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REVIEW ARTICLE

Reproductive health care across the lifecourse of the female cancer patient

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Abstract

Reproductive health is a key component of cancer care and survivorship, encompassing gynecologic issues ranging from contraception and fertility to treatment of sexual dysfunction and menopause. Yet, oncology providers are often unfamiliar with the management of gynecologic issues. In order to address the unmet needs of female cancer patients, reproductive health should be addressed at the time of cancer diagnosis and continue through survivorship. Universal screening for pregnancy intention can guide counseling on contraception and fertility preservation. Safe and efficacious contraceptive options for both patients undergoing active treatment and cancer survivors are available and can often offer non-contraceptive benefits such as regulation of menses. Prompt referral to reproductive endocrinology specialists allows patients to explore options for fertility preservation prior to the receipt of cancer-directed therapies. Due to a rapid drop in hormone levels, treatment-induced menopause often results in severe symptoms. In patients with induced menopause, balancing the risks of hormone therapy compared to the decreased quality of life and health concerns associated with early menopause may help patients with difficult decisions regarding symptom control. Cancer treatment impacts sexual function with both physical changes to the vulvovaginal tissues and altered relationship dynamics. Open discussions on the impact to sexual health are paramount to quality of life after cancer. While more data is needed in many areas, proactive management of reproductive health issues is crucial to quality of life in cancer survivorship. In this article, we review contemporary management of the reproductive health of the female cancer patient.

Keywords Cancer survivorship · Reproductive health

Introduction

In the USA, an estimated 859 reproductive-aged women per 100,000 will be diagnosed with cancer yearly [1]. With advances in multimodal cancer treatment, 5-year survival approaches 80% in patients diagnosed younger than age 50 [1]. The reproductive health care needs of this population of cancer patients are a vital and often overlooked component of survivorship.

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Fertility preservation

Fertility preservation is a key survivorship issue recognized by the American Society of Clinical Oncology (ASCO) [2]. Health care providers should inform women of the impact of planned cancer therapy on fertility and refer at risk patients to a fertility specialist as soon as possible. Counseling regarding an individual patient's risk for ovarian failure is ideally provided prior to initiation of cancer therapy.

Chemotherapy, particularly with alkylating agents, as well as radiation targeting the pelvis, is directly toxic to primordial follicles and can lead to ovarian failure and subsequent infertility. The risk of premature ovarian failure varies by age, chemotherapy agent or combination used, cumulative dose, and duration of treatment [3]. The ideal fertility preservation treatment should be individualized based on patient age, diagnosis, partner status, time prior to starting treatment, and her desire for future childbearing [4]. Available fertility preservation options include embryo, oocyte, and ovarian tissue cryopreservation (Table 1). Additionally, treatment modifications including ovarian

Table 1 Summary of fertility preservation options

Fertility preservation technique	Description	Candidates	Benefits	Drawbacks
Embryo cryopreservation	-Controlled ovarian hyperstimulation followed by oocyte retrieval, insemination, and cryopreservation of embryos	-Can delay treatment 2–3 weeks -Has male partner or willing to use donor sperm	-Highest success rates -Established technique	-Requires delay of treatment -Financially costly
Oocyte cryopreservation	-Controlled ovarian hyperstimulation followed by oocyte retrieval and cryopreservation of mature eggs	-Can delay treatment 2–3 weeks -Postpubertal females without partners or those with religious or moral objections to freezing embryos	-No longer considered experimental -Greater reproductive flexibility	-Requires delay of treatment -Financially costly -Not as efficient as embryo cryopreservation
Ovarian tissue cryopreservation	-Freezing strips of ovarian cortex that are harvested by laparotomy or laparoscopy	-Prepubertal girls -Females who cannot delay treatment	-Usually no delay in treatment -Can be piggy-backed to port placement	-Still considered experimental -Ovarian tissue could be seeded with cancer cells making future transplantation risky
Ovarian transposition	-Surgically moving one of both ovaries out of the pelvis	-Females with planned pelvic radiation	-Usually no delay in treatment -Uterus and ovaries preserved	-Surgery required -Ovary moved out of normal anatomic position so ART may be needed

