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SEXUAL DYSFUNCTION IN GYNECOLOGIC CANCER PATIENTS

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Abstract – *Objective:* *Sexual dysfunction is prevalent among gynecologic cancer survivors and strongly impacts on the quality of life (QoL), but the subject is poorly diagnosed and treated.*

Materials and Methods: *A comprehensive literature search of English language studies on sexual dysfunctions due to gynecologic cancer treatment has been conducted on MEDLINE databases.*

Results: *Surgery, radiation, and chemotherapy can cause any kind of sexual dysfunction with different mechanisms: psychological and relational, hormonal and pharmacological, neurological and vascular, side effects of chemo and radiation therapies, and direct effects of surgery on sexually involved pelvic organs. Many patients expect their healthcare providers to address sexual health concerns, but most have never discussed sex-related issues with their physician, or they do not receive a proper treatment or referral. This can have medical legal consequences, because it must be discussed and documented before starting treatment.*

Conclusions: *Oncology providers can make a significant impact on the QoL of gynecologic cancer survivors by informing patients and by asking them for sexual health concerns. Counseling is per se beneficial, as it improves QoL. Furthermore, it permits a proper referral and resolution of most symptoms.*

KEYWORDS: *Gynecologic cancer, Sexual dysfunction, Vulvar cancer, Vaginal cancer, Cervical cancer, Endometrial cancer, Ovarian cancer, Ospemifene.*

INTRODUCTION

The proportion of people living with and surviving gynecologic cancer is growing. This has led to increased awareness on the importance of quality of life (QoL), including sexual functions, in those affected by cancer. Sexual dysfunction is a very frequent and underestimated long-term complication of gynecologic cancer treatments[1].

Despite the high prevalence of sexual dysfunction in gynecologic cancer survivors, attention to sexual health issues by healthcare providers is still suboptimal. Patients would like to have more information regarding the effects of treatment on sexual health before therapy and desire counseling post-treatment to address sexual health[2], even if most of them do not ask directly.

Seventy-four percent of long-term gynecologic cancer survivors believe physicians should regularly ask about sexual issues, but 64% state that physicians never initiates the conversation during their care[3].

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. Sexual activity, behaviors, and sex-related problems of over 3000 U.S. adults 57 to 85 years of age have been investigated and it has been found that the majority of older adults engage in intimate relationships and regard sexuality as an important part of life[4].

In order to help all staff involved in gynecologic cancer treatment, a review of the literature is presented.

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METHODS

A comprehensive literature search of English language studies on sexual dysfunctions due to gynecologic cancer treatment was conducted in MEDLINE databases.

RESULTS

Even though gynecologic cancer treatments greatly affect sexual health, for cultural reasons this subject is poorly studied and under-discussed. This can have medical legal consequences, because this issue must be discussed and documented before starting treatment.

Reasons why gynecologic oncology surgery, radiation and/or chemotherapy can cause sexual dysfunction are listed in Table 1.

Most of the consequences of cancer treatment are psychological, as body image and relation are often affected. Cancer impacts dramatically on woman's sexuality, sexual functioning, intimate relationships and sense of self. Sexual functioning can be affected by illness, pain, anxiety, anger, stressful circumstances and medications. There is a growing acknowledgment that these needs are not being appropriately addressed by health providers. Psychotherapy plays an essential role in the management of these issues. A review of the literature reveals that the recent trends among health psychologists are to utilize psycho educational interventions that include combined elements of cognitive and behavioral therapy with education and mindfulness training. Intervention studies have found positive effects from this approach, particularly within the areas of arousal, orgasm, satisfaction, overall well-being, and decreased depression. The essential part of success is the providers' appreciation of this serious problem and willingness and comfort in addressing it[5].

Most of the patients undergo early menopause from ovariectomy or from the effects of chemo or radiotherapy on ovaries. Surgical menopause affects female sexual performance mostly because of reduced vaginal lubrication[6], so proper evaluation in each case and adequate treatment of vaginal atrophy are very important.

TABLE 1. Reasons why gynecologic oncology surgery, radiation, and/or chemotherapy can cause sexual dysfunction.

Psychological and relational
Hormonal and menopausal
Pharmacological effects
Side effects of chemotherapy and radiotherapy
Neurological and vascular damage to pelvis
Direct effects of surgery on sexually involved organs.

Some drugs can further affect sexuality, like antidepressants or drugs used for co morbidities like cardiovascular drugs.

Side effects of chemotherapy and radiotherapy can increase the frequency of genito-urinary infections or induce a mechanic vulnerability to the vaginal epithelium, which enhances atrophy related symptoms[7].

The effect on pelvic organs can be indirect when there is a neurological and/or vascular damage.

