

Cancer Education Day – Dec. 13, 2019

**Management of Post-Menopausal Symptoms
in Breast Cancer Patients**

Dr. Greg Hasen

Menopause

- * Menopause is a normal, natural event, defined as the final menstrual period (FMP), confirmed after 1 year of no menstrual bleeding;
- * Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually due to aging;
 - * Naturally (spontaneously) average age ~51;
 - * Prematurely from medical intervention (e.g. bilateral oophorectomy, chemotherapy, radiation);
 - * At any time from impaired ovarian function.

Hot Flashes

- * Thermoregulatory dysfunction at hypothalamus
- * Risk factors: Obesity
Smoking
Ethnic background
Genetic variants
- * Neurokinin B: Hypothalamic neuropeptide thought to be associated with VMS.

Hot Flashes

How Long?

Mean duration is 4.9 years.

but 30% for >10yrs

8-9% persist into late menopause.

SWAN Study: (Study of Women across the Nation)

Mean duration 7.4 yrs

Longer if earlier menopause, and African American
and shorter in Asian/Hispanic groups

Defining Menopause: STRAW+10 Staging System

Menarche

Final Menstrual Period (FMP)

0

STAGES	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early		Late	
					PERIMENOPAUSE					
Duration	Variable				Variable	1-3 yrs	2 yrs (1+1)		3-6 yrs	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow / length	Variable length Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhoea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine • FSH • AMH • Inhibin B			Low Low	Variable Low Low	↑ Variable Low Low	↑>25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very low Very low		
Antral Follicle Count			Low	Low	Low	Low	Very low	Very low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms <i>likely</i>	Vasomotor symptoms <i>most likely</i>			Increasing symptoms of genitourinary syndrome of menopause (GSM)

*Blood draw on cycle days 2-5; **Approximate expected level based on assays using current international pituitary standard; ↑ = elevated.

Hot Flashes

Management:

Behavioural

Complementary/Alternative therapies

Hormonal therapy

EPT, ERT, TSEC

Alternative Treatments

- * Clonidine (continuous release patch
less side effects but more expensive)

Delivers 0.1 mg/d TTS-1

0.2 mg/d TTS₂

0.3 mg/d TTS₃

New modalities:

Neurokinin receptor antagonists (NK₃R antagonist)
since increased NKB pulsatility is seen in women with VMS
blocking the receptors does seem to be promising

*possible elevated ALT/AST enzymes in current studies so not
widely available currently*

Complementary & Alternative Therapies

- * Phytoestrogens: Isoflavones, Lignans, Coumestans
- * Isoflavones; Soybeans, chickpeas and lentils
- * Lignans; Flaxseed, lentils, grains, fruits and vegetables
- * Review of 11 randomized clinical trials only 3 demonstrated a beneficial effect

Effectively acting as a SERM so not recommended in high doses for ER Pos breast cancer pts.

Complementary Alternative Therapies

- * Black Cohosh (*Actaea racemosa*)

systematic reviews and meta-analyses no better than placebo

** also SERM so concern with ER+ Breast Ca pts**

No evidence of benefit compared to placebo:

Acupuncture, Evening of Primrose Oil, Flaxseed, Ginseng, Dong Quai, Wild Yams, Progesterone creams, Wintergreen oil

Alternative Options

* **Gabapentin** 900 mg (300mg tid) more effective than placebo

****may be more effective than SSRI/SNRI****

- Headache, dizziness, disorientation
- Sedating effects limit daytime use in some patients
- Single dose at bedtime decreases frequent awakening

SSRI: selective serotonin reuptake inhibitor

SNRI: serotonin and norepinephrine reuptake inhibitor

SSRI/ SNRI

Paroxetine, Sertraline and Fluoxetine blocks the activation of Tamoxifen to active metabolites.

****Avoid in patients on Tamoxifen.****

Venlafaxine blocks this minimally - safe

Citalopram is first choice 20mg/d optimal dose

How Long

Suggested to try for 2 years if for vasomotor symptoms and taper off if SSRI/SNRI

If symptoms return, resume and try in another 2 years

Genitourinary Symptoms of Menopause (GSM)

Formerly defined as:

Vulvo- Vaginal atrophy as well as
Urinary symptoms of menopause

(Urgency, Frequency, Nocturia, Dysuria
and frequent UTI's)

GSM

- * Vaginal atrophy, dryness, dyspareunia, frequent vaginal infections
- * Urgency, Frequency and Nocturia
- * Frequent UTI's, microscopic hematuria



GSM

The vulvovaginal region is very sensitive to estrogen decline, with a series of consequences that impact directly on the quality of a woman's life:

weakness and laxity of the vaginal mucosa,

dryness, itching and burning,

pain during sexual intercourse (dyspareunia).