Access to fertility options may vary based on country/state legislature

transposition and fertility-sparing surgery may be appropriate [4]. A woman's available treatment options may vary based on location, as many countries have regulatory legislation in place that can limit access to assisted reproductive technology. Legal differences between countries exist in regard to patient eligibility criteria, embryo freezing and storage, and gamete donation as well as regulatory differences in reimbursement and state funding [5]. Embryo cryopreservation is the "gold standard" fertility preservation option offering the highest chances of a future live birth with success rates that can approach 50% per embryo depending on age [6]. Women who choose embryo cryopreservation for fertility preservation must have a male partner or be willing to use donor sperm.

For women who do not have a male partner, including postmenarchal adolescent patients, or women with religious or ethical objections to embryo freezing, oocyte cryopreservation is an option recognized by ASCO as a standard therapy for fertility preservation [7]. Egg freezing has decreased efficiency compared to embryo cryopreservation because of sensitivity of oocytes to damage by ice crystals during freezing and thawing [8]. In recent years, advances in oocyte cryopreservation techniques have allowed 70–90% of cryopreserved oocytes to survive the freeze-thaw process [9]. In vitro fertilization (IVF) outcomes with cryopreserved oocytes have similar pregnancy rates to fresh IVF rates [10].

As both embryo and oocyte cryopreservations require controlled ovarian hyperstimulation, they introduce risk of ovarian hyperstimulation syndrome (OHSS) that could result in serious complications including venous thromboembolism and stroke in severe cases. Another risk of OHSS is increased serum estradiol levels as high as 20 times normal physiologic levels. This is of particular concern with estrogen receptor-positive malignancies such as breast and endometrial cancers. Aromatase inhibitors such as letrozole can be added to protocols to minimize serum estradiol levels during controlled ovarian hyperstimulation. Similar number of total oocytes retrieved, length of ovarian stimulation, and fertilization rate are observed compared with protocols without letrozole [11, 12].

Ovarian tissue cryopreservation remains an emerging but still experimental modality involving harvesting and freezing ovarian cortex, allowing preservation of oocytes within primordial follicles. Benefits of ovarian tissue cryopreservation include that it can be performed in prepubertal females, it eliminates the need for available sperm, and it can be performed immediately without a cancer treatment delay [13]. The first live birth after autotransplantation of human ovarian tissue was reported in 2004 [14]. To date, there have been at least 130 live births after ovarian reimplantation [15].

Ovarian transposition, or oophoropexy, is a strategy that can be offered to women with planned pelvic radiation for diseases such as locally advanced rectal cancer. This surgical procedure involves moving one (most commonly) or both ovaries out of the pelvis and away from the radiation field preferably by laparoscopy [16]. The ovary can be transposed

to the lateral abdominal wall along the ipsilateral paracolic gutter, or with ligation to the uterosacral ligament for midpelvic or abdominal radiation, respectively, and can be done be done unilaterally or bilaterally [3]. A combined approach with removal and cryopreservation of one ovary and transposition of the other is gaining popularity [17]. Oocyte retrieval from the transposed ovary can be performed transabdominally if needed.

Pregnancy intention and contraception

Although cancer treatment (including cytotoxic chemotherapy and radiation) may negatively impact fertility, it does not eliminate the risk of pregnancy. Unintended pregnancy rates in cancer patients have not been described, but data suggest that young cancer patients are more likely to terminate a pregnancy than aged-matched controls [18]. Pregnancy at the time of cancer treatment is rare, but can carry significant morbidity in regard to maternal delay of treatment and teratogenicity [19]. Despite the importance of assessing sexual activity and pregnancy intention in cancer patients, providers rarely assess reproductive concerns of patients with cancer adequately [20].

Pregnancy intention screening is a first step in assessing needs of reproductive-aged women. A health initiative has simplified this assessment into "One Key Question" to be asked by all primary providers: "Would you like to become pregnant in the next year?" [21]. Women who answer "yes" can then be offered preconception counseling and appropriate referral depending on chronic medical problems, and women who answer "no" can be counseled on their contraceptive options. Those who are ambivalent can have patient-centered discussions with their health care provider to determine their individual needs. This initiative has not conventionally been applied to reproductive-aged female cancer patients, but screening with this tool for pregnancy intention in the general population could improve referrals for contraceptive counseling or to reproductive endocrinology specialists to discuss fertility preservation.

