

**Patient Handout**

**NON-HORMONAL & HORMONAL WAYS TO REDUCE EFFECTS OF**

**MENOPAUSE AND CANCER TREATMENT ON THE VULVA & VAGINA**

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The medical approach to sexual problems after cancer is to prevent or address pain first. Pain with sex is a powerful inhibitor of sexual response and a common and expected problem for females impacted by cancer. For those who do overcome pain, or change how they have sex in order to avoid pain, low interest in sex, also known as low libido, may still be a problem. Studies show that the quality of the couple’s relationship along with emotional and psychological factors are just as important as prevention/treatment of pain and addressing fatigue/low interest. Ongoing support from a therapist, social worker, sex therapist, sexologist, or oncosexologist, starting at diagnosis and continuing into survivorship can help couples stay connected and reduce anxiety. Your provider can point you in the direction of qualified professionals in your area. In addition, yoga, massage therapy, and mindfulness stress reduction have all been shown to reduce stress and improve wellbeing related to cancer treatment.

This handout is offered as a communication aid for patients and their providers. It is not a substitute for professional medial advise, diagnosis, or treatment.

**NON-HORMONAL OPTIONS**

**I. Information**

1. **Vulvar Skin Care Guidelines**

 See [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Patients.

 **B. Websites**

* Ergoerotics®: Comfortable sexual solutions related to pain, disability and aging, [www.ergoerotics.com](http://www.ergoerotics.com)
* A Women’s Touch Sexuality Resource Center, [https://sexualityresources.com/](https://sexualityresources.com/%22%20%5Ct%20%22_blank)
* [www.AdamEve.com](http://www.AdamEve.com) and [www.TooTimid.com](http://www.TooTimid.com) for vibrators and sex toys

 **C. Nutrition & Supplements**

While not our area of expertise, there is some evidence that diets high in omega-3 fatty acids and containing adequate vitamin A, vitamin B and beta-carotene may improve self-reported vaginal dryness. Erika Hempstead, Integrative Health Coach and friend to the All of Me project, has written a Patient Handout on Nutrition and Supplements for Vaginal Dryness. It can be found at [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Patients.

**II. Over-the-Counter Products**

 **A. Vaginal Moisturizers**

 If radiation therapy includes the pelvis, the ovaries are likely to be irradiated. This results in menopause with low blood estrogen levels. Symptoms of menopause can include dryness and irritation of the vulva, vagina, and bladder. Together, these symptoms have been called genitourinary syndrome of menopause (GSM); they used to be called vulvo-vaginal atrophy. In addition to the hormonal effects of menopause, radiation itself can inflame, thin, and scar tissues.

 While estrogen is the most effective way to reverse the changes of menopause, it is not appropriate for, or recommended for all patients. Non-hormonal options, including vaginal moisturizers, thicken the vagina, making it more elastic and reducing pain with penetration. Packaging for the following three products recommends insertion every 2-3 days. However, there is some evidence to suggest that daily use may be more effective in females impacted by cancer. Try the product for 6 weeks to decide if it is helpful. If helpful, vaginal moisturizers are intended for regular use, whether or not you’re having sex or vaginal penetration. They are safe and should be used indefinitely.

* **Hyalo Gyn**®, 8 pre-filled applicators for $22.49 at [www.amazon.com](http://www.amazon.com). See also

 <http://www.hyalogyn.com/>

* **Replens**™ **Long-lasting Moisturizer**, 8 pre-filled applicatorsfor $23 at CVS, Walgreens, Target, and Walmart. $23 Coupon available online.

 <http://www.replens.com/Products/Replens-Long-Lasting-Moisturizer/>

* **Revaree**® Vaginal Inserts, 10 inserts for $40 with automatic recurring delivery or $55 for one-time purchase at <https://try.hellobonifide.com>. Active ingredient is hyaluronic acid. Insert with finger.

 **B. Vaginal Lubricants**

 Plant-based oils like coconut or olive oil are recommended with every episode of vaginal penetration. A lubricant does not need to be used if you are not having penetration. See Vulvar Skin Care Guidelines at [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Patients.

 **C. Barrier Creams and Ointments**

These skin protectants are often recommended for pain after radiation therapy. Examples include A&D Ointment®, Zinc Oxide Ointment, and Desitin®. They are not meant for internal vaginal use, but can be used on the vulva and the skin around the anus. Ointments with zinc oxide have antibacterial and antifungal activity. They may be all you need for a mild yeast infection of the skin. Keep in mind that barrier products will prevent absorption of other skin medications. For example, if a petrolatum or zinc oxide-based ointment is routinely applied to the vulva, skin medications like hydrocortisone or estrogen cream will not be absorbed.

**III. Devices**

1. **Dilators**

 Dilators are simple, smooth devices used to stretch the vagina. They come in various sizes and are usually made of plastic or silicone. Dilators are used to prevent and treat problems with vaginal penetration. Plastic dilators are smoother and may be less irritating than silicone for some, but expert advise from patients suggests that it’s a good idea to have different options depending on your situation and the location of scaring or vaginal narrowing. It may take using two different types of dilators to get the best results. For more information about dilator use, go to [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Patients, Dilators. You will find guidance for dilator use from North American, British, and Australian sources.

 In addition, Dr. Alessandra Graziottin and her colleagues have published dilator recommendations in Chapter 27, Sexual Rehabilitation After Gynecologic Cancers, p. 205-222 of Cancer, Intimacy and Sexuality: A Practical Approach, by Reisman & Gianotten, eds., Springer International Publishing AG, Switzerland, 2017. This is a publication by the *European Society of Sexual Medicine*. The authors recommend pelvic floor physical therapy, including dilator use starting 4 weeks after treatment, to be done 2-3 times per week for 1-3 minutes and to be continued for 9-12 months. In their own practice, however, they recommend “earlier start and twice daily [dilator] use for 5 minutes.” They also recommend starting vaginal estrogen therapy “the sooner the better,” before treatment-related menopause affects vaginal tissues. They recommend continuing vaginal estrogen, “such as estriol in gel,” lifelong.