Gynecological invasive surgery creates most of the difficulties in treating sexual dysfunctions. Procedures for fertility preservation, laparoscopy, sentinel lymph node mapping, robotic and risk-reducing surgery can decrease treatment sequelae[8].

RISK-REDUCING SALPINGO-OOPHO RECTOMY (RRSO)

Women with Hereditary Breast Ovarian Cancer Syndrome (*BRCA1 or BRCA2 gene mutations)* have up to a 60% lifetime ovarian cancer risk and up to an 84% breast cancer risk[9]. Not only cancer treatments cause gynecological dysfunctions but also when gynecologic surgery is prophylactic as for risk-reducing salpingo-oophorectomy (RRSO) in BRCA patients.

Hereditary nonpolyposis colorectal cancer associated with mutations in DNA mismatch repair genes (most commonly *MLH1 and MSH2)* have up to a 60% lifetime risk of endometrial cancer and up to a 12% risk of ovarian cancer.

Prophylactic bilateral mastectomy reduces the risk of breast cancer by more than 90%, but its sexual side effects can be the loss of skin and nipple sensation, scars, and changes in self-image.

Prophylactic RRSO, removal of their ovaries and fallopian tubes by the age of 35 years or on completion of childbearing, reduces the risk of ovarian cancer by more than 80% and breast cancer by 50%. Sex affecting side effects can frequently be the abrupt and severe side effects of surgical menopause including vaginal dryness and irritation, pain with penetration, decreased arousal, and loss of desire.

The prevalence of female sexual dysfunction (FSD) after RRSO is 74% and hypoactive sexual desire disorder (HSDD) is 73%[10].

Sexually active women belonging to the RRSO group report higher levels of sexual discomfort, lower levels of sexual pleasure, and lower sexual activity than the controls. Hormone replacement therapy (HRT) users in the RRSO group have reported less discomfort compared with nonusers, but there is no association between HRT use and sexual pleasure score. These are the main hypothesis to explain that:

- Maybe more postmenopausal symptoms are elected for HRT
- Women without substantial complaints represent the nonusers
- Systemic estrogen increases the level of SHBG [thereby reducing the concentration of bioavailable androgens. This effect may not only contribute to the lack of therapeutic effect regarding sexual dysfunction, but even impair androgen-related aspects of sexual functioning.
- HRT might simply not have the assumed effects on sexual functioning.

VULVAR CANCER

Oncological treatment of vulvar cancer creates sexual morbidity because in recent years more younger, sexually active, women are presenting with vulvar intraepithelial neoplasia (VIN) and vulvar cancer due to human papillomavirus infection[1,11,12]. Previously only 5% of gynecologic cancers occurred in the vulva and vulvar cancer and, usually, in older women.

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[13].

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[14,15].

Additional improvements in surgical morbidity included radical local excision and sentinel lymph node dissection in early-stage patients without compromising survival[16,17]. Despite the lower radicality of present surgical treatments, the number of young affected women is increasing, making this subject more important nowadays.

Women treated with vulvar surgery suffer detrimental effects on psychological function, sexual function, and relationships with their partners. The psychological and relational effects of anatomical changes related to surgery, and the pain and difficulties with intercourse, cause depression and distress both for premalignant and malignant lesions[18-20].

Physical changes following surgery may include vaginal narrowing, numbness along the scar, removal of the clitoris, and change in tissue quality[19,21,22].

When compared to healthy controls, women undergoing vulvectomy have significantly more sexual dysfunction before and after surgery[20].

Patients who are not sexually active following radical vulvectomy cite genital complications from their surgery as the reason for abstinence[23].

Age, depression, and worsening functional status are risk factors for sexual dysfunction in vulvar cancer[24], while there is no association with the extent of surgical resection[25].

Vulvectomy patients in whom the clitoris has been spared, like those who have undergone laser or partial resection of the clitoris report significantly fewer problems with arousal in comparison to those whose clitoris has been ablated[20].

Inguinofemoral lymphadenectomy is a part of surgical management in certain vulvar cancer patients. Sentinel lymph node dissection has been shown to decrease sexual morbidities, while complete groin dissection is more associated with sexual dysfunction and surgery complications, both in the short term (infection and wound breakdown) and long-term (lymph edema)[26]. Lymph edema is associated with poor QoL in vulvar cancer patients[27] and has been shown to negatively impact sexual functions[28].

Early detection and treatment are important as lymph edema is a chronic, progressive condition and it is associated with poor QoL and sexual dysfunction.

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.

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 is observed in a longitudinal study on vulvar cancer patients 6 months after surgery with or without adjuvant radiation and do not improve during the 2 year follow-up[22].

Inguinal radiation negatively impacted the ability to achieve orgasm in a cross-sectional study[25].

