Gynecologic Oncology 140 (2016) 359–368

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide

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HIGHLIGHTS

- Sexual dysfunction is a prevalent, yet under-recognized and under-treated morbidity of gynecologic cancer treatment.
- A comprehensive review of sexual problems experienced by gynecologic cancer survivors is presented.
- A practical, evidence-based approach to sexual health concerns in patients during and after treatment is discussed.

ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form 5 November 2015
Accepted 6 November 2015
Available online 7 November 2015

Keywords:
Sexual health
Female sexual dysfunction
Quality of life
Gynecologic cancer

ABSTRACT

Objective. The diagnosis and treatment of gynecologic cancer can cause short- and long-term negative effects on sexual health and quality of life (QoL). The aim of this article is to present a comprehensive overview of the sexual health concerns of gynecologic cancer survivors and discuss evidence-based treatment options for commonly encountered sexual health issues.

Methods. A comprehensive literature search of English language studies on sexual health in gynecologic cancer survivors and the treatment of sexual dysfunction was conducted in MEDLINE databases. Relevant data are presented in this review. Additionally, personal and institutional practices are incorporated where relevant.

Results. Sexual dysfunction is prevalent among gynecologic cancer survivors as a result of surgery, radiation, and chemotherapy—negatively impacting QoL. Many patients expect their healthcare providers to address sexual health concerns, but most have never discussed sex-related issues with their physician. Lubricants, moisturizers, and dilators are effective, simple, non-hormonal interventions that can alleviate the morbidity of vaginal atrophy, stenosis, and pain. Pelvic floor physical therapy can be an additional tool to address dyspareunia. Cognitive behavioral therapy has been shown to be beneficial to patients reporting problems with sexual interest, arousal, and orgasm.

Conclusion. Oncology providers can make a significant impact on the QoL of gynecologic cancer survivors by addressing sexual health concerns. Simple strategies can be implemented into clinical practice to discuss and treat many sexual issues. Referral to specialized sexual health providers may be needed to address more complex problems.

Contents

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http://dx.doi.org/10.1016/j.ygyno.2015.11.010
0090-8258/

1. Introduction

Gynecologic cancers are estimated to comprise over 94,000 new cancer cases in the U.S. in 2015. The most common site of diagnosis is uterine cancer followed by ovarian, cervical, and vulvar cancer [1]. In 2014 there were 14.5 million cancer survivors living in the U.S., 14% of which were gynecologic cancer survivors, and this number is anticipated to grow to almost 19 million by 2024 [2]. With the growing number of gynecologic cancer survivors, attention to survivorship and quality of life (QoL) is crucial to the comprehensive care of patients.

According to the World Health Organization, sexual health is a state of physical, emotional, mental, and social well-being in relation to sexuality [3]. Sexual dysfunction refers to problems during any phase of the sexual response cycle. The prevalence of sexual dysfunction in the general U. S. population is approximately 40% [4,5], but can approach 90% in gynecologic oncology patients [6], with associated poor psychosocial adjustment and QoL [7]. Gynecologic malignancy and treatment with surgery, chemotherapy, and/or radiation directly affect the sexual and reproductive organs. Sexual morbidity affects gynecologic cancer patients immediately following treatment [8] and during long-term survivorship [9,10].

Despite the high prevalence of sexual dysfunction in gynecologic cancer survivors, attention to sexual health issues by healthcare providers has been suboptimal. Patients feel they would benefit from more information regarding the effects of treatment on sexual health before therapy and desire counseling from a provider post-treatment to address sexual health concerns [11,12]. Seventy-four percent of long-term gynecologic cancer survivors believed physicians should regularly ask about sexual issues, but 64% stated a physician never initiated the conversation during their care [10]. Understanding, evaluating, and treating the sexual health issues encountered during treatment and survivorship are crucial to the comprehensive care of gynecologic cancer patients.

Many survivors are older women and some clinicians believe that sexual health issues are less important to these women. Research indicates this is not true. Lindau and colleagues investigated the sexual activity, behaviors, and sex-related problems of over 3000 U.S. adults 57 to 85 years of age and found that the majority of older adults engage in intimate relationships and regard sexuality as an important part of life [5].

The following related topics are beyond the scope of this review (although also critically important): sexual health concerns related to infertility, sexuality in patients undergoing risk-reducing bilateral salpingo-oophorectomy (BSO), breast cancer survivorship, and partner-related sexual dysfunction. This article will focus on the sexual health issues faced by gynecologic cancer survivors and discuss treatment options for the most common problems.

2. Impact of gynecologic cancer on sexual health

2.1. Endometrial cancer

Endometrial cancer is the most common gynecologic malignancy in Western countries, and it is estimated 54,870 new cases will occur in the United States in 2015 [13]. The majority will occur in postmenopausal women and surgery is the primary treatment for most patients. Standard surgical approach includes hysterectomy, BSO, with surgical staging with selective pelvic and para-aortic lymphadenectomy. Minimally invasive surgery has widely replaced laparotomy as the preferred surgical approach, providing improved blood loss, postoperative pain, complications, and length of hospital stay [14,15] without compromising survival [16].

