

Review Article

Sexuality, Intimacy, and Menopause Symptoms (SIMS) in Ovarian Cancer Patients

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Abstract

Objective: To review the sexual health concerns of women with ovarian cancer and how these concerns can be managed.

Methods: A comprehensive review of the literature.

Results: Issues of sexuality, intimacy, and early menopause significantly impact the quality of life of patients following diagnosis and treatment of ovarian cancer. Unfortunately many providers do not address these issues in the pre-treatment or perioperative period. Furthermore, patients do not often alert their providers to their symptoms. While systemic hormone therapy may improve many of the issues, its use is controversial given the association it has with cancer recurrence. However, other non-hormonal treatments exist including selective serotonin reuptake inhibitors, antiepileptics, natural remedies, and pelvic floor physical therapy. In addition psychological care and the involvement of the partner can be helpful in managing the sexual health concerns of these patients. At the time of diagnosis or at initial consultation, women should be informed of the potential physiologic, hormonal, and psychosocial effects of ovarian cancer on sexuality and also that we have a multi-modal approach to dealing with them.

Conclusion: Women undergoing treatment of ovarian cancer often suffer from sexual morbidity, intimacy issues and early menopause. These are undertreated problems. Successful treatment requires the provider's awareness of the problem, ability to identify it, and willingness to treat it.

ABBREVIATIONS

SIMS: Sexuality Intimacy and Menopause Symptoms

INTRODUCTION

Sexuality, Intimacy, and Menopausal Symptoms (SIMS) are common among women treated for ovarian cancer [1-4], with almost fifty percent of women experiencing some dysfunction [5]. Ovarian cancers are a histologically diverse set of malignancies that affect women across the age spectrum and necessitate treatment which can range from the removal of one ovary to an extensive debulking surgery combined with chemotherapy (often multiple lines) and radiation. The degree of sexual dysfunction a patient experiencing is directly related to the extent of the treatment she has undergone. As a result of their treatments, patients suffer from physical and psychological morbidity including vaginal dryness resulting in dyspareunia, loss of sensation in the genital area, decreased libido, hot flashes, decreased sexual desire, decreased ability to achieve orgasm, depression, anxiety, changes in self image and interpersonal relationship changes with their partners and loved ones. While many of these changes can be attributed to the change in circulating hormones and hormone regulation after oophorectomy, chemotherapy and radiation also influence SIMS.

Sexual dysfunction in women with ovarian cancer

SIMS encompasses a broad range of physical and psychological symptomatology, always contextualized by the patient's age, menopausal status, baseline sexual function, and personal relationship status. Many premenopausal women will experience abrupt menopausal symptoms secondary to hypoestrogenemia after cytoreductive surgery or gonadotoxic chemotherapy, inducing hot flashes, mood changes, and vaginal dryness or atrophy [2,4]. Regardless of menopausal status, when sexual activity is attempted, ovarian cancer survivors report significantly higher levels of discomfort and decreased pleasure with sexual activity in comparison to age matched controls in the general population [6]. Many women struggle with initiation or maintenance of sexual arousal and with attainment of orgasm [1]. Apart from the physical symptoms, greater than 50% of ovarian cancer patients reported decreased libido and lack of desire to initiate intercourse, compared to 25% of healthy controls. However, both groups place similar value on the importance of sexual activity, highlighting the need for appropriate interventions to enable ovarian cancer patients to maintain a high quality of life with satisfactory sexual function [6].

