Pelvic PT Distance Journal Club: November 2018 (Moderator: MJ Strauhal PT, DPT, BCB-PMD)

Topic: Why should pelvic PT’s be knowledgeable of menopausal changes in the urogenital region and the history of menopausal hormone therapy (MHT)?

Background:

- Menopause is defined as the point in time when menstrual cycles permanently cease due to the natural depletion of ovarian function from aging or due to surgical induction (i.e., prophylactic oophorectomy with breast cancer) or medical induction (i.e., with drugs) at a younger age.
  - The diagnosis is typically made retrospectively after the woman has missed menses for 12 consecutive months. It marks the permanent end of fertility.
- In 2020, more than 50 million U.S. women will be older than 51 years of age, the mean age when menopause occurs.
  - Three quarters of these women will report symptoms such as hot flashes or night sweats, sleep disturbances, mood changes, vaginal dryness, and dyspareunia. Untreated menopausal symptoms are associated with higher health care costs and loss of work productivity.
  - The use of menopausal hormone therapy (MHT) continues to be one of the most controversial and debated topics in women’s health.
    - Since the 2002 publication of findings from the Women’s Health Initiative (WHI), anxiety about the risks of using MHT have dominated clinical discussions and decision making about MHT. Misperceptions about the reported data (data was not properly interpreted or communicated) and the use of MHT continue to perplex both clinicians and patients. MHT use has dropped by 80% from 2002 to the present (Manson 2016). Most primary care residency programs in the United States do not provide adequate education in women’s health in general or in menopause management in particular (Manson 2016). “Medicine has lost a generation of trainee physicians who currently do not have adequate knowledge about [MHT] and how to prescribe it” (Lobo 2017).
    - JoAnn Pinkerton, MD, director of the North American Menopause Society (NAMS) and chair of the advisory panel that issued the 2017 position statement on MHT from NAMS believes that “fear has been driving the conversation about hormone therapy” (Haelle, 2017). New data and the new 2017 position statement go a long way in helping to reduce that fear and the confusion about menopause and the appropriateness of using MHT.
    - In particular, local vaginal estrogen therapy is “substantially underutilized” and class labeling required by the FDA that appears on all medication that include estrogen regardless of dose or route, “do not appear to be relevant to low dose vaginal estrogen” (Kingsberg 2017)
    - The pelvic PT should be knowledgeable of the physiological changes that take place with menopause, especially as they relate to genitourinary health, make appropriate decisions related to differential diagnosis when vaginal pain and irritative voiding symptoms are reported by their menopausal patients, and be informed of current evidence related to MHT, allowing them to educate their patients and advocate for them regarding possible interventions.

Several of these articles are full access online for personal use only:


- Genitourinary syndrome of menopause (GSM) is a new term describing menopausal changes associated with the vulva, vagina, and lower urinary tract (LUT) and includes genital symptoms (dryness, burning, irritation, sexual symptoms (lack of lubrication, discomfort, pain), and urinary symptoms (urgency, dysuria, UTI’s)
  - Replaces the terms vulvovaginal atrophy and atrophic vaginitis
  - GSM is the accepted term by ISSWSH and NAMS
- Table 1 is relevant for the pelvic PT to assist with identifying symptoms (reported by the patient) and signs (observed by the practitioner) of GSM
- Prevalence of GSM 45-63% of postmenopausal Western women
- Symptoms include vaginal dryness (most common symptom), dyspareunia, vaginal irritation, itching, vaginal tenderness, vaginal bleeding or spotting during intercourse
  - Symptoms directly related to reduced circulating levels of estrogen
    - Estrogen receptors are present in the vagina, vulva, PFM, endopelvic fascia, urethra, bladder trigone
    - Loss of estrogen results in anatomic and histologic changes in the genital tract like reduced collagen and hyaluronic acid and elastin, thinning of the epithelium, altered smooth muscle function, increased connective tissue density, fewer blood vessels, increased vaginal pH (increasing vulnerability to irritation, trauma)
    - LUT shares common embryonic origin with the female genital tract and loss of estrogen results in dysuria, urgency, frequency, nocturia, UI, recurrent UTI’s
      - Presence of urge UI increases with time in women with estrogen deficiency
      - Postmenopause UI may be related to a change in urethral closure pressure and intrinsic sphincter deficiency related to altered connective tissue from loss of estrogen
      - Recurrent UI’t’s in older women may be better treated with local vaginal estrogen therapy versus multiple courses of antibiotics
    - Low estrogen in postmenopausal women causes vasomotor symptoms that often improve over time
      - In contrast, GSM is chronic and progressive if left untreated
      - Significant QOL impact on sexually active postmenopausal women
      - Greater sexual dysfunction and poorer QOL in younger women who undergo abrupt menopause due to surgery, use of GnRH agonists (i.e., Lupron), hypothalamic amenorrhea, cancer treatment (chemotherapy, pelvic radiation, endocrine therapy)
- Goal of treatment of GSM is to relieve symptoms
  - Non-hormonal lubricants 1st line treatment per NAMS
    - OTC water, silicone, oil based
    - Reduce friction related irritation
  - Long-acting vaginal moisturizers (must be used consistently)
    - Decrease vaginal pH
    - [Short term] studies show efficacy equivalent to local vaginal estrogen
Vaginal dryness is prevalent among women of all ages, but particularly common during and after menopause. Low-dose vaginal estrogen therapy (creams, tablets, rings) has shown subjective and objective effectiveness for vulvovaginal AND LUT symptoms. Low-dose preparations are considered “safer” than systemic HT due to low serum levels of estrogen.

**Article #2: (a review article) Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition?** Climacteric. 2016; 19: 151-161.

- Vaginal dryness is prevalent among women of all ages, but particularly common during and after menopause.
  - One of the many symptoms of GSM and reported by up to 57% of postmenopausal women.
  - Lack of natural lubrication is a commonly encountered sexual problem clinically.
    - Causes include: advancing age, hormonal changes, menopause, breastfeeding, stress, conditions like DM, IBD, chronic heart failure, MS, as well as RT, chemo, antidepressant use.
    - Common cause of dyspareunia (“recurrent or persistent pain with sexual activity that causes marked distress” DSM-IV).
    - In DSM-V (2013) it was proposed that the diagnoses of vaginismus and dyspareunia be collapsed into a single diagnostic entity called genito-pelvic pain/penetration disorder. This diagnostic category is defined according to five dimensions: one of the following should occur persistently or recurrently to establish a diagnosis: 1) difficulty in vaginal penetration, 2) marked vulvovaginal or pelvic pain during penetration or attempt at penetration, 3) fear or anxiety about pain in anticipation of, during, or after penetration, 4) tightening or tensing of pelvic floor muscles during attempted penetration, 5) medical co-morbidity.
      - The fusion of the diagnoses of dyspareunia and vaginismus was based on the conclusion that the two disorders could not be reliably differentiated, for two main reasons. Firstly, the diagnostic formulation of vaginismus as “vaginal muscle spasm” was not supported by empirical evidence. Secondly, fear of pain or fear of penetration is commonplace in clinical descriptions of vaginismus. After testing five alternative models of female sexual function, it was concluded that the diagnoses vaginismus and dyspareunia overlapped to a great degree.
  - The female sexual response cycle is mediated by neurotransmitters and a combination of neuromuscular and vasocongestive events.
    - Estrogen plays a role and when levels fall it can result in vulvovaginal atrophy (VVA), thinning and inflammation.
    - REVIVE (Real Women’s Views of Treatment Options for Menopausal Vaginal ChangEs) found the most common symptoms to be dryness (55%), dyspareunia (44%), irritation (37%) affecting enjoyment of sex in 59%.
    - VVA may be successfully managed by a variety of OTC and prescription treatments depending on symptom severity, effectiveness and safety for individual patients, and patient preference.
• Choices include personal lubricants, moisturizers, topical (local) vaginal estrogen, hormone therapy (systemic), SERMs (ospremifene)