Many women with early-stage disease can be observed following surgery, but even in the absence of adjuvant therapy, patients are at risk of having sexual dysfunction. Onujiogu et al. reported a prospective evaluation of the prevalence of sexual dysfunction in early-stage (I–IIIa) endometrial cancer patients 1 to 5 years from primary surgical treatment ($N = 72$) [6]. Eighty-nine percent of participants had some form of sexual dysfunction determined by the Female Sexual Function Index (FSFI) score of <26 and pain was the most commonly affected domain. Only 18% of participants received adjuvant radiation therapy, suggesting that sexual dysfunction is prevalent among patients treated with surgery alone [6]. A prospective study by Aerts et al. investigated sexual adjustment in surgically treated endometrial cancer patients compared to women who underwent a hysterectomy for benign indications and healthy controls ($N = 84$ in all groups) [17]. There was no difference in reported sexual function in endometrial cancer patients before and after surgery. Furthermore, no difference in sexual function occurred in relation to the type of surgery (laparoscopy v. laparotomy) or the performance of lymphadenectomy. However, compared to healthy controls endometrial cancer patients reported more sexual dysfunction before and after surgery. Endometrial cancer patients had significantly more entry dyspareunia at 1 year compared to patients who had a hysterectomy for benign indications, and decreased sexual arousal, desire, and entry dyspareunia at 2 years compared to the healthy controls. Differences found between these three groups should be interpreted with caution as they were significantly different in age, menopausal status, education, and hormone replacement therapy use which could influence reported outcomes [17].

For patients with higher risk of recurrence and higher stage disease, adjuvant therapy in the form or radiotherapy and/or chemotherapy is typically recommended. The Post-Operative Radiotherapy in Endometrial Cancer (PORTEC-2) investigated the outcomes and adverse effects of vaginal brachytherapy (VBT) compared to external beam radiotherapy (EBRT) for the treatment of high-intermediate risk endometrial cancer [18]. No difference in vaginal recurrence was found between the treatment groups, but less gastrointestinal side effects were reported in patients who received VBT. Longitudinal QoL assessment at 5 years showed there were no differences in sexual function between VBT and EBRT patients. However, when compared to an age-matched control population, participants in the study reported significantly more vaginal dryness and lower sexual interest, activity, and enjoyment [19].

Several small cross-sectional studies have not shown a difference in sexual function in endometrial patients undergoing hysterectomy and VBT compared to women who received hysterectomy alone [20,21] or compared to a healthy postmenopausal control [22]. Nonetheless, Quick et al. showed that compared to before the diagnosis of cancer, the majority of patients felt their vagina was smaller and reported increased vaginal dryness, more pain with intercourse, and less interest in sex [21]. In a study by Damast et al., 81% of patients who underwent

hysterectomy with adjuvant VBT reported sexual dysfunction. Participants also scored lower on all domains of the FSFI than the index population of healthy women ages 18–74, but not significantly worse than a postmenopausal control [22].

Nunns et al. prospectively evaluated sexual function and vaginal morbidity of endometrial cancer patients who received adjuvant VBT (N = 32) or EBRT (N = 43) following surgical staging [23]. Twenty patients were sexually active prior to treatment and 13 (65%) reported changes in sexual activity due to treatment, including decreased libido and frequency of sex, and 12 (60%) reported dyspareunia. Vaginal changes following radiation included vaginal stenosis, vaginal scarring, mucosal telangiectasia, and mucosal atrophy. Vaginal stenosis was not more likely to develop with the combination of EBRT and VBT [23].

In summary, the treatment of endometrial cancer presents many challenges to sexual health for female survivors. Even patients treated with surgery alone report high rates of sexual dysfunction. Surgery and adjuvant radiation are associated with vaginal morbidity and decreased sexual interest, arousal, and satisfaction.

2.2. Cervical cancer

The surgical treatment of early-stage cervical cancer can include cervical conization, simple hysterectomy, or radical hysterectomy with pelvic lymphadenectomy. Radical hysterectomy is associated with negative effects on sexual health and QoL [24]. Short-term sexual health consequences include orgasmic problems, vaginal shortening, dyspareunia, lymphedema, genital numbness, and sexual dissatisfaction [25]. Persistent sexual health concerns include lack of sexual interest (25%), lymphedema (19%), genital numbness (71%), and insufficient lubrication (24%) [25–27]. Compared to simple hysterectomy, radical hysterectomy patients experience lower vaginal blood flow during arousal [28]. Furthermore, radical hysterectomy patients self-reported worse sexual function across all FSFI domains compared to patients who underwent cervical conization [29]. Compared to healthy women, more patients treated with radical hysterectomy report diminished sexual function both before and after surgery [30].

Radical hysterectomy has detrimental effects on bowel and bladder function that can directly and indirectly affect sexual function. Traditional radical hysterectomy is associated with urinary retention, urinary incontinence, constipation, and urgency [27]. These complications are likely due to disruption of the hypogastric and splanchnic nerve plexuses during surgery [31]. Nerve-sparing modifications have been proposed to decrease these postoperative morbidities. Compared to traditional radical hysterectomy, nerve-sparing radical hysterectomy has shown improvements in short- and long-term bowel and bladder function, less postoperative complications, and improved sexual function [32].

Many patients with cervical cancer are diagnosed in their reproductive years. The median age of diagnosis is 49, and over 38% of patients are diagnosed under age 45 [1]. Radical trachelectomy is a safe fertility-sparing surgical option for some women with early-stage cervical cancer who have not completed childbearing [33–36]. Longitudinal comparisons in patients treated with radical trachelectomy versus radical hysterectomy showed no differences in mood, distress, sexual function, and QoL [9,37]. Many women in both treatment groups faced depression, distress, and sexual dysfunction, although improvement over time was noted in these domains. Yet, for the majority of patients after radical trachelectomy and radical hysterectomy, FSFI scores remained below the clinical cut off score, suggesting persistent sexual dysfunction [9,37].