GSM

During menopause, the mucosa is metabolically quiescent,
-fibroblasts become inactive fibrocytes,
-unable to actively produce collagen, hyaluronic
acid and other molecules needed for adequate
glycoprotein ground matrix.

Results in dry mucosa as it is dehydrated and less well nourished
meaning it is fragile and more prone to infections.

GSM

With low water content in the connective tissue, both nutrients and lymphocyte defenses find it harder to migrate through the connective tissue matrix to reach the epithelium.

Without nourishment, the epithelium thins, which reduces the shedding of superficial cells, resulting in decreased glycogen in the vaginal lumen.

GSM

Numbers of lactobacilli, which feed on glycogen and serve to maintain proper acidity in the vaginal environment, are therefore reduced.

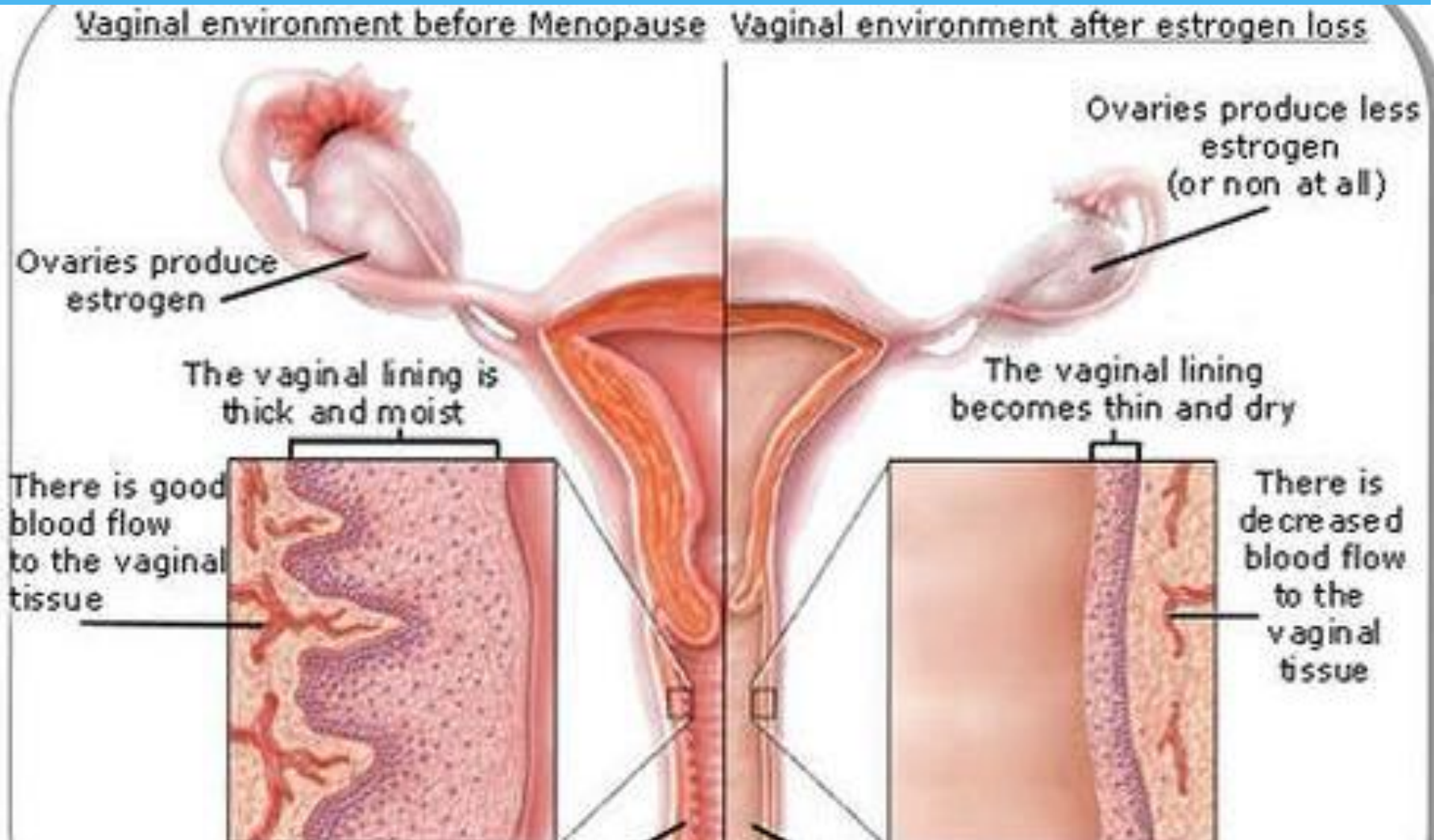
The pH thus increases, favoring attacks by pathogenic bacteria and the onset of infections.

