious mutation are something of a self-selected group with shared characteristics. Even having received a positive result, these women typically do not regret their decision to pursue testing and they attain a sense of empowerment from knowing their genetic status. And compared to those who forgo or delay testing, they have a higher degree of health literacy [1]. Nevertheless, young genetically positive women are faced with confusing and conflicting recommendations related to RRM and childbearing during a vulnerable time of life. Their decision making can be confounded depending on who is giving advice and how information is conveyed [2]. A

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genetic counselor, for example, might objectively present data on a particular mutation's penetrance and age associated risk and a breast surgeon might tell the same patient to take their time and pursue high risk screening until after childbearing or beyond. Other practitioners, however, might advise a genetically positive young woman to pursue urgent RRM, sometimes portraying the patient as a "ticking time bomb" with regard to their breast cancer risk. The way in which objective data is presented can also cause confusion. A BRCA1 carrier in her young 30's might react very differently to being told that her real time breast cancer risk is 20% as opposed to having an 80% risk of not being diagnosed with breast cancer. Given this, it is not surprising that more than any other factor, young genetically positive women ask for clear and objective messaging, updates on new data as well as ongoing communication with genetic counselors and physicians [3].

Breast Cancer Treatment Implications for Childbearing

Women who choose to delay RRM need to understand not only their age adjusted risk of breast cancer, but also the impact of that diagnosis on subsequent childbearing. Inherent to these are the differences between BRCA1 and BRCA2 mutations. While RRM is offered to both BRCA1 and BRCA2 patients, these two separate groups may have different considerations related to embarking on surgery to prevent breast cancer. BRCA1 mutation carriers, for example, should be counseled not only about the young age of diagnosis but also the fact that 75% of breast cancers are triple negative and have a high likelihood of requiring chemotherapy for treatment [4]. This putative need for chemotherapy can affect fertility and future childbearing potential and this may be a motivating factor for early RRM. Conversely, BRCA2 mutation carriers are typically diagnosed later and most commonly develop hormonally driven cancers. While less frequently requiring chemotherapy, these cancers are treated with 5–10 year courses of tamoxifen or aromatase inhibitors, the latter requiring ovarian suppression. Not only do teratogenicity and temporary menopause preclude pregnancy during treatment, but the duration of these treatments often render future childbearing impossible due to maternal age and need for risk reducing oophorectomy. These significant ramifications of a cancer diagnosis and its varied treatment on future fertility and childbearing potential are often highly influential in considering RRM and its timing.

Nonsurgical Risk Reduction

Nonsurgical risk reduction options for young BRCA positive women are also fraught with confusion and contradiction even among researchers and clinicians. This, in turn, results in mixed or incomplete messaging delivered to genetically positive young women. One such example is the recommendation to use oral contraceptive pills given the 45% risk reduction it confers for ovarian cancer. While most studies have shown that the associated breast cancer risk is negligible or none at all, some case-controlled studies have shown an increased risk for breast cancer related to oral contraception pills [5]. Similarly, while studies show risk reduction for BRCA2 and to a lesser degree for BRCA1 carriers by taking tamoxifen, it's side effects and teratogenicity result in very low use in genetically positive young women, particularly those intending to bear children [6]. The contradictory risks of and protection conferred by pregnancy are another source of confusion. While full term pregnancy is protective, the interval during and immediately following pregnancy carry an increased risk of breast cancer. And while early pregnancy is protective in the general population, later pregnancy is protective in BRCA1 carriers [7] and yet this option is limited by the recommendation to undergo salpingo-oophorectomy between ages 35 and 40.

High Risk Screening During Pregnancy and Lactation

Official recommendations for high risk screening during pregnancy and lactation do not exist. Clinical and self-breast exam are more difficult due to hormonal changes of pregnancy and imaging must take into account decreased sensitivity as well as real and perceived risks to the fetus from contrast dye and ionizing radiation Annual MRI starting at age 25 is the mainstay of screening young genetically positive women and ideally should be updated prior to trying to conceive. MRI, however, is contraindicated during pregnancy due to teratogenic effect of gadolinium dye in animal models. And while mammography is approved by the American College of Radiology for use in pregnancy, it plays a minimal role. Screening mammography is not recommended until age 30 even in non-pregnant BRCA positive women and the limitations in sensitivity during pregnancy as well as uninformed or perceived concern about ionizing radiation results in limited use. Diagnostic mammography, however, should be used to evaluate any worrisome finding that might arise during pregnancy. Ultrasound's safety makes it the first-line diagnostic imaging tool during pregnancy, but it is not recommended for screening due to its user dependent nature and poor specificity [8].