Radiation therapy in the form of EBRT and VBT with or without concurrent chemotherapy (chemoradiation) plays a major role in the treatment of cervical cancer both in the primary and adjuvant setting. Radiation therapy has been associated with major vaginal toxicity including stenosis, shortening, atrophy, fibrosis, and dyspareunia [38–42]. Primary or adjuvant radiation therapy has been associated with greater sexual dysfunction and vaginal toxicity compared to surgery alone in cervical cancer patients [24,43]. The combination of surgery and radiation is associated with more vaginal shortening compared to radiation alone [8]. A few longitudinal studies have investigated the effects of radiation on QoL, sexual function, and emotional distress [8,39,44,45]. Mantenga et al. reported that patients who received concomitant chemoradiation experienced deterioration in body image that did not recover to baseline and 10–15% of patients suffered from severe anxiety long-term [44]. Lymphedema and menopausal symptoms negatively impacted long-term QoL [44]. Compared to age-matched controls, cervical cancer patients treated with radiation had significantly more sexual dysfunction and vaginal morbidity including decreased libido (85%), dissatisfaction in sexual life (30%), reduced vaginal dimension (50%), dyspareunia (55%), and lack of lubrication (35%) [45]. The majority of patients with dyspareunia and lack of lubrication were distressed by their symptoms [45].

In summary, cervical cancer patients experience sexual dysfunction following radical surgery and radiation therapy. Vaginal morbidity and bladder and bowel dysfunction negatively affect sexual health following radical hysterectomy. These morbidities can be reduced with less radical, nerve-sparing surgery. Women who undergo radical trachelectomy are not immune to changes in sexual function. Radiation, either as primary therapy or following surgery, results in the highest degree of sexual dysfunction and vaginal morbidity.

2.3. Ovarian cancer

Ovarian cancer accounts for 3% of cancers in women, but is responsible for more deaths than any other cancer of the female reproductive system [1]. The majority of patients present with advanced-stage disease. Primary treatment typically consists of a sequence of surgery and chemotherapy. Surgery involves hysterectomy, BSO, omentectomy, lymphadenectomy, and tumor debulking with the goal of optimal cytoreduction, either before or after chemotherapy. Removal of the ovaries results in hormonal alterations that can cause adverse changes in sexual health [46]. Menopausal symptoms triggered by cancer therapy can be more abrupt, prolonged, and intense [47], and if not managed can lead to diminished QoL, function, and sexual desire [48]. Sexually active ovarian cancer patients who had their ovaries removed prior to menopause had significantly lower sexual pleasure compared to ovarian cancer patients who were postmenopausal at the time of surgery [49].

In an online survey, 57% of ovarian cancer patients in the U.S. and Canada reported that their sexual life had been negatively affected by cancer and its treatment [50]. Survivors experience decreased libido, decreased arousal, problems with orgasm, and difficulty with intercourse due to treatment related side effects [51–53]. Worsening sexual discomfort has been related to diminished physical and social well-being [51]. Compared to healthy women, ovarian cancer survivors report increased vaginal dryness, more dyspareunia, less sexual activity, and lower libido [49,54]. Sexually active survivors are more likely to be younger, married, not actively receiving treatment, less fatigued, and report a better QoL and social functioning [49,54].

Sexual function in ovarian cancer patients can vary depending on the types of treatment received. Bukovic et al. investigated sexual function in ovarian cancer patients based on treatment modality, comparing surgery alone in early stage ovarian cancer patients (group 1), the combination of surgery and chemotherapy (group 2), and advanced inoperable or metastatic ovarian cancer patients receiving chemotherapy alone (group 3) [55]. Sexual satisfaction was decreased in all patients following treatment, but was more pronounced in groups 2 and 3. The greatest concern was pain with intercourse and most patients reported body image changes. While the majority of patients felt sexual health is important after ovarian cancer treatment, this opinion varied across the groups (74% v 65% v 47%, respectively) [55].

Germ cell tumors (GCTs) of the ovary present in younger patients and treatment can have repercussions on future fertility and sexual health. The GOG investigated the long-term reproductive health and sexual function of GCT survivors treated with surgery and platinum-based chemotherapy [56]. Fifty-three percent received fertility sparing surgery, of which 87% reported resumption of menses. Survivors reported less sexual pleasure and lower sexual functioning compared to controls. Patients who did not receive fertility-sparing surgery reported more discomfort with intercourse [56].

In summary, the majority of ovarian cancer survivors face negative effects on sexual function following treatment. Poor sexual function is associated with impaired QoL. Surgically-induced menopause and chemotherapy are associated with decreased sexual satisfaction. It is crucial to note the majority of ovarian cancer patients feel sexual health is important.

2.4. Vulvar cancer

Vulvar cancer comprises approximately 5% of gynecologic malignancies and the age of onset varies. Traditionally, vulvar cancer occurred in older women, but in recent years younger women are presenting with vulvar intraepithelial neoplasia (VIN) and vulvar cancer due to human papillomavirus infection [57,58].

Treatment of vulvar cancer is based on the size, location, and suspicion for lymph node metastases and consists of primary surgery with or without adjuvant radiotherapy or primary radiotherapy [59]. Surgical treatment of vulvar cancer has evolved from a radical "en bloc" resection of the vulva with bilateral groin and pelvic lymph node dissections to a triple incision technique and omission of pelvic lymphadenectomy [60,61]. Additional improvements in surgical morbidity included radical local excision and sentinel lymph node dissection in early-stage patients without compromising survival [62,63]. Despite changes in the surgical approach to vulvar cancer, sexual morbidity remains prevalent.

Women treated with vulvar surgery suffer detrimental effects on psychological function, sexual function, and relationships with their partners. Fear of anatomical changes related to surgery, fear of pain with intercourse, depression, worsening body image, and psychological distress have been reported in women undergoing vulvectomy for premalignant and malignant lesions [11,64,65]. Physical changes following surgery may include vaginal narrowing, numbness along the scar, removal of the clitoris, and change in tissue quality [64,66,67]. When compared to healthy controls, women undergoing vulvectomy have significantly more sexual dysfunction before and after surgery [65]. A study by Gunther et al. reported that patients who were not sexually active following radical vulvectomy cited genital complications from their surgery as the reason for abstinence [68]. Age, depression, and worsening functional status are risk factors for sexual dysfunction in this population [11,69]. More extensive vulvar excision was associated with poorer sexual function and QoL in a study by Likes et al. [69], but other studies found no association with the extent of surgical resection [11,70]. Patients who underwent laser or partial resection of the clitoris reported significantly more problems with arousal compared to vulvectomy patients in whom the clitoris was spared [65].