The impact of cancer treatments and therapies on sexual health

Sexual dysfunction most commonly occurs after treatments

involving surgical cytoreduction, chemotherapy, and radiation [7]. Surgical management of gynecologic malignancies can bring about sexual dysfunction by altering physiology and perceived body image. While ovarian cancer encompasses a number of histologically diverse cancers, the surgical treatment of ovarian cancer usually consists of removing the cervix, uterus, and ovaries. Interestingly, women after total hysterectomies have no difference in sexual function when compared to women after supracervical hysterectomies [8]. Therefore, in the cytoreductive surgeries, sexual dysfunction symptoms are thought to be secondary to loss of systemic hormones. After oophorectomy, there is a clear decrease in sexual function and desire, particularly in the younger premenopausal patients [7,9-12]. The effect of oophorectomy on sexual function in postmenopausal women is less clear. The studies evaluating the impact of oophorectomy of sexual function in postmenopausal women have been inconsistent. One cross-sectional study involving 1,352 women ages 57 to 85 who had either bilateral oophorectomy or retention of their ovaries showed that removal may not play a strong role in function and sexual ideation in older women [9,13]. Conversely, another survey showed 75% of patients complained of orgasmic dysfunction and 62% had issues with dyspareunia following surgery for ovarian cancer in postmenopausal women [14]. Additional studies have reported that removal of postmenopausal ovaries reduces sex steroid levels, in turn leading to a decline in sexual function [9]. Regardless of these opposing studies, the removal of postmenopausal ovaries decreases testosterone and androstenedione. Loss of androgenic hormones leads to decreases in estrogen levels as both testosterone and androstenedione are converted in the periphery to estrogen [15]. The loss of these androgenic hormones exacerbates the hypoestrogenic state but also further contribute to sexual dysfunction as they are implicated in driving libido. Given these findings, oophorectomy in a postmenopausal woman will lead to a decline in levels of androgens and estrogens. This lower hypogonadal state may result in decreased libido, worsening hot flashes, mucosal atrophy and vaginal dryness. These symptoms, along with changes in patient's body image perception following surgery, will lead to worsening of sexual dysfunction [16].

Patients receiving chemotherapy for ovarian cancer can be separated into two groups: 1) those with at least one ovary remaining in situ (i.e. fertility-sparing surgery with unilateral oophorectomy in a minority of patients and recipients of neoadjuvant chemotherapy), and 2) those who are status post bilateral oophorectomy, representing the majority of patients.

In the patients in the first group, chemotherapy can have a host of effects on sexual function. Most notably, chemotherapeutic agents (including platinum-based therapies used in the majority of ovarian cancer patients) target dividing cells which can affect the production of estrogen androstenedione in granulosa and theca cells. Similar to surgery, chemotherapy can place a patient into menopause, and these patients may have similar symptoms as their surgical cohort. They are afflicted with vaginal dryness, atrophy, hot flushes and decreased libido. Practically, patients report decreased sexual pleasure and decreased sexual activity [17].

In the second group, sexual dysfunction is also reported.

These complaints are most pronounced in patients with recurrent disease and in married patients [18]. As many as 53% of patients have been reported to have no sexual activity in the month following diagnosis and while starting chemotherapy and 75% of women are at high risk for sexual dysfunction. Qualitatively, women report decreased desire for sexual intercourse, increased pain and dryness, and difficulty in discussing these topics with their partners and their physicians [19].

Radiation therapy is uncommon in ovarian cancer treatment and largely limited to palliation of symptomatic metastases in advanced disease. There are no studies looking specifically at ovarian cancer patients receiving radiation therapy and sexual function.

The impact of cancer treatment of intimate relationships

It is now well known that cancer and its treatment can have significant consequences on the quality of life of patient and the family members, particularly the patient's intimate partner [20]. Sexuality and intimacy are important components of quality of life [21], and there is a growing body of evidence reporting that cancer can result in dramatic changes to sexuality, intimacy, and sense of self, therefore negatively affecting the relationships [22,23]. These changes can lead to emotional disruptions between couples [24], as well as feelings of isolation, anxiety, depression [25], or inadequacy [26]. Reported disruptions stem from decreases in sex drive of the patient and/or the partner, fear of initiating sex, losing "normality" within the sexual relationship, and feeling unwanted because of cessation of sex [23,27,28]. More importantly, intimacy and other forms of affectionate contact can also be lost when sexual intercourse ceases in disease context [29] the fear of the patient/partner that any intimacy might lead to sexual intercourse, which might be unpleasant, not possible or deemed inappropriate [30,31]. The new dynamics between the patient and the partner in the context of a care giving relationship as well as the new definition of 'appropriate' sexual conduct after cancer might have an adverse effect on the couple's private life.

In a study evaluating the changes in sexuality and intimacy after the diagnosis and treatment of cancer, Hawkins et al. reported cessation or decreased frequency of sex and intimacy in 79% of male partners of women affected by cancer [30]. Changes to sexuality were associated with feelings of self-blame, reflection, sadness, anger and lack of sexual fulfillment [30]. In the same study, male partners of women diagnosed with gynecological cancer expressed conflicting emotional states including worry about their significant other's health; desire to engage in sexual activity, and guilt about wanting to increase sexual intimacy. Understandably, these conflicting emotional states can lead to resentment and withdrawal from sexuality and intimacy, subsequently causing overall relationship discord [32,33].

