Atrophy

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Disclosures and Conflicts of Interest

No financial relationships or conflicts of interest to disclose.
Learning Objectives

• Recognize typical sexual dysfunctions associated with treatment of a variety of conditions
  • Sjogren’s Syndrome, breast and gynecologic cancers
• Understand what treatment options to offer and when to institute them
• Be aware of the etiology and treatment approach to sexual dysfunctions in these populations
Special Populations

- Sexual dysfunction from *Sjogren’s Syndrome*

- *Breast cancer survivors* with atrophic vulvovaginitis from hypoestrogenism and adjuvant therapies

- Treatment of gynecologic cancers with *surgery, chemotherapy and radiation therapy*
Sjogren’s Syndrome

• Systemic autoimmune disease with lymphocytic infiltration of salivary, lachrymal, vestibular glands and systemic autoantibodies

• 2nd most common systemic autoimmune disease after Rheumatoid Arthritis.

• Greatest incidence ages 40-60. F:M=10:1

• Decreased glandular secretion and mucosal dryness, fatigue, arthralgia, polyarthritis
Gynecologic Effects of Sjogren’s Syndrome

- Inflammation of vaginal mucosa and lymphocyte mediated destruction of major and minor vestibular glands
- Vulvar pruritus and burning, vaginal dryness and dyspareunia.
  - Vaginal symptoms more severe than vulvar symptoms
- Gynecologic symptoms don’t correlate with severity of lachrymal or salivary symptoms, duration of disease, prednisone dosage, or presence of anti-SSA or SSB antibodies
Sjogren’s Syndrome

- Dutch study 2014 (N=46)
- Administered 7 validated questionnaires
  - FSFI: Female Sexual Function Index
  - FSDS: Female Sexual Distress Scale
  - ESSDAI and ESSPRI: Disease Activity Index
  - MFI: Multidimensional Fatigue Inventory
  - HADS: Hospital Anxiety and Depression Scale
  - MMQ: Maudsley Marital Questionnaire (relationship satisfaction)
  - Rand-36 Health Survey (health related QOL)
Dutch Study Results

- 56% had sexual dysfunction by FSFI, 67% never discussed their sexual complaints with their Rheumatologist
- SS pts had significantly more sexual dysfunction in domains of desire, arousal, orgasm, lubrication and pain compared to healthy controls.
- Increased distress in sexual function and impaired sexual function
- Increased need for lubricants, decreased relationship satisfaction, decreased QOL
- Increased fatigue, depression, anxiety
- All findings irrespective of disease duration and activity
Suggested Treatments

- Vaginal dryness has the greatest effect on QOL
  - Sexual lubricants
  - Vaginal moisturizers
- Topical Estrogens mentioned, no data
- Ask patient about sexual complaints
Genitourinary Challenges of Breast Cancer Treatments

- **Anti-Estrogen Triple Threat:**
  - Premature surgical menopause after prophylactic salpingo-oophorectomy
  - Chemotherapy induced ovarian failure
  - Anti-estrogen effects of endocrine therapies: SERMs, aromatase inhibitors
Breast Cancer & Hypo-estrogenism: SERMs & AIs

**SERMs:** Tamoxifen: metabolized to endoxifen which binds to estrogen receptors to lock activity.
- Is an antagonist to ER+ breast cancer cells, but is an agonist to alpha ERs in the vagina.
- *Vaginal dryness rate 8%*

**Aromatase Inhibitors:** Oppose aromatase-mediated conversion of androgens to estrogens by more than 95%, significantly reduce plasma estrogen to <1pg/mL.
- *Vaginal dryness rate 18%*
Challenges in Gyn Cancer Treatment: Surgery

Simple or Radical Hysterectomy
Pelvic, para-aortic or inguinal lymphadenectomy
Bilateral salpingo-oophorectomy
Omentectomy and tumor debulking
Vulvectomy +/- clitorectomy