Inguinofemoral lymphadenectomy is a part of surgical management in certain vulvar cancer patients. Complete groin dissection is associated with infection and wound breakdown in 20–40% of patients and long-term lymphedema in approximately 30% [71]. Sentinel lymph node dissection has been shown to decrease these morbidities, but is not an appropriate alternative for all patients [63]. Lymphedema is associated with poor QoL in vulvar cancer patients [72] and has been shown to negatively impact sexual function [73]. Early detection and treatment are important as lymphedema is a chronic, progressive condition.

Radiation therapy has various roles in the treatment of vulvar cancer. In the adjuvant setting, radiation therapy can be administered to the vulva to treat positive or close surgical margins and to the groins and pelvis in the setting of positive lymph nodes to prevent recurrence and improve survival. In advanced vulvar cancer not amenable to surgical resection, definitive chemo-radiation is recommended. Research evaluating sexual health following radiation for vulvar cancer patients is scarce. In a longitudinal study by Weijmar Schultz et al., a profound reduction in the ability to induce arousal and orgasm as well as a decrease in the perception of positive genital sensation during arousal and orgasm was observed in vulvar cancer patients 6 months after surgery with or without adjuvant radiation ($N = 10$, 4 received radiation) and did not improve during the 2 year follow-up [67]. In a cross-sectional study by Hazewinkel et al., inguinal radiation negatively impacted the ability to achieve orgasm [70].

In summary, vulvar surgery negatively impacts sexual function regardless of the extent of surgical resection. Lymphedema is associated with poor QoL and sexual dysfunction. More research is needed to investigate the effects of radiation on sexual health in vulvar cancer survivors.

3. Evaluation and assessment of sexual health in the gynecologic cancer survivor

Identification of patients suffering from sexual health issues is essential in improving QoL, distress, and sexual function. An algorithm for addressing sexual health in the gynecologic cancer survivor is shown in Fig. 1. Female cancer survivors should be asked about their sexual function at regular intervals and assessment should include their sexual function before cancer, current sexual activity, and how cancer treatment has affected their sexual health and relationship with their partner. The NCCN recommends the Brief Sexual Symptom Checklist for Women as a primary screening tool (Fig. 2) [74,75]. Another option is a single-item screener for self-reporting sexual problems recently published by the Patient-Reported Outcomes Measurement Information System® (PROMIS®) group and the Scientific Network on Female Sexual Health and Cancer (Fig. 2) [76]. More in depth assessment can be achieved by using the FSFI (a 19-item instrument) and the PROMIS® Sexual Function and Satisfaction measures (PROMIS® SexFS- an 81-item instrument), both of which have been validated in cancer patients [77,78].

Assessment should also include a review of past medical, surgical, sexual, social, and cancer treatment history with inquiry of a history of pain with examinations. Attention to current medications is important to identify medications that may affect sexual function, as well as documentation of previously used strategies to address vaginal health. Relationship dynamics are key to optimal sexual function and inquiring about relationship satisfaction and partner health status, including sexual function, is necessary. Pelvic exam should include standard components of routine screening and surveillance. The external and internal genitalia should be inspected for evidence of edema, scarring, stenosis, atrophy, bowel or bladder incontinence, infection, and other potential causes of discomfort. Vulvar mapping in patients who report pain by using a Q-tip test can help localize pain [79]. Assessment of pelvic muscle function, tension, and strength can identify areas of dysfunction. Dilators can be used to assess current and desired vaginal capacity and progress over time in patients reporting dyspareunia, stenosis, shortening, vulvovaginal atrophy and pain with exams. Thorough evaluation is important in identifying the likely contributors to vulvovaginal pain and/or sexual dysfunction so that the appropriate intervention may be administered.

The demands of a gynecologic oncology clinical practice are high and conversations about sexual health can be challenging. Providers may experience personal embarrassment, feeling of insufficient knowledge about the diagnosis and treatment of sexual dysfunction, and lack of community resources [80]. By simply inquiring about vulvovaginal and sexual health, providers allow the patient an open avenue to discuss concerns and can dispel myths regarding sexuality after cancer