While the benefits of performing risk reducing mastectomy before childbearing include reduction in early onset of cancer and elimination of the need for screening, a significant disadvantage is the inability to breast feed. Furthermore, while reproductive factors which impact on breast cancer risk in the general population do not reliably apply to BRCA carriers,

breast feeding has been shown to be protective, particularly in BRCA1 carriers [7]. As with pregnancy, screening is limited in women who delay RRM in order to breast feed. Self and clinical breast exam are difficult to interpret during lactation but workup for masses, thickening, pathologic nipple discharge, and nodal findings require thorough evaluation and all imaging modalities are available. Again, guidelines for screening during lactation do not exist. However, in women planning to breast feed for more than 6 months, it is reasonable to resume imaging as practiced prior to pregnancy. Concern has been raised about the efficacy of MRI during lactation due to diffuse enhancement brought about by the hypervascularity of the breast as well as increased T2 signaling due to milk production. While MRI scanning to define the extent of disease in known cancers has shown excellent sensitivity, data related to MRI screening during lactation is limited [9]. Concern about the safety of MRI scanning in lactating women has been addressed by studies showing that the amount of gadolium dye passed to the breast feeding infant is a fraction of 1% of the allowable dose. It is therefore recommended that women resume breast feeding without delay after undergoing MRI [9]. For women who plan to breast feed for a limited time, it is recommended that surveillance imaging resume 8 weeks after cessation to maximize sensitivity and specificity [8].

Efficacy of RRM

The principal goals of RRM in BRCA carriers–prevention of breast cancer and achieving a high level of patient satisfaction-have largely been realized. Many have written about the heightened risk of residual breast tissue in individuals with a germ-line mutation, and this concern has in fact been borne out during the era when subcutaneous prophylactic mastectomies were performed. Excessive cases of breast cancer following mastectomy were reported during that era, including in women who were retrospectively found to be BRCA carriers as well as others whose family history strongly suggested the same [10]. Included in these studies are tragic scenarios of women presenting with stage 4 disease and dying of breast cancer who did not know that there was any possibility of developing breast cancer following prophylactic surgery. With the abandonment of subcutaneous in favor of standard mastectomy, large series with long follow up have reported little to no cases of breast cancer following risk reducing surgery in genetically positive women. The multi-center Dutch cohort study reported by Heemskerk-Gerritsen et al has 10 year follow-up and reports a 1% incidence of breast cancer in BRCA1 carriers and no cases in BRCA2 carriers who underwent prophylactic mastectomies [11]. BRCA1 and BRCA2 positive patients partaking in the Prevention and Observation of Surgical Endpoints (PROSE) study have had no cases of breast cancer to date after prophylactic surgery [12]. The most recent and arguably boldest development has been the use of nipple sparing technique in BRCA carriers undergoing RRM. Even with the theoretical concern of breast cancer developing in retained tissue behind the nipple as well as the documented issue of peripheral breast tissue being left behind because of small incisions and challenging exposure, results to date have been excellent. A multicenter retrospective review of 548 risk reducing nipple sparing mastectomies in BRCA positive patients is reporting no cases of breast cancer, albeit with median follow up of 34 months [13]. It is important to realize that these procedures are done by experienced breast surgeons and follow up times are short and therefore more time and widespread reporting is needed to confirm safety. While the decision to pursue RRM prior to childbearing must take into consideration not being able to breast feed, we have observed – and the literature has reported – cases of milk production after childbirth in women who underwent nipple sparing mastectomies. While this finding raises concern about potentially dangerous residual breast tissue, observation is considered acceptable and surgical removal of the nipple areolar complex is not necessary [14].