Barriers to identifying and treating sexual dysfunction

Multiple barriers to identification and treatment of sexual dysfunction in ovarian cancer patients exist. The obstacles begin with the initiation of the discussion about sexual dysfunction between a patient and her provider. A 2007 survey

of the members of the New England Association of Gynecologic Oncologists (NEAGO) revealed that while a majority of gynecologic oncologists reported comfort with the topic of sexual health, 85% of male providers and 73% of female providers stated that time constraints limited their ability to formally address sexuality and sexual function with their patients [34]. Furthermore, many healthcare providers report beliefs that patients will independently raise the topic of sexual dysfunction if they are experiencing symptoms [35]. In contrast, patients report hesitancy to broach the subject and report feeling similar time constraints during visits as their providers [36].

Once the need for treatment of sexual dysfunction is identified, effective treatment presents distinct challenges. Sexual dysfunction in ovarian cancer survivors is often multimodal, and single approach treatment is frequently insufficient. Many providers, while agreeing with the importance of addressing these issues, feel poorly equipped to manage them [36,37].

Many of the physical changes induced by cytoreductive surgery and subsequent chemotherapy result in abrupt hormonal changes and premature menopause in previously premenopausal patients. Sexual pain, often attributable to hypoestrogenemia and vaginal dryness (but may also result from postoperative changes), can lead to profound anxiety about sexual activity and negatively impact sexual desire, even when a patient expresses an interest in intercourse. However, hormone replacement in gynecologic cancer patients remains controversial, and many providers are hesitant to prescribe it. However, to date no evidence exists that HRT adversely affects progression or survival in a majority of ovarian cancer patients, although substantial further research is needed [38-42].

Beyond the physical sequelae of treatment, the psychosocial ramifications of dealing with their disease and treatment are complex. Many patients are dealing with depressive symptoms, fatigue, or profound changes in their self-image as a consequence of diagnosis and treatment and addressing her mental health and emotional well-being is often instrumental in improving a patient's sexual function [43,44]. Furthermore, as previously discussed, the patient herself is not the only person impacted by her disease. Partners of ovarian cancer patients often become the primary caregivers, often assisting with basic activities of daily living, including toileting and hygiene. Apart from the physical exhaustion partners can experience from the constant provision of care, the patient may be repositioned as a "cancer patient" rather than a sexual partner [45]. For these reasons, a multimodal approach, encompassing management of physical symptoms, individual psychosocial support and treatment, and partner engagement, may be necessary to fully address sexual dysfunction in some patients.

Hormonal therapies

For patients with ER positive cancers, which typically include Granulosa Cell Tumors or Low Grade Serous Carcinomas, physicians need not worry about topical estrogen therapy given the lack of long term systemic absorption through healthy vaginal mucosa. Furthermore, generally speaking, there are few contraindications to topical estrogen therapy in cancer survivors [7].

Topical estrogen therapies are helpful in patients who suffer from vaginal stenosis and atrophic symptoms. This topical therapy, available in a cream, ring, or tablet form, has been helpful for patients with ovarian malignancies. In women with ovarian cancer, topical estrogen can be used safely and easily following surgery. For these patients, topical estrogen therapy is a fast way for patients to regain elasticity, blood flow and lubrication to the vaginal tissue. Topical estrogen therapy is safe for women with gynecologic malignancies, including women with estrogen receptor (ER) positive cancers [48]. Some studies have shown low levels of systemic estrogen following initiation of topical therapy secondary to the poor barrier properties of atrophic vaginal mucosa [49]. Following initial topical estrogen treatment of the vaginal mucosa, tissue integrity is regained thereby preventing any further systemic absorption. For patients with ER positive cancers, which in ovarian cancers are typically Granulosa Cell Tumors or Low Grade Serous Carcinomas, physicians need not worry about topical estrogen therapy given the lack of long term systemic absorption through healthy vaginal mucosa. With these findings, there are few contraindications to topical estrogen therapy in cancer survivors [7].