GSM

Purpose of treating vaginal atrophy is to promote and recover pre-menopausal metabolic activity by means of a new synthesis not only of collagen, but also of hyaluronic acid, glycosaminoglycans and proteoglycans.

This helps to regain hydrated mucosa which in turn restores a proper trophic supply to the tissues, thus reinstating all the functions typical of younger healthy tissue.

Postmenopausal Changes



GSM

Treatment options:

- Lubricants and moisturizers
- Estrogen : Premarin,
Estragyn,
Vagifem,
Estring
- Laser therapy

Treatment Options for Vaginal Atrophy Symptoms

Lubricants:

Water soluble and oil based

Moisturizers:

Replens- glycerine-mineral oil-polycarbophil combination.

Hyaluronic or Glucaronic acid containing agents
(aminoglycans)

Vaginal Estrogens

Premarin cream (0.625 mg conjugated equine
estrogens/gm -estradiol)

Estragyn cream (estrone) (alcohol free/ scent free)

Vagifem 10 ugm tablets (estradiol) = 1.14 mg/yr

** 4 ugm tablet as effective although less
so for urinary symptoms if placed too
high in the vagina**

Estring 7.5 ugm/d over 90 days (estradiol)

Newer Options for Vaginal Atrophy

Ospemifene (Osphena): SERM. oral medication
positive effects on vagina but negative for breast
and uterine receptors.

****Doesn't help and may aggravate VMS****

DHEA 6.5mg vaginal suppository nightly
(recently approved by Canada Health)
85% improvement in dryness
SE: vaginal discharge

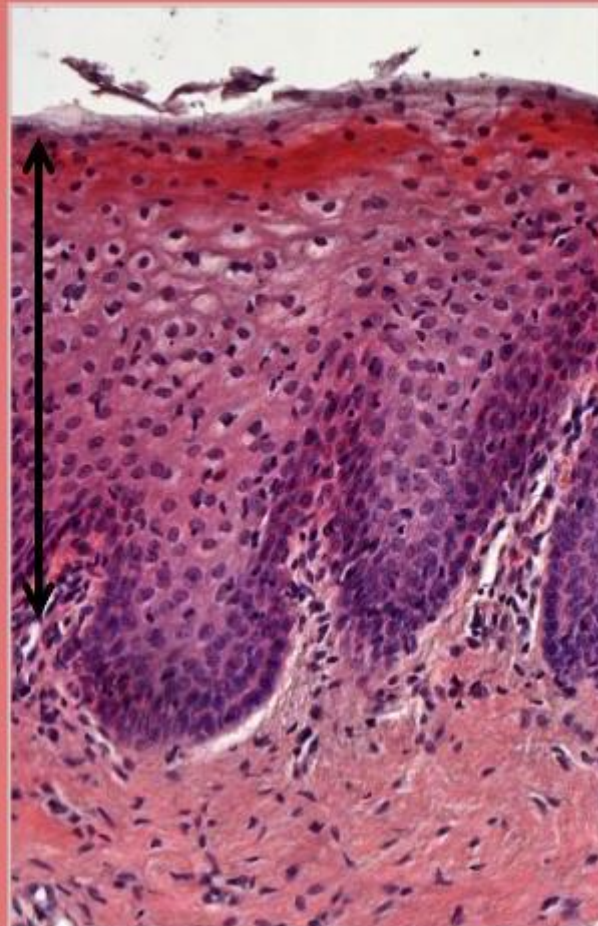
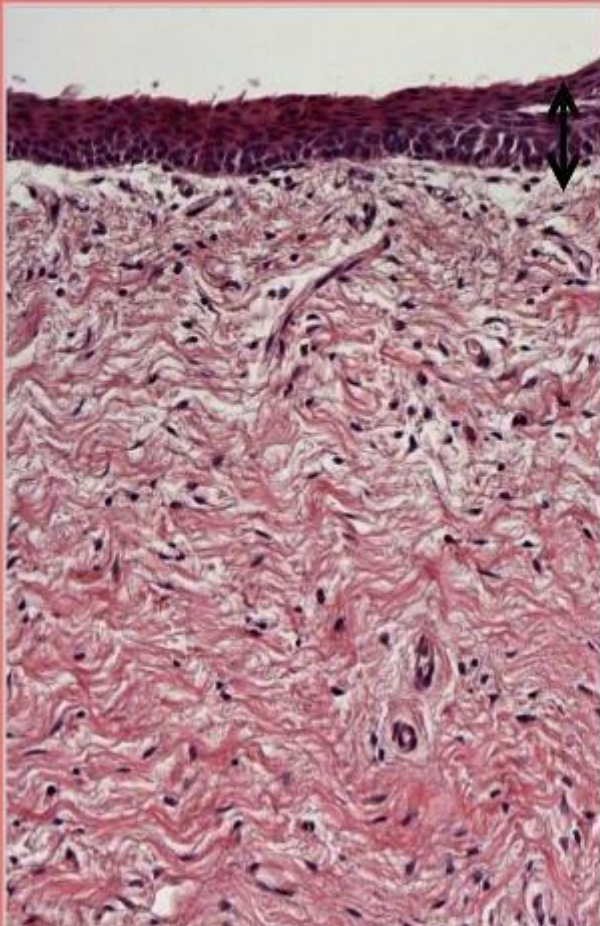
Laser Therapy for Vaginal Atrophy