Among women who have received or are currently receiving cancer treatment, those who do not desire pregnancy should be offered contraception even in the absence of regular menstrual cycles, as menstruation is not a reliable indicator of fertility. A summary of available contraceptive methods is outlined in Table 2. Choosing a contraceptive method can be challenging in cancer patients given the potential higher risks associated with hormonal methods, including venous thromboembolism (VTE), and unique medical needs dependent on cancer type.

While limited evidence-based resources regarding contraceptive use in the cancer survivor are available, the Center for Disease Control's (CDC) Medical Eligibility Criteria (MEC) for Contraceptive Use is an available tool to determine a patient's contraception options based on medical history. These guidelines should be used in conjunction with additional expert guidance to help providers consider relative risks associated with contraceptive use for each patient [22]. Based on the MEC, women with active cancer, defined as those receiving therapy, within 6 months of remission or with a diagnosis of metastatic disease, are often counseled to avoid combined oral contraception pills which contain estrogen due to its prothrombotic actions [23]. Progestin-only contraceptive methods, which do not increase risk of VTE, may be an option if DVT is a significant concern [24]. These recommendations should be individualized as the benefits of pregnancy prevention may outweigh the risks associated with contraception.

Long-acting reversible contraception (LARC), which includes subdermal implant and intrauterine device (IUD), is increasingly advocated as first-line contraception for all women given efficacy, ease of use, and safety profile [25]. After placement, LARCs require no additional user actions to be effective and can last for 3 to 10 years depending on the device. Despite a historical risk of infection with one specific IUD (Dalkon Shield), this issue has not been seen with newer devices [26]. Although LARCs are both safe and efficacious, they are underutilized by cancer survivors [27].

The copper intrauterine device (Cu-IUD) is currently the only non-hormonal LARC available in the USA and has no restrictions for use in hormonally mediated cancers like breast cancer. However, increased menstrual bleeding associated with the Cu-IUD can be problematic, especially in the setting of chemotherapy-induced anemia or thrombocytopenia. Concurrent medical problems like heavy menstrual bleeding, anemia, severe immunosuppression, and tamoxifen use warrant consideration of local progestin therapy with a levonorgestrel releasing intrauterine device (LNG IUD) [28]. There are currently four LNG IUDs available in the USA, one of which is low dose and releases approximately 14 mcg per day of levonorgestrel. The systemic absorption of progesterone from an LNG IUD is low and whether the benefits of reduced menses, inhibition of the endometrium, and contraception outweigh the risks must be evaluated on a case by case basis [28]. An increased risk of breast cancer among LNG IUD users has not been observed [29]. A small case-control study of women who continued use of LNG IUD after diagnoses of breast cancer demonstrated no impact on breast cancer recurrence [30]. Progestin-containing subdermal hormonal implants placed in the arm are also available on the market. However, their use in cancer patients and cancer survivors is limited by the high prevalence of irregular bleeding among users of this method [31].

Emergency contraception methods, used to prevent conception within 72 h after an unprotected sexual act, should also be considered in this population. Options for emergency contraception include several types of hormonal pills (one containing estrogen and the progestin levonorgestrel, a levonorgestrel-only pill, and the ulipristal acetate pill) and