Multiple studies have confirmed that systemic HRT in ovarian cancer survivors does not increase disease recurrence or mortality, and in fact may have a survival benefit [50,51]. When it comes to optimizing HRT for post-treatment ovarian cancer patients suffering from sexual dysfunction, no major studies have compared different methods of therapy initiation. Therefore, it is best to follow guidelines by professional organizations and optimize to individual patient. Per American College of Obstetricians and Gynecologists and North American Menopause Society (NAMS) current guidelines, local estrogen is the first line advisable therapy for alleviation of vaginal symptoms [52,53]. Low dose systemic therapy can be used in those who have failed local therapy. When choosing oral versus transdermal systemic administration, transdermal is chosen for patients with higher cardiovascular or thromboembolic risk and with more years elapsed since menopause. Given the elevated risk of thromboembolic disease in patients with ovarian cancer, transdermal is likely the best first line.

In terms of non-estrogen therapies, several options have been evaluated. Ospemifene, an oral estrogen agonist/antagonist has been shown to improve vaginal symptoms, though this is contraindicated in patients with past or current thromboembolic disease [54]. Testosterone has been shown to increase sexual function and satisfaction among postmenopausal women, however this is not FDA approved for use in women in the US [55]. Tibolone is a synthetic steroid with estrogenic, progestogenic, and weak androgenic effects that was proposed for treatment of these symptoms, however it has not been shown to improve sexual function and is not FDA approved for use in the US [56].

Non-Hormonal therapies

In addition to hormonal preparations, there are a number of non-hormonal therapies which can improve SIMS. The first one to consider is black cohosh extract. It is the most extensively used and researched natural alternative to HRT. There is some disagreement among experts on the utility of black cohosh in

the treatment of menopausal symptoms. While a 2012 Cochrane Review suggested there was no benefit of using black cohosh, there have been many other studies which have suggested otherwise [57-60]. For example, in a randomized, double-blind, placebo-controlled, multicenter study of 340 postmenopausal women, Remifemin was found to improve hot flashes, vaginal atrophy, and psyche when compared to placebo [57]. From our extensive experience with patients suffering from SIMS, there is a clear benefit from using the black cohosh extract (Enzymatic Therapy, Green Bay, Wisconsin, United States) and the side effect profile is null. For the natural treatment of decreased libido and sexual pleasure, providers can consider preparations using extract of Maca Root or Ashwagandha Root. These extracts have been preliminarily shown to have a positive effect on libido, sexual dysfunction, and sexual performance and pleasure [61-65]. Although more research is needed, these products can certainly be considered as an alternative or adjunct to other pharmacotherapies in patients suffering from sexuality or intimacy issues.

SSRIs and SNRIs were initially used for management of vasomotor symptoms occurring secondary to GnRH agonist treatment for men with prostate cancer and women with breast cancer [32,66,67]. Although this class of antidepressants can have some efficacy in managing vasomotor symptoms, they may also worsen sexual functioning by decreasing libido [32]. Besides decreased libido, there is a spectrum of sexual dysfunction associated with various antidepressants. Therefore, providers should take the likelihood of adverse sexual effects into account when prescribing SSRIs or SNRIs [68]. Among many SSRIs and SNRIs that are frequently prescribed, citalopram and escitalopram have proven better efficacy in controlling vasomotor symptoms with a more tolerable side effect profile when compared to venlafaxine and fluoxetine [69,70]. Additionally, limited uncontrolled studies of mirtazapine, a structurally unique SSRI, and bupropion, which acts on dopamine and norepinephrine, were associated with better control of hot flashes with decreased adverse effects on sexual functioning than SSRIs/SNRIs [32,71,72].

Vaginal atrophy and dryness can be debilitating. Vaginal moisturizers are non-hormonal products used several times a week to improve tissue quality whereas vaginal lubricants are liquids or gels applied to the external genitalia and vaginal introitus to minimize dryness and discomfort temporarily during sexual activity [73]. Vaginal moisturizers, such as polycarbophilic moisturizers (e.g. Replens) or vaginal pH-balanced gels (e.g. RepHresh Vaginal Gel) can be recommended to patients who experience these symptoms. The literature is mixed on the effectiveness of these moisturizers versus placebo but given the null side effect profile and our positive experience with it clinically, it is recommended as a first line approach if the provider is trying to avoid hormonal therapy [74,75]. Vaginal lubricants can also be helpful during sexual activity. They are used to minimize dryness, pain, irritation, and mucosal tears. They come in a variety of forms but most commonly are water or silicone based.