Histologic evaluation:

similar short-term improvement in vaginal epithelial maturation in post-procedural vaginal wall biopsies with the use of intravaginal laser as that seen with local estrogen.

Histologic Changes

2 MONTHS AFTER 1 TREATMENT



*B&A pictures
with the same
enlargement*

Intravaginal Laser for Genitourinary Syndrome of Menopause and Stress Urinary Incontinence

Types of lasers used for intravaginal therapy

- Pulsed CO₂
- Er:YAG.

How Does It Work?

Fractional CO₂ Laser

(MonaLisa Touch)

How Does Laser Therapy Work?

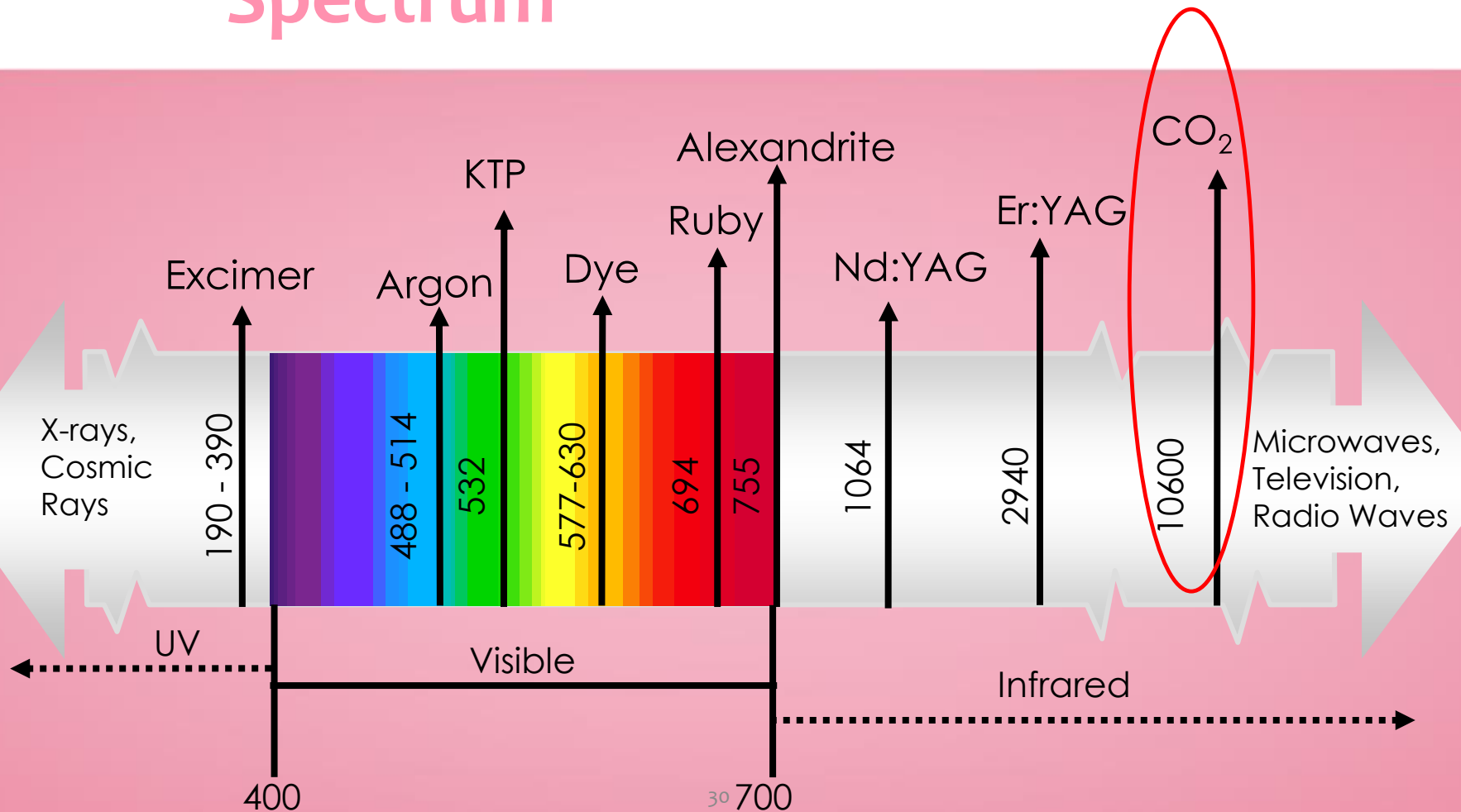
Produces a micro-ablative thermal effect up to 0.2 mm in depth that results in expression of heat-shock proteins.