Table 2 Summary of contraceptive options

Type of contraception	Preparation	Failure rate	Benefits	Contraindications	Considerations
Barrier	Condom	18–21%	STI protection Easily accessible	None	
	Diaphragm	12%	Non-hormonal	None	Requires fitting by health care provider
Combined estrogen/progesterone	Pill (take daily) Vaginal ring (change monthly) Patch (change weekly)	9% 9% 9%	Ovarian cancer risk reduction Can treat heavy menstrual bleeding, painful periods, endometriosis	Severe hypertension Stroke Severe cardiac disease Migraine with aura Smoking and age > 35 SLE (with APA) History of VTE Hepatocellular adenoma or hepatoma Decompensated liver cirrhosis Breast cancer or other estrogen-dependent malignancy	Not recommended in active cancer given VTE risk
Systemic progesterone only	Pill (take daily) Injection (administered every 3 months)	9% 6%	Endometrial cancer risk reduction Can treat heavy menstrual bleeding, painful periods, endometriosis	Breast cancer	Can cause irregular bleeding Injection may delay fertility after cessation
Intrauterine device	Levonorgestrel releasing (effective up to 3 or 5 years)	0.2–0.8%	Can treat heavy menstrual bleeding and induce amenorrhea in a portion of women Convenient use	Distorted uterine cavity GTD with suspicion of intrauterine disease Active purulent cervicitis or PID	Can reduce polyps and endometrial hyperplasia in women taking tamoxifen
	Copper (effective up to 10 years)	0.2–0.8%	Non-hormonal Convenient use	Distorted uterine cavity GTD with suspicion of intrauterine disease Active purulent cervicitis or PID	Can increase menstrual pain and bleeding Can be used as emergency contraception
Implant	Subcutaneous arm implant (effective up to 3 years)	0.05%	Simple insertion Convenient use	Breast cancer	Can result in unpredictable bleeding pattern
Permanent sterilization	Bilateral tubal ligation Vasectomy	0.15–0.5%	Only permanent form of contraception	Contraindications to surgery	Irreversible, risk of patient regret Less surgical risk for vasectomy compared to tubal ligation

STI, sexually transmitted infection; *SLE*, systemic lupus erythematosus; *APA*, antiphospholipid antibody; *VTE*, venous thromboembolism; *GTD*, gestational trophoblastic disease; *PID*, pelvic inflammatory disease

the non-hormonal copper IUD. Although no studies have addressed the risks associated with emergency contraception in cancer patients, the lack of estrogen and the short duration of use (1–2 doses) make the risks low and this method can be used regardless of the medical condition [23].

Contraception may offer non-contraceptive benefits such as reducing menstrual blood loss and suppressing menses during cancer therapy. The choice of agent for menstrual suppression should be tailored to individual patient after evaluation of risk-benefit ratio. Potential options include combined oral contraceptive pills, progestin-only methods with pills, depot medroxyprogesterone acetate, contraceptive implant, or LNG IUD and GnRH agonists. If a patient is using a method of contraception prior to the start of cancer therapy with menstrual suppression or reduced dysmenorrhea, the method should be continued through treatment [32]. For patients who develop menorrhagia during chemotherapy, the gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate offers a lower risk of thromboembolism compared to hormonal methods and causes a hypoestrogenic state within 2 weeks

of administration that can successfully prevent severe bleeding [33]. Associated severe vasomotor symptoms can be managed with progestin add-back therapy. In patients who have not been treated with prophylactic suppression, acute bleeding can be managed with short-term hormonal therapy including combined oral contraceptives, intravenous estrogen, and oral medroxyprogesterone acetate for patients with contraindications to estrogen [32].

Sexual function

Chemotherapy, pelvic radiation, or surgery often negatively impact sexual health and quality of life for cancer survivors. Despite the prevalence of sexual dysfunction among female cancer survivors, this issue is infrequently addressed by providers [34, 35]. Reasons for this communication gap are multifactorial and include lack of provider training, discomfort or perceived discomfort in addressing the topic, and limited time during visits to manage the complex nature of sexual dysfunction [34, 36]. Although gynecologic cancer survivors are a specific population where sexual dysfunction is highly prevalent and often persists well beyond cancer treatment, the problem is not limited to those women diagnosed with ovarian, endometrial, or cervical cancer [37]. Breast cancer patients may feel a loss of "womanhood" following mastectomy, and colon cancer patients may receive radiation impacting vulvovaginal health; graft versus host disease can affect the lower genital tract and chemotherapy can impact sexual desire for all patients.