Dyspareunia can be a result of radiation changes or associated with atrophy and/or vaginal dryness. When this symptom is

identified, vaginal dilators are often recommended. They come in various sizes, shapes, and colors and are usually made of silicone or plastics. They can be used a few times a week or even daily and should be used with estrogen cream if allowed or else vaginal lubricants. They can be left in place anywhere between 10-60 minutes to achieve optimal results. It can often take up to a month before significant results are achieved. Although adherence to recommendations for vaginal dilator use has been reported to be low in this population due to factors such as aversion to the practice and intrusiveness of the mechanism [76,77], counseling prior to initiation of treatment and educating women about dilator use may increase adherence [32,78].

Physical therapy

Pelvic floor physical therapy has become an increasingly utilized modality for treatment of pelvic floor dysfunction [79], but is understudied for sexual dysfunction [80,81]. Pelvic floor muscle strengthening, relaxation techniques with biofeedback, stretching and massage are promising strategies that can benefit cancer survivors [32,79]. Among these strategies, biofeedback has been studied for treatment of sexual dysfunction in vulvar pain syndrome patients [82]. A small randomized control trial evaluated the use of pelvic floor muscle training in gynecologic cancer survivors and found that the intervention group reported improvement in sexual functionality and quality of life [83]. Given the safety of this therapy, pelvic floor physical therapy can be a helpful addition to a multidisciplinary approach to treating sexual dysfunction in gynecologic cancer patients [32].

Psychological therapy

Gynecological cancer survivors experience many changes in body image and feelings of well-being, which in turn affect sexuality and intimacy [32]. Anxiety and negative feelings associated with a cancer diagnosis can cause further deterioration in sexual functioning. Subsequently, patients might develop overall decreased quality of life and depressive symptoms [84-86].

Cognitive behavioral therapy (CBT), which focuses on mindfulness and the impact of maladaptive thoughts on human behavior, has been shown to have efficacy in treating psychosocial concerns of gynecological cancer patients [87,88]. In a study with 31 gynecological cancer survivors with self-reported sexual dysfunction, Brotto et al., randomized patients to either three 90-minute CBT sessions or to a control group waitlist arm [89]. Patients who underwent the CBT sessions reported significant improvements in sexual arousal and desire both at the immediate completion of the therapy and at 6-month follow-up. On the other hand, patients in the waitlist arm experienced no significant changes in sexual dysfunction [32,89].

Another promising approach to address sexual dysfunction in gynecological cancer survivors is psycho-educational intervention [90]. In a clinical trial of 22 women with early stage gynecological cancer and female sexual arousal disorder, Brotto et al., evaluated the impact of psycho-education on sexuality and relationships [91]. In this trial, psycho education was associated with positive effect on sexual desire, arousal, orgasm, satisfaction, sexual distress, depression, and overall well-being [91]. By

implementing CBT and psycho-education in a multidisciplinary platform, cancer care providers can improve patient satisfaction and quality of life for their patients [32,92].

Long term outcomes

For women who undergo treatment of ovarian cancer, SIMS can persist years after they complete their therapy [17,93-95]. In a study of ovarian cancer survivors 5 years post-treatment, overall patients had an excellent quality of life, but sexual symptoms persisted, with as many as 57% of patients reporting a decline in their sexuality since their diagnosis of cancer [96]. In another study, it was identified that symptoms were more severe in women younger than 45 years old [97]. They experienced worse sexual activity, poorer body image, perceived worse vaginal function, and experienced more severe menopausal symptoms. With proper interventions and time, however, ovarian cancer survivors can approach an acceptable quality of life compared to aged matched counterparts [98].

CONCLUSIONS

Many ovarian cancer survivors suffer from SIMS and these symptoms can be debilitating to many aspects of the patients lives. Using a multimodal and interdisciplinary approach can be helpful in treating SIMS. Psychotherapy can assist with lack of desire and orgasms and help address other psychological and interpersonal issues. These issues need to be addressed early by providers and non-biased information needs to be provided. A lack of knowledge about the sexual problems patients can suffer from or a discomfort with the topic in general can no longer be an excuse for allowing women to suffer from the morbidity associated with SIMS. We suggest that at an initial consultation the Gynecologic Oncology team discuss not only the medical and surgical plan moving forward but also quality of life issues such as SIMS and to discuss a plan to deal with such problems if they do arise. Furthermore, there are many resources that exist today and healthcare providers should be encouraged to take advantage of them so that they can provide as comprehensive care as is possible.

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