Stimulates growth factors, such as transforming growth factor-beta, that induce synthesis of new extracellular matrix, collagen, and elastin fibres. (neocollagenesis)

Results in restoration of connective tissue and increased glycogen levels.

This type of laser typically targets symptoms of VV Atrophy and sexual dysfunction.

Electromagnetic Spectrum



Symptom Improvement (%)

After 3 Treatments MonaLisa Touch®

* BURNING	84%
* ITCHING	85%
* DRYNESS	76%
* DYSPAREUNIA	72%
* LAXITY	90%

*Courtesy of Prof. S. Salvatore – Hospital San Raffaele, Milan (Italy)

Candidates for Fractional Laser

- * Patients who present with vaginal health changes due to decrease in estrogen
- * Patients with history of breast cancer, VTE, or other contraindications to systemic estrogen therapy
- * Patients with inadequate response to estrogen therapy or decline of treatment results with estrogen

Contraindications

- Vaginal, cervical, or other lesions in the treatment area that have not been evaluated and diagnosed
- Active vaginal or vulvar infection (herpes, candida, HPV, STDs)
- Pregnant or within 3 months postpartum
- Prolapse beyond hymen (Grade 3)
- History of radiation to vaginal/ colo-rectal tissue
- History of reconstructive pelvic surgery with “mesh kits”
- History of impaired wound healing
- History of keloid formation

Er:YAG Laser

- * Induces a photothermal effect penetrating up to 0.5 mm inside the vaginal epithelium and causing up to 30% superficial tissue volume shrinkage.
- * This superficial shrinkage results in a mechanical pull of the deep tissue layer, in addition to a neo-collagenesis and angiogenesis from heat effect, thereby improving vaginal thickness, elasticity, and firmness.²⁴
- * The treatment indications for this type of laser encompass GUSM symptoms of VVA and sexual dysfunction, SUI, and pelvic organ prolapse

Controversies re: Laser Therapy

The literature supporting the intravaginal use of laser for GUSM and SUI is limited to short-term observational studies.

No real comparative studies with local estrogen as the group that uses the short course of vaginal estrogen does not continue its use past 12 weeks.

No RCTs comparing to the gold standard of local estrogen.

No comparative controlled or randomized trials to a sham device, as it is proven in literature that there can be a significant placebo effect.

No studies which address recurrent UTIs, (which is a pre-eminent issue in uro-gynecology and one of the main applications in the use of local estrogen.

Summary and Recommendations

2018 SOGC Practice Guidelines

1. In patients declining or with apparent contraindication to local estrogen, intravaginal laser therapy may be considered for short-term relief of symptoms associated with genitourinary syndrome of menopause. (Weak, Low).
2. There is insufficient evidence to offer intravaginal laser therapy as an equivalent modality to local estrogen for the treatment of genitourinary syndrome of menopause (including vulvovaginal atrophy, lower urinary tract symptoms, and sexual dysfunction). (Strong, Very Low).