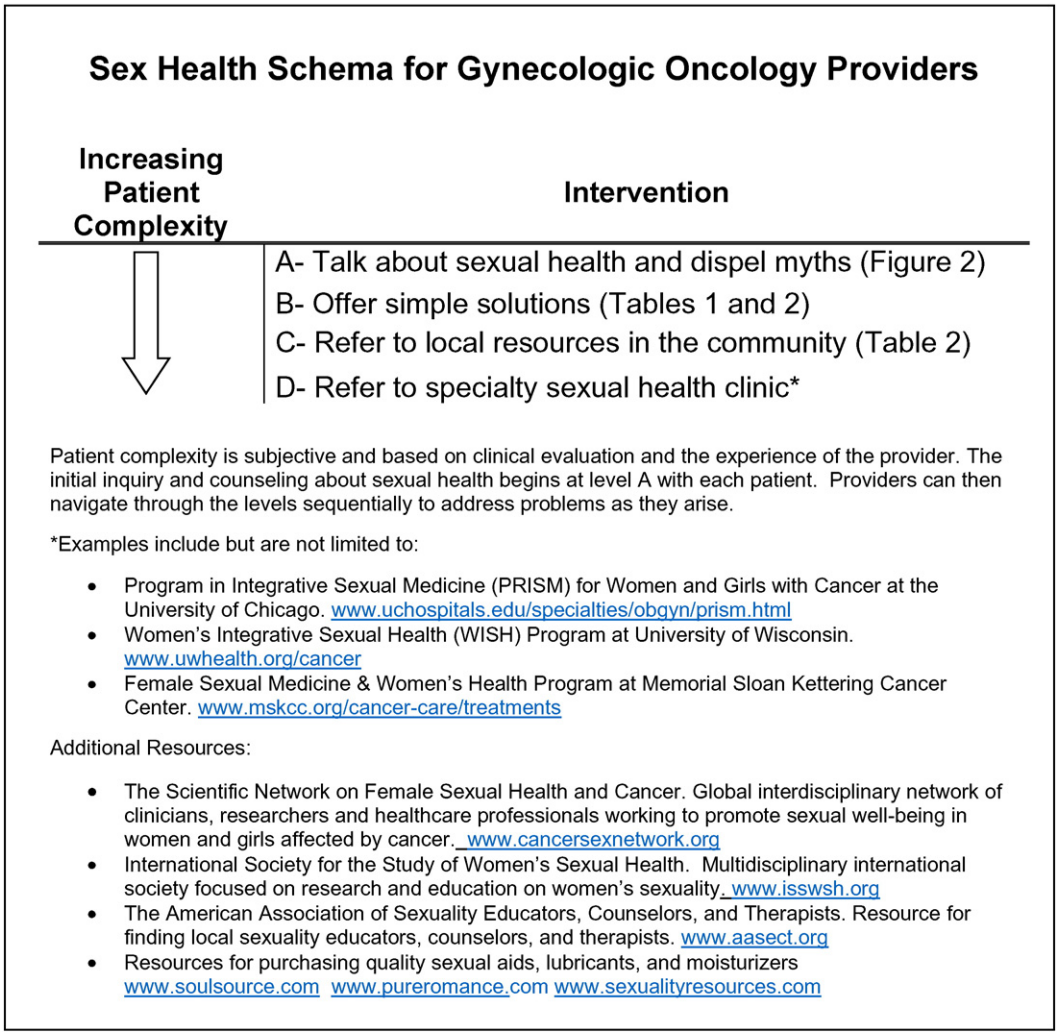

Fig. 1. Schema and resources for promoting sexual health in gynecologic cancer survivors based on level of patient complexity.

treatment. An efficient system of inquiry, assessment, and triage of treatment and referrals can be incorporated into a busy clinical practice.

4. Treatment strategies for female sexual dysfunction

The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) contains updated diagnoses and criteria for female sexual dysfunction in response to changing theories about the female sexual response cycle. The DSM-5 presents 3 domains of female sexual dysfunction: female sexual interest/arousal disorder, female orgasmic disorder, and genito-pelvic pain/penetration disorder [81]. In order to meet criteria for the diagnosis of female sexual dysfunction, symptoms must be present for at least 6 months and cause clinically significant distress. Although DSM-5 diagnostic criteria of these 3 domains of female sexual dysfunction will be presented, treatment options discussed may be helpful to women with these issues who may not fully meet criteria for a disorder.

4.1. Female sexual interest/arousal disorder

To meet criteria for female sexual interest/arousal disorder a patient must report a lack of or significantly reduced sexual interest/arousal that is manifested in at least 3 of the following: reduced interest in sexual activity, reduced sexual/erotic thoughts or fantasies, reduced initiation of sexual activity and typically unreceptive to a partner's attempts to initiate, reduced sexual excitement/pleasure during sexual activity in 75–100% of sexual encounters, reduced sexual interest or arousal in response to any internal or external sexual cues, reduced genital or non-genital sensations during sexual activity in 75–100% of sexual encounters [81].

The basis of desire and arousal in women is multifactorial. From a physiologic standpoint, genital vasocongestion occurs almost immediately after erotic stimulation and this is mediated by pelvic sympathetic and parasympathetic nerves [82]. However, perceived arousal often does not correlate with genital response [83]. Desire can be negatively impacted by many psychological factors including stress, anxiety, depression, poor body-image, and sexual abuse or trauma [84]. Psychotherapy is commonly used to treat patients with desire and arousal problems, especially if they are acquired or situational. Associated psychological factors should be addressed before or concurrently with the symptoms of diminished desire and arousal. Studies reporting the treatment of female sexual interest/arousal disorder in gynecologic cancer survivors are limited. However, a study by Brotto et al. evaluated the effects of a mindfulness-based cognitive behavioral therapy program on sexual function in endometrial and cervical cancer survivors who reported significant sexual desire and/or arousal concerns [85]. The results of treatment were compared to a wait-list control. Treatment was associated with improved FSFI domains of desire, arousal, lubrication, orgasm, satisfaction, and overall FSFI score. Treatment did not improve pain, but did reduce sexual distress and increase perceived genital arousal [85]. Referral to a provider who specializes in cognitive-behavioral therapy and sexual psychoeducation would likely benefit