• Underreporting and undertreatment of vaginal dryness is common
  • Barriers to seeking and using treatment include lack of awareness of physiological changes associated with menopause and availability of effective/well-tolerated treatment, reluctance to discuss symptoms, safety concerns, inconvenience, inadequate relief from available treatments
  • Lubricants and moisturizers differ in composition with advantages and disadvantages, associations between ingredients and potential biological effects, and their intended use

• Table 1 lists commonly used moisturizers and lubricants available world-wide, their ingredients, and their osmolality
  o Lubricants are available as water-based, silicone-based, or oil-based and are rapid acting for short-term relief
    ▪ Ingredients in water-based lubricants impact pH and osmolality
  o Moisturizers must be applied regularly to achieve rehydration of the mucosal tissue and their effects are more long-term
    ▪ Ingredients change the fluid content of the endothelium and low the pH (maintaining vaginal moisture and acidity) and affect osmolality
    ▪ Beneficial for women with VVA/GSM (both those sexually active and those not)
  o pH, osmolality, and presence of certain ingredients in lubricants and moisturizers may be associated with detrimental biological effects (fertility, exposure to STIs, risk of UTIs, allergic reactions?)

• Figure 1 shows that the osmolality and pH of lubricants and moisturizers vary widely
  • WHO recommends that osmolality should not exceed 380 mOsm/kg with upper limit of 1200 mOsm/kg
  • Greater osmolality (by way of SIM assay- sulfide, indole, motility which is a sensitive measure of mucus membrane tolerance) is associated with genital burning, heat, itching and cytotoxicity
  • In healthy adults, normal vaginal pH ranges from 3.8-4.5 and rectal pH ~7.0 and pH of 3 or less “are not acceptable for human use”
  • Other considerations include individual components of the product (and the individual?), parabens, glycols (glycerol/glycerine, propylene glycol), microbicides (nonoxynol-9), and preservatives (chlorhexidine)
  • Fecundity (fertility) is also affected by ingredients
    o Optimum pH for sperm in cervical mucus is 7.2-8.5
    o Optimum osmolality for sperm is 270-360 mOsm/kg

• Key practical issues
  o Impact of vaginal dryness on QOL is underestimated
  o Women are reluctant to raise the problem with their HCP and HCP often do not proactively raise the issue
  o There is a lack of knowledge of effective treatment options that are available
    ▪ Challenges include 1) educating both women and their HCP 2) identifying and eliminating agents that cause irritation 3) misdiagnosis and mistreatment
    ▪ Table 2 can be very helpful to the HCP in recommending appropriate products
  o There is likely to be a synergistic effect of using lubricants/moisturizers even if local vaginal estrogen or a SERM is used