In summary, vulvar surgery negatively impacts sexual function regardless of the extent of surgical resection. More research is needed to investigate the effects of radiation on sexual health in vulvar cancer survivors. Until then, gynecology oncology providers should inform and get informed about symptoms of sexual dysfunction in this population, and if possible and safe they must be treated.

CERVICAL CANCER

Cervical cancer is diagnosed in women younger than the other gynecological cancers; the median age of diagnosis is 49, and over 38% of patients are diagnosed under the age of 45[29].

The surgical treatment of early-stage cervical cancer can include cervical conization which has few sexological consequences[1].

Radical trachelectomy is a safe fertility-sparing surgical option for some women with early-stage cervical cancer who have not completed childbearing[30-33]. Longitudinal comparisons in patients treated with radical trachelectomy versus radical hysterectomy have shown no differences in mood, distress, sexual function, and QoL[34,35]. Many women in both treatment groups have faced depression, distress, and sexual dysfunction, although an improvement over time has been noted in these domains.

Radical hysterectomy is associated with negative effects on sexual health and QoL[36].

Short-term sexual health consequences include orgasmic problems, vaginal shortening, dyspareunia, lymph edema, genital numbness, and sexual dissatisfaction[37].

Persistent sexual health concerns include lack of sexual interest (25%), lymph edema (19%), genital numbness (71%), and insufficient lubrication (24%)[37-39].

Compared to simple hysterectomy, radical hysterectomy patients experience lower vaginal blood flow during arousal[40].

Furthermore, radical hysterectomy' patients have self-reported worse sexual function compared to patients who underwent cervical conization[41]. Compared to healthy women, more patients treated with radical hysterectomy report diminished sexual function both before and after surgery[42].

Radical hysterectomy has detrimental effects on bowel and bladder function that can also, directly and indirectly, affect sexual functions.

Traditional radical hysterectomy is associated with urinary retention, urinary incontinence, constipation, and urgency[39]. These complications are likely due to disruption of the hypogastric and splanchnic nerve plexuses during surgery[43].

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 functions, less post-operative complications, and improved sexual function[44].

External pelvic and vaginal radiation therapy with or without concurrent chemotherapy (chemo radiation) 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[45-49].

In cervical cancer patients, primary or adjuvant radiation therapy has been associated with greater sexual dysfunction and vaginal toxicity compared to surgery alone[36,50]. The combination of surgery and radiation is associated with more vaginal shortening compared to radiation alone[51].

Lymph edema and menopausal symptoms negatively impact on long-term QoL[52]. Compared to age-matched controls, cervical cancer patients treated with radiation have 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%)[53]. The majority of patients with dyspareunia and lack of lubrication are distressed by their symptoms[53].

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. Vaginal estrogens can be used in squamous cell cervical, vaginal and vulvar cancers[54].

Ospemifene can be a safe option, as provided there are no contraindications, like concomitant breast cancer still in treatment or thrombosis[55]. It could also be use proposed in other selected cases of symptomatic not estrogens sensitive cancers like vulvar.

ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecologic malignancy, typically occurring in postmenopausal women. Surgery is the primary treatment for most patients, and can cause sexual dysfunctions[1].

The standard surgical approach includes hysterectomy, bilateral salpingo oophorectomy, 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, less post-operative pain, complications, and length of hospital stay, without compromising survival[56].

Many women with early-stage disease can be observed following surgery, but even in the

absence of adjuvant therapy, patients are at risk for sexual dysfunction. 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) has been performed[57]. Eighty-nine percent of participants have referred some form of sexual dysfunction determined by the Female Sexual Function Index (FSFI) score less than 26 and pain has been the most commonly affected domain. Only 18% of participants have received adjuvant radiation therapy, suggesting that sexual dysfunction is prevalent among patients treated with surgery alone.

A prospective study has investigated the 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)[58]. Compared to healthy controls endometrial cancer patients have reported more sexual dysfunction before and after surgery. Endometrial cancer patients have had significantly more entry dyspareunia at one year in comparison with patients who have had a hysterectomy for benign indications, and a decreased sexual arousal, desire, and entry dyspareunia at two years compared to the healthy controls.

For patients at 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) has 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[59]. No differences in vaginal recurrence are found between the treatment groups, but less gastrointestinal side effects are reported in patients who received VBT. Longitudinal QoL assessment at 5 years has shown there are no differences in sexual function between VBT and EBRT patients. However, when compared to an age-matched control population, participants in the study have reported significantly more vaginal dryness and lower sexual interest, activity, and enjoyment[60].

Several small cross-sectional studies have not shown any differences in sexual function in endometrial patients undergoing hysterectomy and VBT compared to women who have received hysterectomy alone[61,62] or compared to a healthy postmenopausal control[63]. Nonetheless, compared to before the diagnosis of cancer, the majority of patients felt their vagina being smaller and have reported increased vaginal dryness, more pain with intercourse, and less interest in sex[62].