- **Effects:** shorten vagina, fibrosis around vaginal cuff, damage to autonomic nerves reduce vaginal blood flow and subjective arousal. Lymphedema, numbness, altered bowel and bladder function, vaginal narrowing, removal of clitoris, numbness in scar, change in tissue quality.
- Surgical menopause symptoms abrupt, prolonged, intense
- Oophorectomy for germ cell tumors impacts future fertility
Challenges of Gyn Cancer Treatment: Chemotherapy

- Chemotherapy induced ovarian failure:
  - 40% in 40 year olds
  - 90% in 50 year olds
Challenges of Gyn Cancer Treatments: *Radiation Therapy*

- *Radiation* creates vaginal stenosis, vaginal scarring and shortening, mucosal atrophy, fibrosis, mucosal telangiectasia, resulting in dyspareunia and difficulty reaching orgasm.

- *Surgery + radiation* resulted in more dyspareunia, decreased lubrication, decreased arousal, decreased libido, decreased sexual frequency, reduced vaginal dimensions.

- *Treatment for Rectal Cancer*: Radiation tx leads to fibrosis, adhesions, shortening of the vagina, and atrophy. Ovaries often in the field of radiation, leading to permanent menopause.
The Bottom Line

• 89% of pts receiving treatment for cervical or endometrial cancer report some form of sexual dysfunction by FSFI, pain most common

• Gyn cancer treatment can affect all domains of sexual functioning: desire, arousal, lubrication, orgasm, pain, frequency and satisfaction

• Fear of anatomical change, fear of dyspareunia, worsening of body image also contribute to sexual dysfunction

• Only 10-28% of cervical cancer patients received information of sexual sequelae before treatment

-Lammerink 2012
Ask the Right Questions

• “Has cancer treatment affected your sexual life?”
• “Are you experiencing changes in your sexual desire, arousal, or orgasm?”
• “Are you experiencing pain with sexual activity or do you avoid sexual activity because of pain?”
• “Did it ever seem that there was a blockage in the vagina that prevented sexual activity? Or that your vagina got smaller in width or length?”
Question 1:

Women treated for gynecologic cancers are not candidates for systemic hormone replacement therapy

• True

• False
Management Strategies: **Systemic**

- **Use of systemic hormone therapy:**
  - Squamous cervical cancer is not considered an estrogen responsive tumor: **OK**
  - Cervical adenocarcinoma is treated like endometrial cancer: **NO**
  - Hormone therapy is not contraindicated in vulvar or vaginal cancers: **OK**
  - Use of hormone therapy in ovarian cancer showed no difference in overall disease free survival and increased quality of life: **OK**
  - Systemic HRT in endometrial cancer had a RR of 1.27 for cancer recurrence: **NO**
Systemic Estrogen Therapy in Breast Cancer Survivors: **NO**

*Systemic estrogen therapies are contraindicated due to increased risk of cancer recurrence:*

- **HABITS trial**: (Scandinavian, 2008, N=447) closed prematurely due to increased breast cancer recurrence (HR=3.3). 4 year follow-up showed more than twice the rate of breast cancer in the estrogen arm (HR=2.4)

- **Stockholm trial** (2005, N=378) closed prematurely for safety concerns, although no significant increase in recurrence noted.

- **LIBERATE trial** (2011, N=3100) studies safety of Tibolone, terminated early for increased breast cancer events and metastases in the Tibolone arm (15.2% vs 10% placebo arm, HR=1.4)
Question 2:
Breast cancer survivors should not be given local vaginal or vulvar estrogens

• True
• False
Committee on Gynecologic Practice
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The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer
ACOG Recommendation #1

“Non-hormonal approaches are the first-line choices for managing urogenital symptoms or atrophy-related urinary symptoms experienced by women during or after treatment for breast cancer.”