Identifying sexual difficulties in female cancer survivors should be considered in the same categories as female sexual dysfunction in the general population and include (1) sexual interest/arousal disorder, (2) female orgasmic disorder, and (3) genito-pelvic/penetration disorder [38]. Most common among female cancer survivors is low desire and arousal, decreased lubrication, and pain [36]. These symptoms can be caused by cancer treatments that abruptly induce menopause and may be exacerbated by adjuvant hormonal therapy such as aromatase inhibitors. Major surgery can negatively impact body image, and pelvic radiation often results in physical changes to the vagina including vaginal fibrosis and loss of lubrication. Psychological factors including depression and anxiety associated with a cancer diagnosis and/or changes in relationships can contribute to sexual health concerns in female cancer patient and survivors.

The first step in the management of sexual health is identifying those patients with sexual function concerns. Screening can occur both in oncology and primary care settings. While there is not a gold standard for screening tool for sexual dysfunction, several brief assessments have been proposed. They include the National Comprehensive Cancer Network (NCCN) recommended Brief Sexual Symptom Checklist for Women, the Arizona Sexual Experience Scale (ASEX), and Single-Item Screener for Self-Reporting Sexual Problems [34, 39, 40]. The more detailed Female Sexual Function Index (FSFI) involves 19 questions and has been validated in cancer patients [41]. For those who wish to discuss sexual concerns, assessment should include review of individual goals to improve sexual health, cancer treatment history, medications that may affect sexual function, relationship satisfaction, partner health status, and presence of concurrent mental health issues like depression and anxiety. A careful gynecologic exam should include assessment of vulvar and vaginal changes including atrophy, adhesions, and/or stenosis. Using cotton swab for vulvar mapping and assessing pelvic muscle tension can help localize pain [37].

Because sexual dysfunction in female cancer survivors is often multifactorial, treatment is individualized to a patient's goals and often takes a multimodal approach (Fig. 1). ASCO recently published recommendations for interventions to address sexual problems in people with cancer [42]. When adverse effects of treatment contribute to sexual difficulties such as pain or tissue quality changes, providing information about symptom management can improve function. In general, improved symptom management leads to improved sexual response. Cognitive-behavioral therapy involving both patients and partners or an integrative approach that includes some aspect of sexual counseling has also may improve sexual desire in cancer survivors [43]. For hypoactive sexual desire disorder, the Food and Drug Administration (FDA) approved flibanserin as treatment in premenopausal women based on results of increase in sexually satisfying events [44]. This drug, however, has not been studied in cancer survivors and is only approved in premenopausal patients. Additionally, it holds a warning for risk of severe hypotension and syncope in patients who consume alcohol while taking the medication, those who take CYP3A4 inhibitors, and those with liver impairment [37]. Generalizing findings to cancer survivors is challenging and research is needed regarding the safety and efficacy in patients with complex gynecologic and medical history.

In patients with female orgasmic disorder, medication review for the presence of selective serotonin reuptake inhibitors (SSRI) is necessary. SSRI have known negative effects on sexual function with up to 57% of patients reporting delay or inhibition of orgasm [37]. Providers can discuss reducing dose of SSRI or changing antidepressant to bupropion which does not share the sexual side effect profile of SSRI. Consensus from the International Society for Sexual Medicine suggests directed masturbation technique which involves education on self-awareness exercises and reaching orgasm through self-stimulation in combination with cognitive-behavioral therapy for treatment of female orgasmic disorder [45].

Genito-pelvic pain with penetration, or dyspareunia, is common among cancer survivors and often a result of vulvovaginal atrophy from hypoestrogenism. A strategy for