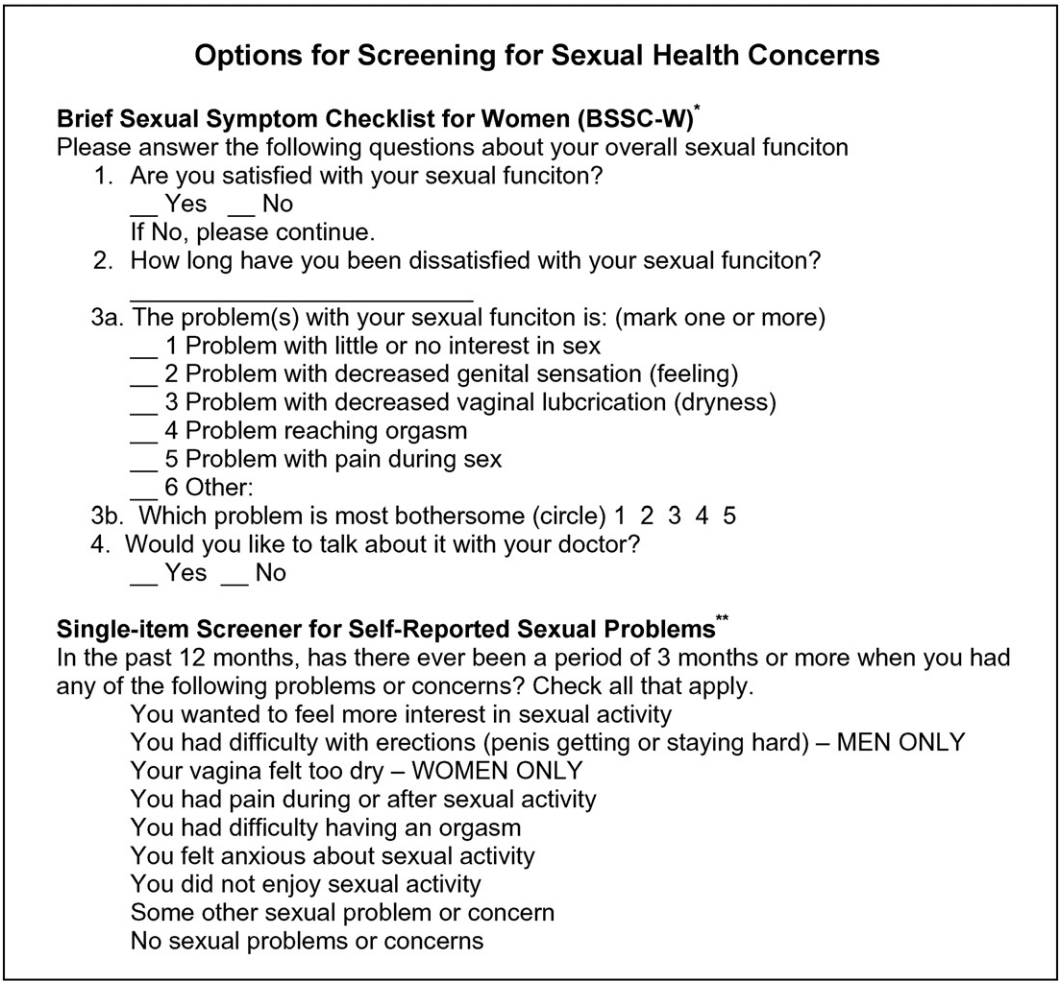

Fig. 2. Options for screening for sexual health problems in gynecologic oncology survivors. *Reprinted with permission from Hatzichristou D, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. *J Sex Med*. 2010;7:337–348. **Proposed by the PROMIS® group and the Scientific Network on Female Sexual Health and Cancer. Reprinted with permission from Flynn K, Development and Validation of a Single-Item Screener for Self-Reporting Sexual Problems in U.S. Adults, *JGIM*. Online publication 18 April 2015.

patients with sexual interest and arousal concerns. Many psychologists and health educators have expertise in counseling about sexual health matters. Certified sexual health providers are available in many communities.

In August 2015 the U.S. Food and Drug Administration approved flibanserin daily at bedtime for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women [86]. Flibanserin is a postsynaptic 5-HT_{1A} agonist and 5-HT_{2A} antagonist. FDA approval was based on 3 phase-3 randomized placebo-controlled trials that included 3548 premenopausal women with HSDD (2310 treated with filbanserin, 1238 treated with placebo) [87–89]. Compared to placebo, flibanserin daily at bedtime significantly improved the number of satisfying sexual events, sexual desire, and distress related to low desire over a 24 week treatment period. The most frequent adverse events included dizziness, somnolence, nausea and fatigue occurring in 9–12% in flibanserin-treated and 3–8% placebo-treated women. In a recent randomized placebo-controlled clinical trial investigating the efficacy of flibanserin in treating postmenopausal women with HSDD, similar efficacy and adverse events were found [90].

A few additional issues warrant consideration about flibanserin. The August 2015 FDA approval of flibanserin contained a Boxed Warning highlighting the risk of severe hypotension and syncope in patients who consume alcohol while taking flibanserin, in those who also use moderate or strong CYP3A4 inhibitors, and in those who have liver impairment. Flibanserin is contraindicated in these patients. Also, if no improvement in sexual desire or associated distress is noted after 8 weeks of treatment, flibanserin should be discontinued. It is not FDA approved for treatment of postmenopausal women and has not been studied in cancer populations. The trials conducted in premenopausal women had strict inclusion criteria, including using DSM-IV criteria for the diagnosis of HSDD and excluding women taking medications commonly prescribed to oncology patients [87–89]. The trial conducted in postmenopausal women excluded women with a "gynecologic disorder," history of hysterectomy or oophorectomy, symptomatic vaginal atrophy, and many other minor gynecologic issues [90]. Therefore, clinicians should be cautious about generalizing these findings and using the drug for gynecologic cancer survivors. Future research and clinical experience regarding efficacy and safety of flibanserin in more medically and gynecologically complex patients will be helpful in determining its role in this setting.

4.2. Female orgasmic disorder

Female orgasmic disorder is defined as difficultly experiencing an orgasm and/or markedly reduced intensity of orgasmic sensations in 75–100% of occasions of sexual activity [81]. In evaluating women reporting concerns achieving orgasm, it is important to inquire about adequacy, variety, and amount of stimulation during sexual activity [91]. Low education, certain religious beliefs, and feeling guilty about sex are associated with female orgasmic disorder [92] and psychological risk factors include anxiety, depression, poor body-image, and a history of abuse [91,93]. A combined cognitive and behavioral approach is the

recommended approach to treating female orgasmic disorder [91]. Directed masturbation is a behavioral technique that involves graded genital stimulation to facilitate heightened arousal and orgasm and is conducted over multiple weekly therapy visits. Success rates can be as high as 90% and are best when coupled with cognitive-behavioral therapy [91].