- Vaginal lubricants
- Vaginal Moisturizers
- Local Anesthetics
Non Hormonal Therapies

**Vaginal Lubricants:**

- Reduce friction during sexual activity and irritation from clothing
- Best results if used with a vaginal moisturizer 4-7 times per week and applied before and during sexual activity. Provides short term comfort during sex. Apply to both partners
- Products with dyes, perfumes, flavors, “warming” or “stimulating” additives may irritate or burn
- Be aware that petroleum-based lubes increase HIV transmission, degrade latex condoms, increase risk of vaginal infections (BV)
Water Based Lubricants

- Inexpensive
- Compatible with condoms
- Safe to use with latex and silicone dilators and toys
- Dries out easily, may need to reapply
- May feel tacky over time
- Some contain glycerin (increases UTI and yeast)

✓ Sliquid Oceanics
✓ Sliquid Organics Silk
✓ Slippery Stuff
✓ Yes
✓ Good Clean Love
✓ Liquid Assets
✓ Pre-Seed
✓ Luvena
✓ Liquid Silk
✓ Astroglide
✓ Just Like Me
✓ K-Y Jelly
✓ Jo
Silicone Based Lubricants

- Never dries out
- Can be used in water
- Compatible with latex condoms, incompatible with silicone and rubber
- No glycerin
- More expensive
- Difficult to wash off
- Impairs sperm motility

☑ Uberlube
☑ Pjur Eros
☑ Pink
☑ ONE Move
☑ Astroglide Silicone
☑ ID Millennium
☑ K-Y Intrigue
☑ Wet Platinum
☑ Jo
Non Hormonal Therapies

**Vaginal moisturizers:**

- Bio-adhesive polymers which attach to mucin and epithelial cells on vaginal wall. May carry up to 60 times their weight in water. Intended to replace normal vaginal secretions and improve vaginal moisture, fluid volume, pH, elasticity, reduce dryness, itching and dyspareunia.

- Must be used on a regular basis.
Vaginal Moisturizers

- Helps moisturize vaginal lining
- Makes vaginal and vulvar tissues more pliable
- A single application at bedtime can give relief for several days
- Can also be used to moisturize external tissues
- May improve vaginal pH
- May contain glycerin (increases UTI and yeast)

- Replens
- Hyalo Gyn
- Juvagyn
- K-Y Liquidbead
- Luvena
- Silken Secret
- K-Y Silk-E
- Feminease
- Me Again
- Emerita Personal Moisturizer
- Moist Again
- Vitamin E capsules and suppositories
Managing Irritation

• Some water based gels are hyper-osmolar, causing cellular toxicity and damage in vitro. Iso-osmolar and silicone based lubricants don’t have this effect

• Petroleum jelly reported to cause a 2.2-fold increase in BV compared to controls

• Increased colonization with candida species with the use of oils compared to non-users (44.4% vs 5%, P<0.01)

• Preservatives such as propylene glycol and parabens can be irritants and allergens

• Try a 24 hour external application test before vaginal use
Safer Products

- Iso-osmolar lubricants
  - Good Clean Love
  - PRE
- Propylene glycol-free
  - Sliquid H2O
  - Pjur Woman Bodyglide
  - Slippery Stuff
  - Good Clean Love
Local Anesthetic

4% aqueous lidocaine: applied before sex, decreased pain with penetration by 90% compared to placebo

ACOG Recommendation #2

“Among women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms, vaginal estrogen should be reserved for those patients who are unresponsive to non-hormonal remedies.”
The Gold Standard for GUSM: **Vaginal Estrogens**

- **Estring 2 mg**: lowest dose (7.5 mcg estradiol/day)
  - Wear in vagina and change Q 3 months
- **Vagifem**: 10 mcg vaginal tablets:
  - Nightly X 14, then 2-3 nights per week
- **Estradiol or CEE creams**:
  - 0.5-1 gm vaginally nightly X 7-14, then 0.5 gm 2-3 times per week
  - CEE cream FDA approved for 0.5 gm twice weekly or sequentially for 21 days followed by 7 day medication free interval
Local Estrogen: Not Just For Breast Cancer Survivors

- Invaluable for treatment of vaginal stenosis following surgery or radiation for squamous cervical, ovarian, vaginal and vulvar cancers
- Stimulates epithelial regeneration, promotes healing, improves vaginal elasticity and lubrication
- Combine with dilators to ease dyspareunia and prevent stenosis
ACOG Recommendation #3

“The decision to use vaginal estrogen may be made in coordination with a women’s oncologist. Additionally, it should be preceded by an informed decision-making and consent process in which the woman has the information and resources to consider the benefits and potential risks of low dose vaginal estrogen.”
Risk Benefit Analysis