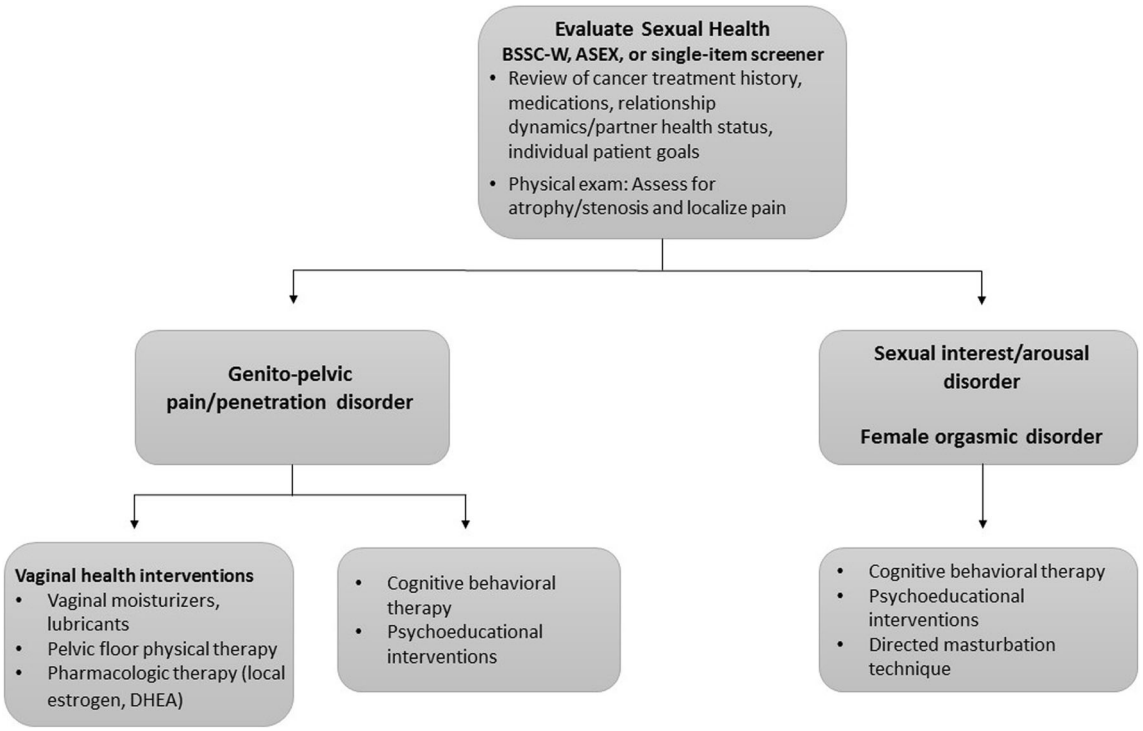

Fig. 1 Pathway for evaluating and treating sexual dysfunction. BSSC-W Brief Sexual Symptom Checklist for Women, ASEX Arizona Sexual Experience Scale

maintaining vaginal health in cancer survivors that includes regular use of vaginal moisturizers 2–5 times weekly, use of vaginal lubricant with sexual activity, performing pelvic floor exercises, and vaginal dilator therapy has been well described and successful [46, 47]. Vaginal moisturizers are intended to be used several times a week to improve tissue quality and overall vaginal health. Over-the-counter preparations include Replens, Vagisil ProHydrate, KY liquibeads, Luvena, and HYALO GYN. A small randomized trial found that Replens was equivalent to vaginal estrogen in improving dyspareunia [48]. Hyaluronic acid and vitamin E products may also reduce vaginal symptoms and dyspareunia [49]. Vaginal lubricants are available over the counter in water and silicone-based preparations and are to be used during sexual activity to minimize pain and mucosal tears with vaginal penetration. The goal of pelvic floor physical therapy is to increase control over pelvic floor muscles with a combination of strengthening and relaxation exercises, trigger point massage techniques, biofeedback, and use of vaginal dilators. Vaginal dilator therapy has both psychological and physical benefit; it can reduce anxiety by allowing patients to gain confidence with penetration in a self-guided, controlled setting and also mechanically stretches tissues for treatment of vaginal stenosis/adhesions.

Menopause

Cancer survivors can often experience more severe symptoms of menopause than women who transition into menopause naturally due to an abrupt drop in hormone levels resulting from treatment. Oophorectomy, pelvic radiotherapy, chemotherapy that reduces ovarian reserve, and anti-estrogenic hormonal therapy can all result in menopausal symptoms including hot flashes, sleep disturbance, myalgia/arthralgia, sexual dysfunction, and vaginal dryness [34]. Premature menopause from oophorectomy is associated with increased all-cause mortality and coronary vascular disease [50]. Patient and providers must weigh risks and benefits of pharmacological treatment for menopause. A summary of treatment options for menopause is reviewed in Table 3.