Many breast cancer survivors, including young women, undergo menopausal changes as a consequence of cancer treatment
  o Vulvovaginal atrophy (VVA/GSM) is reported to be one of the most unpleasant side effects by breast cancer survivors (BCSs)
  o VVA is reported by up to 70% of BCSs and is rarely discussed with their HCP
  o VVA in BCSs will increase because of the current practice of prolonged adjuvant therapies (tamoxifen, AIs)
  o Local estrogen therapy is the most used approach for VVA/GSM, but safety concern exist with BCSs; ACOG recommends non-hormonal approach as 1st line treatment
Survey of 120 Italian breast oncologists (63 males, 57 females) was undertaken to assess their attitudes toward VVA in BCSs
  o Computer-assisted web interviews in 3 sections
    ▪ # of breast cancer patients/year
      • Median of 240 new breast cancer diagnoses/year
    ▪ Adjuvant treatment prescribed according to menopausal status
      • For premenopausal patients, 1st choice is tamoxifen
      • For postmenopausal patients, 1st choice is AIs
    ▪ Attitude toward assessment and diagnosis of VVA
      • Perception (opinion) of VVA grade among BCSs treated with hormone depletion therapy (adjuvant therapy)
        o 60% postmenopausal patients (43% mild, 40% moderate, 17% severe)
        o 39% of premenopausal patients
      • Clinical relevance granted to VVA
        o All considered VVA as a non-transient and primary problem
        o Only 48% explain to patients that VVA could be a consequence of treatment
    ▪ First time discussing VVA with patients
      o VVA is discussed in a follow up visit and only 26.5% address the problem (no sex/gender difference among physicians)
      o 85% are aware of paying inadequate attention to the problem
      o 85% complain that they do not receive enough information on the topic
    ▪ Primary measure as soon as patient revealed VVA
      o 41% refer the patient to GYN
      o 35.1% directly describe treatment options to the patient
  ▪ Knowledge concerning VVA treatment options
    ▪ What kind of drugs they used to treat VVA (see Figure 1)
      o 71.1% prescribe non-hormonal treatments (lubricants/moisturizers)
      o Local vaginal estrogen therapy (ET) is prescribed by 21%
      o HRT prescribed by 4%
    ▪ Attitude toward hormonal and non-hormonal drugs (see Figure 2)
      o 91% consider non-hormonal treatment to be safe, but only 30% perceive them to be effective
      o 15% consider local ET safe, but 79.2% deem it effective
      o Prescribing local ET is driven by severity of symptoms (95.1%), request by patients (26.7%), and for UTIs (16.7%)
      o Only 24.2% prescribe local ET for patients with nonhormone-dependent breast cancer and 7.5% prescribe local ET for hormone-dependent breast cancer at the end of adjuvant treatment
      o 15% do not prescribe hormonal drugs to treat BCSs
If GYN prescribes local ET, only 21.5% will confirm the prescription and 20.8% confirm it only for short duration; 18.9% will confirm if they have non-hormone dependent breast cancer; 20.4% do not agree at all.

Main reasons to not prescribe local ET in BCSs is the probability of increased cancer recurrence (70%), interference with adjuvant rx, or possibility of a lawsuit.

- Attitude of patients when hormonal drugs were prescribed
  - 43% refuse it
  - 36.5% ask for reassurance before using it
  - 20.5% accept it, especially when symptoms are severe

- Oncologist’s knowledge of different available estrogen preparations
  - 70% know about standard high-dose formulations
  - 52.5% prescribe low-dose and gel formulations
  - 1.7% knew of new treatment options like vaginal laser

### Discussion
- VVA is a frequent side effect of treatment reported by BCSs and younger women have higher rates of sexual dysfunction, even beyond treatment
  - Up to 20% of BCSs consider stopping antihormone treatment because of symptoms
- GSM better describes both VVA and LUT symptoms, including sexual dysfunction
  - It is chronic and progressive even after cancer treatment is completed
  - It is inadequately addressed in medical practice
- Local vaginal ET is the preferred treatment for GSM and is more effective than HRT (systemic) for GSM only, and is considered safer for BCSs when low-dose or ultra-low dose formulations are used due to very low serum levels (plasma estradiol levels within the range of postmenopausal levels)
  - Safety concerns still exist, but most studies have small sample sizes and look at variable data points
  - “However, available data from the literature do not show an increased risk of cancer recurrence among women with current or previous breast cancer who use vaginal estrogen to relieve GSM” (see reference #12 ACOG Committee Opinion No. 659)
  - Informed consent process and discussion of risks/benefits must precede the use of local ET
  - “Because of the relevance of the problem, great effort should be done in order to correctly inform health care providers about VVA problems and on the different available treatments”

### Journal Club Discussion:

How familiar are you with GSM and its implications in the pelvic PT population? Do you feel confident that you understand the physiological changes that take place with GSM and are able to assess for this condition? How might this impact your plan of care?

How do you see your role as a pelvic PT regarding this information?

Do you typically advise your patients regarding treatment options for GSM? Do you refer them back to their HCP? If they are a BCS, do you send them to the ONC or GYN?