Summary and Recommendations

2018 SOGC Practice Guidelines

3. Short-term observational studies of small patient number with the use of intravaginal laser have demonstrated improvements in symptoms of stress urinary incontinence.
- * There is insufficient evidence to offer intravaginal laser therapy as an effective modality for the treatment of stress urinary incontinence over alternate managements such as pelvic floor physiotherapy, incontinence pessaries, or surgery. (Strong, Very Low).

Rationale for Development of *Tissue-Selective Estrogen Complexes (TSECs)*

- TSEC -

The partnering of a SERM with one or more estrogen(s) to achieve pharmacologic results based on their blended tissue-selective activity profile

Relief Tips for the Top 5 Menopausal Symptoms

- * Fatigue. Weight gain. Hot flashes. Low libido. Hair loss. These are a few of the most common and troubling complaints of women who are experiencing symptoms of menopause and most often motivate them to find help.
- * “People should NOT tough it out or chalk their symptoms up to ‘getting old.’ There is HELP.” Listed below are some beneficial hints for acquiring the relief you need. Some symptoms are a touch more complex and may respond best to an additional comprehensive approach.

Relief Tips for the Top 5 Menopausal Symptoms: **Fatigue**

“I have no energy and feel fatigued all the time.”

- * Sporadic sleep is one of the most common problems we see during perimenopause and menopause. Hormonal balance depends on sufficient rest and optimal nutrition. And your ability to rest and make good dietary choices directly affect your hormonal balance.
- * Relief tip: Take two minutes a day to just breathe. Find a relaxing spot where you can be alone for a little while to reflect. Take time to notice your breathing, each breath, in and out. Moderately intense activity even walking can also boost certain neurotransmitters in the brain and elevate your energy level.

Relief Tips for the Top 5 Menopausal Symptoms: Weight Gain

“I’ve had it with gaining weight, depression and feeling tired all the time. I can’t work out when I have don’t have any energy.”

- * Changing hormones can alter how we store weight. When your body undergoes stress (such as in menopause) it stores up calories as part of its “survival mode.” The typical American diet doesn’t help.
- * Relief tip: Try to decrease your intake of refined carbohydrates. Try eating more high-quality protein, vegetables, healthy fats, and some fruit. Be mindful of carbohydrates. By including extra fiber and healthy protein in your diet, you can help your body retain steady blood sugar levels, and you’ll be less likely to store away those calories as fat.

Relief Tips for the Top 5 Menopausal Symptoms: **Hot Flashes**

“I’ve started perimenopause early. Hot flashes especially affect my scalp. I have sweat running down my face and neck from my hair.”

- * When you experience a hot flash, the heat-regulating sensor in your brain picks up a signal that your body needs to get rid of heat. Perceived stress can bring on a hot flash in a second. So can some foods and drinks, such as sugar, caffeine, alcohol, and hot spices.
- * Relief tip: Wear layers of clothing. Try choosing several thin layers of clothing so you have the option of removing the layers if you start to feel warm. It sounds very simple, but it really can reduce stress to plan what to wear ahead of time.

Relief Tips for the Top 5 Menopausal Symptoms: **Low Libido**

“I’m so tired of not being interested in sex.”

- * Physical changes, such as vaginal dryness, may make sexual activity painful. It’s not uncommon for women to experience a decrease in libido during menopause.
- * Relief tip: Know your options. Eat a healthy, balanced diet and make sure you’re getting enough omega-3 essential fatty acids to help support cell membranes. If this doesn’t help, vitamin E suppositories can help restore thin vaginal tissue. It’s important to be informed! You have more options than lubrication!

Relief Tips for the Top 5 Menopausal Symptoms: Hair Loss

“I started losing handfuls of hair in the shower. I knew then that I had to find help.”

- * Our hormones are connected to the growth and shedding cycle of our hair in an intimate way. An imbalance between estrogen and testosterone can contribute to thinning hair. Some women only begin to notice this during menopause or perimenopause. Stress also plays a role here, as it affects the scalp and it affects the adrenal glands which in turn affect your hormones.
- * Relief tip: Vitamins and minerals are essential to healthy hair. Be sure you're getting vitamins B (especially B6 and B12), C, D, and E, calcium, magnesium, copper, zinc, iron, and fish oil with essential fatty acids. Don't forget the trace minerals as well.