Menopausal hormone therapy (MHT) with estrogen is the most effective treatment for vasomotor symptoms, with oral and transdermal formulations showing comparable efficacy [51]. The largest trial of MHT was the Women's Health Initiative (WHI) which randomized women to receive MHT or placebo. Data from the WHI demonstrated a complex pattern of risks and benefits of MHT. While absolute risks of MHT were small, women in the treatment arm had increased risks of stroke, venous thromboembolism, and gallbladder disease compared to women receiving placebo [52]. Breast cancer risk was increased in the combined estrogen plus medroxyprogesterone acetate patients, but not in women post-hysterectomy using estrogen alone. The attributed annual risk was less than one additional case of breast cancer diagnosed per 1000 users of combination hormonal therapy [52]. As the hypothesis leading to this trial was that MHT would improve cardiovascular outcomes, the majority of women in

Table 3 Summary of treatment options for menopause

	Treatment	Preparation
Non-hormonal therapy		
Systemic	SSRI[a] Venlafaxine Gabapentin Pregabalin Clonidine	Oral
Local	Vaginal moisturizers	Prefilled vaginal applicators (Replens, Vagisil ProHydrate) Ovule insert (KY Liquibeads)
	Vaginal lubricants	Water based Silicone based
Hormonal therapy		
Systemic	Estrogen alone (women without uterus)	Vaginal ring Transdermal estradiol (patch, gel, lotion, spray) Oral
	Estrogen and progestin (women with uterus)	Oral (tablet combining estrogen and progestin) Transdermal (patch combining estradiol and progestin)
	Estrogen and SERM	Oral conjugated equine estrogen combined with bazedoxifene
	SERM[b]	Oral ospemifene
Local	Estrogen	Vaginal cream Vaginal tablet Vaginal ring
	DHEA (prasterone)	Vaginal insert

SSRI, selective serotonin reuptake inhibitor; *SERM*, selective estrogen receptor modulator; *DHEA*, dehydroepiandrosterone

[a] Avoid pure SSRI in women with breast cancer on aromatase inhibitors

[b] For treatment of dyspareunia and vaginal atrophy

the trial were postmenopausal and the average age was 63 years old at enrollment. Risk of adverse events related to MHT was much lower for younger women ages 50 to 59. Accordingly, WHI results should not be extrapolated to young cancer survivors with iatrogenic (induced) menopause. The benefits of MHT beyond symptom management include preserving bone density and preventing osteoporosis-related fractures.

The decision for treatment with MHT should be individualized based on patients' cancer history, chronic medical problems, and background risks. Systemic MHT is appropriate for select female cancer survivors, but should be avoided in patients with a history of hormonally mediated cancer such as ER/PR-positive breast cancer, hormonally mediated uterine sarcoma, advanced endometrial cancer, and granulosa cell tumors [34]. The North American Menopause Society recommends that for women with induced menopause who are otherwise candidates for MHT, early initiation of MHT and continued use at least until the median age of menopause (52 years) [51]. In treating vasomotor symptoms, MHT with combination estrogen and progestin for survivors with an intact uterus and estrogen alone for survivors without a uterus is available in oral, transdermal, and vaginal ring formulations. Estrogen transdermal formulations and micronized progestin should be considered first line given lower rates of thromboembolism [53]. Young menopausal cancer survivors can be treated with oral contraceptives as an alternative to MHT.

Other therapies include the combination of selective estrogen receptor modulator with estrogen, creating a tissue selective estrogen complex. There is currently an FDA-approved conjugated estrogen and bazedoxifene for treatment of postmenopausal women which is also contraindicated for patients with hormonally mediated cancers [34, 54].

Non-hormonal therapy options include low-dose SSRI and SNRI antidepressants, anti-convulsants including gabapentin and pregabalin, and the antihypertensive agent clonidine. Caution is advised in prescribing a pure SSRI, in particular paroxetine and fluoxetine, in breast cancer patients given that these drugs inhibit the enzyme that metabolizes tamoxifen, resulting in reduced concentrations tamoxifen's active metabolite endoxifen and possible adverse effect on clinical outcomes [55]. In contrast with SSRIs, the SNRI venlafaxine does not inhibit the enzyme that metabolizes tamoxifen. A study of non-hormonal pharmacologic treatment of menopausal symptoms in breast cancer patients suggests that venlafaxine and gabapentin both reduce hot flash severity, with more patients preferring venlafaxine over gabapentin [56].