In another study, the 81% of patients who underwent hysterectomy with adjuvant VBT have reported sexual dysfunction. Participants also have scored lower on all domains of the FSFI than the index population of healthy women aged 18-74, but not significantly worse than a postmenopausal control[63].

Sexual function and vaginal morbidity are prospectively evaluated in endometrial cancer patients who received adjuvant VBT (N=32) or EBRT (N=43) following surgical staging[64]. Twenty patients were sexually active prior to treatment, 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[65].

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. Further sexual problems come from the fact that the majority of these patients are overweight or obese and have related co-morbidities (diabetes and hypertension), with possible sexual side effects of related drugs. Finally, endometrial cancer is highly estrogen sensitive, ovaries must be removed and it is not safe to use estrogens in most of these patients, so sexual therapies for dyspareunia are limited.

In this frame, Ospemifene could be considered a good therapeutic option as, in randomized, placebo-controlled, double-blind trials in postmenopausal women, it showed no clinically significant endometrial effects[66]. However, at the moment there are no specific data collected in endometrial cancer patients and further studies are needed.

OVARIAN CANCER

Ovarian cancer is responsible for more deaths than any other cancer of the female reproductive system even though it accounts for only 3% of cancers in women[29]. The majority of patients present with advanced-stage disease and primary treatment typically consist of a sequence of surgery and chemotherapy, strongly affecting sexuality[1].

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[67].

Menopausal symptoms triggered by cancer therapy can be more abrupt, prolonged, and intense[68], and if not managed can lead to diminished QoL, function, and sexual desire[69]. 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[70].

Most of the ovarian cancer patients (57%), in an online survey, reported that their sexual life had been negatively affected by cancer and its treatment[71].

Survivors experience decreased libido, decreased arousal, problems with orgasm, and difficulty with intercourse due to treatment-related side effects[72-74]. Worsening sexual discomfort has been related to diminish physical and social well-being[72]. Compared to healthy women, ovarian cancer survivors report increased vaginal dryness, more dyspareunia, less sexual activity, and lower libido. Sexually active survivors are more likely to be younger, married, not actively receiving treatment, less fatigued, and report a better QoL and social functioning[70,75].

Sexual function in ovarian cancer patients has been investigated according to 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)[76]. Sexual satisfaction has decreased in all patients following treatment, but has been more pronounced in groups 2 and 3. The greatest concern is pain with intercourse and most patients have reported body image changes. While the majority of patients felt sexual health to be important after ovarian cancer treatment, this opinion has varied across the groups (74% *vs*. 65% *vs*. 47%, respectively).

Germ cell tumors (GCTs) of the ovary present in younger patients and treatment can have repercussions on future fertility and sexual health. The GOG has investigated the long-term reproductive health and sexual function of GCT survivors treated with surgery and platinum-based chemotherapy[77]. Fifty-three percent have 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 have not received fertility-sparing surgery reported more discomfort with intercourse.

In summary, the majority of ovarian cancer survivors face negative effects on sexual function following treatment. The 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.

Ospemifene could be a safe option[66], as provided there are no contraindications: estrogen sensitive ovarian cancer (like the endometrioid), concomitant breast cancer still in treatment or thrombosis[55]. Unfortunately, there are no specific studies.

CONCLUSIONS

The number of women surviving after a gynecologic cancer is increasing and the related sexual dysfunction so far is largely underestimated. Sexual dysfunction can result from surgery, radiation, chemotherapy, hormonal therapy and/or cytostatic drugs to which is added the psychological discomfort. Other indirect cancer-related effects can contribute like relational, business economic, aesthetic and social problems. After gynecological cancer more the majority of patients suffer from sexual dysfunctions. The percentages of women who have relationships actually broadly underestimate the psychological and relational discomfort, at least transiently, initially, involving nearly every woman treated.

Coping strategies are markedly influenced by psycho-emotional reaction to cancer. Interventions for gynecological cancer can cause visible mutilations (like vulvar treatments) or perceived, symbolic ones, like hysteroanexectomy, with psychological repercussions on self-image. Operated patients complain vaginal dryness, reduced flexibility, and shortening of the vagina. Pelvic pain is a frequent consequence of interventions on genital and pelvic innervations, in addition to sharp and sudden endocrine effect of ovariectomy and radiotherapy or chemotherapy. Giving information and active hearing about sexual issues does not resolve organic sexual dysfunctions but improves the quality of life. The patient feels understood and she can be referred for proper treatment, as there a new promising and safe treatments, like ospemifene[66].

Conflict of Interests

The Authors declare that they have no conflict of interests.

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