Reconstruction in Women Undergoing RRM

Options for reconstruction in the setting of risk reducing surgery do not differ substantively from those offered women who are undergoing surgery and reconstruction for a cancer diagnosis. There is no one-size-fits-all approach for breast reconstruction and multiple different levels of decision-making are involved to arrive at the best possible plan for the individual. Factors weighing into decision making for type of reconstruction involve both medical and personal issues. Because patients undergoing risk-reducing surgery tend to be younger in age than the population diagnosed with breast cancer [15], the majority who undergo risk-reducing surgery do choose to undergo reconstruction.

In general, reconstructive options can be divided into autologous versus implant based options. With implant based reconstruction, time is added to the surgical procedure, 2 to 4 h, and most commonly a smaller tissue expander is placed at the time of mastectomy to allow for effective wound healing, without the traumatized skin being under tension or pressure related to the placement of a full sized implant. In well-selected cases, the direct to permanent implant approach may be undertaken when the viability of the skin and wound healing will not be compromised. Factors weighing into the safety and appropriateness of direct-to-implant approaches involve the careful evaluation of a multiplicity of factors. A large initial skin envelope can be advantageous in allowing enough space for a full sized implant to be placed at the time of mastectomy surgery, particularly in combination with the

desire or acceptance of a smaller final breast size. A nipple sparing mastectomy approach which is commonly offered and undertaken in the setting of risk reducing surgery (when there is no real danger of leaving cancer behind that might extend to the nipple) can also play a role in whether or not a direct to implant approach is viable, given that blood supply to the nipple areolar complex can be compromised after thorough removal of the underlying breast tissue and its associated feeding blood vessels. The goal of optimizing blood flow and viability to the nipple areolar complex may be better served by the placement of a smaller tissue expander, allowing the blood supply to the nipple areolar complex, now dependent solely on the surrounding skin, to recover. When a tissue expander is placed, successive rounds of expansion usually take place in the weeks to months after surgery. After expansion and accommodation of the skin, a subsequent procedure to exchange the temporary tissue expander for the permanent implant is undertaken. Finally, reconstruction of the nipple areolar complex can be undertaken for women who elect not to preserve their own, either with tattooing and/or raising a piece of tissue from the previous scar to create a nipple projection.

Autologous tissue reconstruction involves donation of tissue from a separate site, most commonly the lower abdomen, to create volume for a new breast size and shape, in lieu of implants. This is a much more surgically extensive and intensive procedure, adding on up to 10 h to the overall procedure, and involving major surgery to another anatomic site and a microvascular anastomosis to reestablish blood flow to the harvested tissue in the new site. Considerations for autologous tissue use include ample tissue at the donor site to recreate adequate shape and size for the breast mound(s), adequate vascular supply that could be compromised by prior surgery such as cesarean section or abdominal surgery), and willingness and overall health status allowing one to undergo a larger, albeit one-stage operation. While considerations for autologous reconstruction in the setting of risk reducing surgery are general the same as when performed in the setting of cancer, there are some factors that are important to consider in the risk reducing surgery setting. Specifically, given the young age at which many women elect to undergo risk reducing surgery, including prior to or between child-bearing, considerations for future pregnancy related to strength of the abdominal wall after abdominal wall surgery must be factored in. In addition, while unilateral mastectomy and flap reconstruction is often considered in women with breast cancer and no genetic pre-disposition, risk reducing surgery is always bilateral, and thus the availability of adequate tissue to reconstruct two breast mounds may be a limiting factor in some women. When possible reconstruction should always be offered at the same time as risk reduction surgery, to minimize unnecessary additional procedures, and to preserve the maximal amount of skin desired for reconstruction.

Patient Satisfaction with RRM

The very important issue of patient satisfaction with RRM relates back to how young BRCA positive women decide whether and when to pursue this procedure. Satisfaction levels are generally high, however women who express regret about having undergone RRM tend to be those where the decision did not come from within, but was urged by a doctor [16]. Others continue to suffer undue anxiety about getting breast cancer even after having RRM, and this is more prevalent among those who showed high levels of pre-surgical cancer related distress, including women whose family members had been diagnosed with or died from cancer [17]. Finally, in the same sense that genetically positive women seek ongoing contact from genetic counselors and others involved in decisions about risk reducing surgery, it is essential that women who have undergone RRM be followed and examined by their breast and plastic surgeons on an ongoing basis. Not only is this important for screening purposes, but it provides an opportunity for updated information, ongoing advice about their mutation and other cancer risks, as well as much needed reassurance and consistency of care.