Selective serotonin reuptake inhibitors (SSRI) have well-established negative effects on sexual function with 31–57% of patients reporting delay or inhibition of orgasm [94]. If problems with orgasm are experienced after initiation of an SSRI, allowing tolerance to develop will resolve orgasmic dysfunction in 30–40% of patients by 6 months [95]. Persistent symptoms can be addressed by attempting to decrease the dose or switching to a new antidepressant. Buproprion does not have the same adverse sexual side effects as SSRIs and may improve sexual function [96]. Phosphodiesterase type 5 inhibitors may improve SSRI-induced sexual dysfunction in women, but these drugs are not FDA approved for this indication [97].

4.3. *Genito-pelvic pain/penetration disorder*

The diagnosis of genito-pelvic pain/penetration disorder requires persistent difficulty with any one of the following: vaginal penetration during intercourse; vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts; fear or anxiety about pain in anticipation of, during, or as a result of vaginal penetration; tension of the pelvic floor muscles during attempted vaginal penetration [81]. The treatment of gynecologic malignancy is associated with many causes of genito-pelvic pain and dyspareunia. Many of these symptoms can arise from alterations in vaginal health from surgery, radiation, and chemotherapy causing vaginal shortening, stenosis, atrophy, and dryness. Restoring lubrication and a natural pH to the vagina can help alleviate many problems, especially atrophy, dryness, and pain. Strategies to improve vaginal health and the role of dilators and pelvic floor physical therapy in the treatment of pelvic and genital pain will be discussed below.

There are many non-hormonal options for the treatment of vaginal dryness and atrophy. Vaginal moisturizers are non-hormonal products intended to be used several times a week for overall vaginal health to improve tissue quality and comfort, whereas vaginal lubricants are liquids or gels applied to the external genitalia and vaginal entrance to minimize dryness and discomfort temporarily during sexual activity [98]. Replens® is a polycarbophil based vaginal moisturizer that binds to vaginal epithelium, hydrating the underlying cells, resulting in increased vaginal epithelium maturation and reduced bacterial vaginosis in small groups of women treated for symptoms of vaginal atrophy [99,100]. A small randomized study (N = 40) comparing Replens® to vaginal estrogen showed equivalent improvement in dyspareunia and vaginal irritation. Although vaginal dryness was improved from baseline in both treatments, vaginal estrogen was superior to Replens® [101]. Another type of moisturizer is hyaluronic acid, a glycosaminoglycan that has water retention and lubricating properties. Two studies have compared hyaluronic acid products to vaginal estrogen [102,103]. Both hyaluronic acid and vaginal estrogen improved vaginal atrophy and dryness, decreased vaginal symptoms, and decreased vaginal pH [102,103]. Another study found suppositories with hyaluronic acid, vitamin A, and vitamin E to be effective in reducing vaginal dryness and dyspareunia [104].

Vaginal lubricants are used during sexual activity to temporarily minimize dryness, pain, irritation, and mucosal tears. There are a wide variety of products that can be located over the counter. Water- or silicone-based lubricants are recommended as they wash away with warm soap and water. Petroleum-based lubricants are not recommended because they increase the risk of vaginal infection, damage latex condoms, and can be associated with an unpleasant vaginal odor. For best results, lubricant should be applied to both partners' genitals prior to sexual activity and may need to be reapplied several times. Patients should avoid lubricants with perfumes or flavors as they can be irritants [98]. An example of patient information explaining differences between water- and silicone-based lubricants and moisturizers as well as commercially available products is presented in Table 1.

Osphena® (ospemifene) is currently the only FDA-approved, non-estrogen, oral pill for moderate to severe dyspareunia due to vulvovaginal atrophy in postmenopausal women. It is an oral selective estrogen-receptor modulator that was shown to improve vaginal health, but needs further investigation in cancer populations [105,106]. A small randomized, controlled, double-blind trial, also investigated topical lidocaine in the treatment of severe penetrative dyspareunia in breast cancer survivors. Results indicated that lidocaine applied to the vulvar vestibular tissue before vaginal penetration reduced sexual distress and improved comfort with penetration, but further study is warranted in gynecologic cancer patients [107].

Low dose vaginal and systemic estrogen therapy are effective in treating genitourinary effects of menopause in the general population [108,109]. The Women's Health Initiative reported systemic hormone replacement therapy with estrogen plus progestin is associated with an increased risk of coronary heart disease, stroke, and breast cancer and the risk of treatment outweighs the benefit [110]. Other studies are conflicting on whether unopposed estrogen is associated with increased breast cancer risk [111,112]. Hormone replacement therapy is controversial in patients with hormone-receptor positive cancer. A few retrospective studies have shown that oral estrogen therapy was not associated with increased risk of recurrence in early stage endometrial cancer patients [113,114]. A GOG study by Barakat et al. was designed to test the safety of estrogen therapy in early stage endometrial cancer patients, but closed early due to poor accrual after the Women's Health Initiative results were published and was underpowered to determine the effect of estrogen on recurrence and survival [115]. Low dose vaginal estrogen alleviates symptoms of vaginal atrophy with minimal serum estrogen elevation, and is available in creams, tablets, and rings [108]. Initiation of hormone therapy requires a discussion of risks, benefits, alternatives, and the expert opinion of the treating oncologist. Many survivors of non-hormone receptor positive cancers are acceptable candidates for hormone replacement therapy, especially if they have failed other more conservative treatment options for vaginal atrophy.