• Use of low dose vaginal estrogens does not result in sustained serum estrogen levels exceeding the normal menopausal range

• Lowest rates of systemic absorption found in the ring (5-10 pg/mL) and the vaginal tablet (3-11 pg/mL)

• Creams deliver a more variable dose, but dose can be kept low (80 pg/mL)

• No increase risk of VTE, no increased endometrial proliferation or hyperplasia with local estrogen therapy, additional progesterone not needed
Local Estrogen Use with Tamoxifen and AI’s

• Local estrogen by ring or tablet will cause a small increase in serum estradiol levels which decreases after 1 month of use

• These small serum estradiol increases may theoretically render AI therapy less effective. The threshold for systemic estrogen levels associated with breast cancer recurrence has yet to be determined

• No increase in breast cancer recurrence in patients receiving tamoxifen or AI’s who use local estrogen compared to non-users
Sex Is Good For You!

• A short course of low dose vaginal estrogen therapy may allow resumption of sexual activity.
• Regular sexual activity or vaginal stimulation may prevent the recurrence of dyspareunia.
ACOG Conclusion #4

“Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer who use vaginal estrogen to relieve urogenital symptoms.”
What Are My Other Options?
Question 3:

Ospemifene is safer to use in breast cancer survivors than Bazedoxifene

- True
- False
Emerging Therapies

- **Bazedoxifene**: Marketed in combination with conjugated estrogen for VVA. *It is unknown whether this preparation is safe and well tolerated in breast cancer survivors*

- **Ospemifene**: SERM FDA approved for dyspareunia from VVA. Increases superficial cells, decreases parabasal cells and vaginal pH. *Currently no safety data for use with breast cancer patients, should not be used in this population*

- **Estriol**: end product of estrogen metabolism, does not get aromatized to E2 or E1. Considered a shorter duration and weaker estrogen alternative, may potentially be safer for breast cancer survivors. *No large long term studies to date.*

- **Fractional Microablative CO2 Laser**: stimulates growth of new collagen and elastin fibers. In one study vaginal dryness, burning, itching, dyspareunia and dysuria were significantly improved after 3 applications of laser treatment. *Long term effects unknown, not studied in cancer patients*

- **Flibanserin**: for Hypoactive Sexual Desire Disorder. *Not FDA approved for postmenopausal women, not studied in cancer populations*
Local Androgen Therapy

- **Vaginal testosterone with AIs**: induces proliferation of vaginal epithelium without aromatization to estrogen. May be effective in reversing atrophic changes without raising circulation estrogen levels or compromising AI therapy

- **Dihydroepiandrosterone (DHEA)**: converts to androgen in vagina, binds to both androgen and estrogen receptors. 0.5% DHEA decreased vaginal pH and parabasal cells, increased superficial cells, improved vaginal atrophy symptoms. Could potentially aromatize to estrogen.
Pelvic Floor Physical Therapy

• Intravaginal trigger point and massage therapy, muscle strengthening and relaxation exercises, biofeedback and dilator work
• Improves the flexibility of paravaginal tissues, decreases hypertonicity and vaginismus, improves strength
• Increases blood flow to pelvic floor muscles
• Significant reduction in dyspareunia, improved sexual function, more pain-free encounters
  • Goldfinger et al, 2009
Treatment of Female Sexual Dysfunction

• Sex Therapy
• Mindfulness-based cognitive behavioral therapy program
  ➢ Improved FSFI domains of desire, arousal, lubrication, orgasm, satisfaction and overall FSFI score
  ➢ Reduced sexual distress and increased perceived genital arousal
    • Brotto, LA, et al. 2012
Compile A Local Resource List

- Sex Therapists
- Couple’s Therapists
- Menopause Experts
- Pelvic Floor Physical Therapists
- Cognitive Behavioral Therapists

- American Psychosocial Oncology Society
- Society for Sex Therapy and Research
- American Association of Sexual Educators, Counselors and Therapists
- American Cancer Society and National Cancer Institute
Thank You