Considerations Related to Ovarian Cancer Risk

As women approach 40, the risk of ovarian cancer (typically diagnosed at later stage given limited efficacy of screening modalities) accelerates, and the priority is often given to performing BSO. The benefits of early BSO include dramatic reduction in ovarian cancer risk, as well as breast cancer risk, especially in BRCA2 positive patients, given the associated reduction in estrogen production [18]. Women who have BSO prior to menopause often experience significant menopausal symptoms. These symptoms can be mitigated with hormone supplementation. There is concern that long-term hormone replacement therapy in a woman with intact breasts can increase the risk of breast cancer in an already high-risk situation. With bilateral RRM performed first, this concern is minimized and hormone replacement therapy can be safely offered following BSO. Thus, one benefit of undergoing RRM prior to BSO is the ability to provide hormone supplementation after BSO, given the absence of breast tissue, thereby virtually eliminating the increased risk of breast cancer associated with hormone supplementation to quell hormonal symptoms [19].

A second benefit of undergoing RRM prior to BSO is the potential to combine surgical interventions. As described in the reconstruction section, RRM with reconstruction often involves multiple steps. Performing three procedures at once, bilateral RRM with first stage reconstruction, and BSO, can be a very lengthy procedure, associated with prolonged recovery

from multiple surgical sites. Alternatively, RRM with first stage reconstruction, can be performed in one setting. Then BSO, a relatively short procedure, can be combined with the second stage of reconstruction, namely, insertion of permanent implants. Thus while cancer risk and its reduction takes highest priority in determining the timing and sequencing of risk reducing surgery, logistical and operative factors can also be taken into consideration.

Of course, bilateral RRM does not in any way impact future fertility or child-bearing potential. As previously discussed earlier in the chapter, after RRM, a woman cannot breast feed, and thus careful consideration to timing of surgery as it relates to pregnancy must factor in relative desire to breast feed. The same is not true for risk reducing BSO. BSO is encouraged in women with BRCA1 and 2 mutations due to the strong risk of ovarian cancer, typically accelerating by age 40, and the lack of early detection mechanisms for this particularly lethal cancer as previously discussed [18]. Given that the risk of ovarian cancer typically does not reach significance until the age of 40 (or slightly earlier for BRCA1), fortunately most women with either BRCA1 or BRCA2 have a window of opportunity for natural childbearing corresponding with maximal fertility potential, until risk reducing BSO should be considered.

With regard to BSO, our current state means that childbearing should already be completed. Alternatives such as pre-BSO egg harvest, preservation, and surrogacy are covered elsewhere in this series. Even with personal childbearing, given current state technology, in vitro fertilization (IVF) with pre-implantation genetic diagnosis (PGD) to select out BRCA positive embryos is possible, and offered. This option can be considered in BRCA mutation carriers who do not wish to perpetuate this genetic lineage, in either a male or female offspring.

Conclusion

BRCA positivity in women of reproductive age presents a tangled web of difficult decisions and inherent contradictions compounded by time pressure. RRM confers protection against breast cancer but the decision as to whether and when to pursue it is complicated by mixed and incomplete messaging and often driven by personal and family experience. And, if pursued prior to childbearing, RRM precludes breast feeding. For women who delay RRM, a diagnosis of estrogen positive or negative breast cancer, even if detected early, requires fertility preservation and delay in pregnancy due, for example, to prolonged hormonal therapy. Nonsurgical breast and ovarian risk reduction strategies are effective but also delay childbearing. High risk screening during pregnancy and lactation is possible, though not optimal. All of this is relevant prior to age 40, at which time the complexity is further increased by the risk of ovarian cancer. Elucidating these issues will enable better counseling and support for young women who seek guidelines and ongoing advice.

Declarations

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.

Conflict of Interest Christina Weltz and Elisa Port declare that they have no conflict of interest.

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