The use of vaginal dilators to prevent vaginal stenosis from pelvic radiation is often recommended to gynecologic cancer patients, but data to support its effectiveness is conflicting [116,117] and adherence to dilator use is poor [118]. Regular sexual activity can help maintain vaginal health, but in patients who are not sexually active, dilators can be helpful in vaginal rehabilitation following treatment. Survivors who did not receive radiation therapy may also benefit from dilator use. Dilators (with or without additional vibration) used in combination with lubricants or moisturizers and pelvic floor exercises can be used in patients with dyspareunia, pain with pelvic exams, and vaginal morbidity caused by surgery and estrogen deprivation [98].

Pelvic floor muscles, especially muscle strength, play an important role in sexual function. Patients with stronger pelvic floor muscle contractions on physical exam scored higher on arousal and orgasmic domains of the FSFI compared to women with weak pelvic floor muscles [119]. Furthermore, improved patient control of pelvic floor muscles can decrease pain encountered during intercourse. Pelvic floor physical therapy is often comprised of intravaginal trigger point and massage techniques, pelvic floor muscle strengthening and relaxation exercises, biofeedback, and vaginal dilators. The goal is to improve flexibility of the paravaginal tissue, decrease tension, improve strength, and increase blood flow to the pelvic floor muscles [120]. In a prospective study of 13 patients with vestibulodynia, Goldfinger et al. found that following pelvic floor physical therapy, participants reported significant reductions in pain intensity with intercourse, improved overall sexual function, and more pain-free encounters [120].

Table 1
Lubricants and moisturizers. A non-comprehensive list of lubricants and moisturizers.

	Water-based lubricants To be used with sexual activity	Silicone-Based Lubricants To be used with sexual activity	Moisturizers To be used daily or 2–3 times weekly for comfort
Pros	• Inexpensive • Compatible with condoms • Safe to use with latex and silicone dilators/toys	• Never dries out • Can be used in water • Feels lush • Compatible with latex condoms • Does not contain glycerin and may help to reduce infections	• Helps moisturize vaginal lining • Makes vaginal and vulvar tissues more pliable • A single application at bedtime may give relief for several days • Can also be used to moisturize the external tissues • May improve vaginal pH
Cons	• Dries out more easily, may need to re-apply • May feel tacky over time • Some products may contain glycerin (may increase risk of urinary & yeast infections)	• More expensive • More difficult to wash off • Incompatible with silicone or rubber • Impairs sperm motility	• Some products may contain glycerin (may increase risk of urinary and yeast infections)
Brands	• Liquid Silk™ • Sliquid® Organics Silk • Sliquid® Oceanics • Slippery Stuff® • Yes® • Good Clean Love • Liquid Assets® • Pre-Seed® • Luvena® • Sliquid® Organics Silk	• Uberlube • Pjur® Eros • Pink® • ONE® Move™ • Astroglide® Silicone	• Vitamin E capsules/suppositories • HYALO GYN® • Replens® • K-Y® Liquidbeads®

Many treatment approaches have been presented for common sexual health concerns in gynecologic cancer survivors. Fig. 1 presents a sexual health schema based on patient complexity. Gynecologic oncology providers should be able to provide care across all levels, from basic conversations about sexual health to referrals to a specialty sexual health clinic. Table 2 presents a possible model to triage common sexual health issues.

5. Conclusion

Gynecologic cancer survivors experience sexual morbidity as a result of the diagnosis and treatment of their cancer. Sexual health is important to women in survivorship, but is rarely discussed with providers. Oncology providers can make a significant impact in the quality of life of patients by simply asking about sexual concerns. Most oncology providers are not experts in treating sexual dysfunction, but simple tools can be incorporated in clinical practice to ensure success. Addressing vaginal health issues with moisturizers, lubricants, and/or hormonal therapy (local or systemic), as medically appropriate, can be easily addressed in a surveillance visit. Identifying professionals in the community where patients can be referred for pelvic floor physical therapy, cognitive-behavioral therapy, couples counseling, and sexual education can help patients with more complex sexual issues. Furthermore, national and international resources are available to provide evidence-based recommendations, education, and promote research in women's sexual health.

Sexual health is an under-researched area in gynecologic oncology. Future studies in gynecologic cancer patients should include patient-related outcomes, identify at-risk subgroups who may benefit from early intervention, and expand the treatment options available for sexual dysfunction.

Table 2
Basic triage strategies for the most common sexual health issues in cancer patients utilized by the authors.

DSM-5 diagnosis	Clinical symptom	Treatment options
Genito-pelvic pain/penetration disorder	Vaginal dryness	Moisturizer Lubricant Hormonal therapy[a]
	Pain or vaginal narrowing	Ensure proper tissue quality, moisture, and lubrication (See Table 1) Dilator and/or Vibrator Referral to pelvic floor physical therapy Consider topical lidocaine for the vulvar vestibule (for severe dyspareunia)
Female sexual interest/arousal disorder	Physical cause	Treat any physical issue (see above) Encourage pelvic floor exercises to increase circulation and tone
	No physical cause	Referral to sex therapy or couples counseling
	Related to underlying medical condition	Optimize medical condition Evaluate medication impact
Female orgasmic disorder	Difficulty or inability in achieving orgasm	Treat any physical issue (see above) Vibrator Referral to sex therapy Erotica or romance novels Explore other methods of sexual expression (hugs and caress)

[a] When medically appropriate.

Conflict of interest statement

Dr. Kushner reports that he is the current chair and Dr. Carter reports that she is the current vice-chair of the Scientific Network on Female Sexual Health and Cancer, an organization founded at the University of Chicago and now operated from the University of Wisconsin-Madison, both not-for-profit organizations. Neither Dr. Kushner nor Dr. Carter receive compensation for their roles. The other authors declare no conflicts of interest.

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