For patients with predominately vulvovaginal menopausal symptoms, locally administered estrogen can treat atrophy while minimizing systemic estrogen exposure. An early meta-analysis reported similar efficacy between local and systemic estrogen preparations in the treatment of urogenital atrophy [57]. In the USA, available local therapy includes conjugated estrogens in cream preparation and estradiol in cream, tablet, and ring preparations [58]. While evidence is limited, no difference in efficacy between the types of preparation has been found [59]. In estrogen-dependent breast cancer patients for whom non-hormonal moisturizers and lubricants are ineffective, the decision to use vaginal estrogen should be made after review of the risks and benefits of therapy. There are currently no data to suggest increased risk of recurrence in breast cancer patients using low-dose vaginal estrogen for urogenital symptoms [60]. In women with breast cancer on aromatase inhibitor therapy, vaginal estrogen may result in transient increase in circulating estradiol levels but effect on recurrence is unknown [61].

Other local therapies for genitourinary symptoms of menopause include the FDA-approved vaginal dehydroepiandrosterone (vaginal prasterone). A randomized control trial of breast and gynecologic cancer survivors treated with vaginal prasterone showed significant improvements in sexual desire, arousal, and pain with limited systemic estrogenic activity [62]. Ospemifine is a selective estrogen receptor modulator approved for moderate to severe dyspareunia. It has not been evaluated in the cancer survivor population and is currently contraindicated in survivors with estrogen-dependent cancers. The NCCN suggests that it can be considered in patients with non-hormonally mediated cancers [34].

Gynecologic care of the "previvor"

"Previvors" are a new class of cancer patients who by definition have a higher risk for cancer as a result of pathogenic genetic mutations, but do not have a cancer diagnosis. The diagnosis of *BRCA1/2* or Lynch syndrome is managed with prophylactic surgery, risk-reducing salpingo-oophorectomy (RRSO) with or without hysterectomy, as this procedure has demonstrated utility in preventing cancer. Despite the known cancer prevention benefit of RRSO, the long-term effects on overall health and quality of life remain critical questions for previvors. Symptoms of estrogen withdrawal are prevalent negative side effects for women after RRSO [63, 64]. Fear of these symptoms can also influence previvors' satisfaction with their decision to undergo this risk-reducing procedure [65]. For the majority of *BRCA1/2* mutation carriers, the impact on health-related quality of life of surgical menopause appears to be outweighed by the cancer risk reduction [66].

MHT mitigates many of the side effects of menopause but previvors and physicians are often wary of its use due to perceived risks of cancer promotion [64, 67]. Small studies have shown no increased risk of breast cancer from MHT in *BRCA1* mutation carriers who have undergone menopause and who have no personal history of cancer [67], but few long-term studies are available. For premenopausal previvors who have undergone hysterectomy with RRSO, systemic estrogen without progesterone would not be expected to increase breast cancer risk. A risk assessment of 1299 previvors with *BRCA1/2* mutations compared breast cancer risk in those mutation carriers who had not undergone RRSO to those who had and used MHT following surgery. No increase in breast cancer with MHT following prophylactic surgery was observed [68]. Other studies have demonstrated that systemic MHT in women with *BRCA1* mutations is associated with a *reduced* risk of breast cancer [69, 70]. In the absence of clear evidence to inform the use of MHT post RRSO, clinicians and patients must carefully discuss the potential benefits as well as non-hormonal therapies, in the context of unknown breast cancer risk in this population. The choice to undergo prophylactic mastectomy may alter this perceived risk.

Conclusions

Reproductive health is a key component in caring for the female cancer survivor and stretches across the lifespan from contraception and pregnancy planning to sexual health and menopause. While more evidence-based guidelines are needed, the population of cancer survivors continues to grow, and proactive management of reproductive health issues is central to providing comprehensive care and improving quality of life for this expanding population.

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