 Here is an alphabetical listing of some dilators recommended by those who have used them and medical providers.

* **Dr. Laura Berman® Dilator Set** by CalExotics, 4 hollow plastic dilators with vibration, $20, can be purchased on [www.amazon.com](http://www.amazon.com). AA batteries sold separately.
* **Femmax® Vaginal Dilators:** by Myaid, 4 hollow plastic dilators, $35, can be purchased on [www.amazon.com](http://www.amazon.com)
* **Intimate Rose Silicon Vaginal Dilators:** end is not tapered, allowing dilation further back in the vagina, sets of 4 dilators in small, medium, or large for $80-120. Or, full set of 8 sizes for $180, at [www.intimaterose.com/collections/vaginal-dilators](https://www.intimaterose.com/collections/vaginal-dilators%22%20%5Ct%20%22_blank)
* **MiddlesexMD®**: set of 7 plastic dilators which can be sterilized, $109, at [www.middlesexmd.com](http://www.middlesexmd.com)
* **Milli All-in-One Vaginal Trainer**: Soft silicon covering, single insertion, millimeter by millimeter adjustable size from 15mm to 40mm, digital readout, low and high vibration and charging case, $250, at [www.milliforher.com](http://www.milliforher.com)

1. **Collision Barriers for foreshortened vagina or pain with deep penetration**
* Comfort Ring, $20, at [www.ergoerotics.com](http://www.ergoerotics.com)
* Ohnut™ Rings, $65, 4stackable rings to limit depth of penetration, at [www.betweenthesatinsheets.com](http://www.betweenthesatinsheets.com)
1. **Water Cones-Post Surgical Dilators**

 <https://www.cmtmedical.com/product/cool-water-cones-post-surgical-dilators/>, $15, available in 3 sizes.

**IV. Prescription Products**

1. **Topical Aqueous Lidocaine**, 4%, screw-top, 50 mL. Moisten 3 small or one large cotton ball. Place at the thin fold of skin at the back of the vulva (the fourchette), being sure to include the narrowest part of the vaginal opening (the hymenal ring). Leave in place for 3 minutes. Pat away excess lidocaine before penetration, to limit partner numbness.
2. **Silver Sulfadiazine Cream**, 1% USP, a brand name Silvadene® Cream, is a burn cream recommended by some oncologists for radiation burns of the vulva and is sometimes recommended for vaginal use after completion of radiation therapy. It may reduce absorption of other creams and moisturizers.
3. **EROS Clitoral Therapy Device**, $325, FDA-approved small handheld adjustable female suction devise for female sexual dysfunction at [www.healiohealth.com](http://www.healiohealth.com). Similar devises are available for $35-49 at some online sex shops and at [www.amazon.com](http://www.amazon.com), which carries a ‘Sucking Vibrator for Women’ for $49. The EROS device is included here for completeness’ sake, as it is the only FDA-approved devise for female sexual dysfunction and may increase natural lubrication and arousal.

**V. Pelvic Floor Physical Therapy**

 Treatment is most effective and less painful when vaginal tissues are well estrogenized before pelvic floor physical therapy starts. Referral can help with

* Support for learning how to use dilators
* Treatment of tight or painful pelvic floor muscles (hypertonus)
* Treatment of involuntary contraction of the vaginal muscles with penetration (vaginismus) due to trauma and/or pain

**VI. Yoga for Pelvic Pain**

 Consider yoga if tense pelvic muscles are contributing to pelvic pain. See Mayo Clinic 2019 handout at [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Patients.

**HORMONAL OPTIONS**

**I. Introduction**

The treatment of female sexual problems after cancer depends on the severity of symptoms and exam findings like the degree of atrophy, size of the vaginal opening, and presence of other medical conditions. Lack of affordable FDA-approved treatment options leads some medical providers to recommend over-the-counter (OTC), Internet, or compounded options.

There are many reasons why vaginal and vulvar treatments, and hormonal treatments in particular, may be difficult to use for females who have been impacted by cancer. Putting any medication on or in the genital area can be difficult for females who have experienced sexual trauma. A family history of hormone-sensitive cancer can also cause mixed feelings about using hormonal products. Even if you have had a type of cancer that is not hormone-sensitive and have been told you could use hormonal products, hormone therapy can still trigger anxiety historically based reasons, making it hard to use hormone therapy consistently.

For some females, the loss of hormone function due to cancer treatment feels like a necessary sacrifice in the bargain for recovery from cancer. Use of hormone ‘replacement’ may have a complicated meaning, possibly even meaning that we have not honored a bargain we made with our Higher Power. For all these reasons, an honest and open discussion with your medical provider is important.

**II. Vulvar & Vaginal Products**

There are two types of commonly used vulvar and vaginal hormonal products, estrogens and dehydrepiandrosterone (DHEA). Both are used to reduce the symptoms of genitourinary syndrome of menopause, which include vulvo-vaginal dryness and irritation.

A hormone is a substance produced by a gland. It is transported through the blood to specific cells or tissues in other parts of the body where it binds to specific receptors. During the childbearing years, estradiol, the bio-identical form of estrogen, is produced by the ovaries and travels to receptors in other tissues, like the genital area, bone, and brain, where it acts at estrogen receptors. While DHEA is produced by the adrenal glands and circulates in the blood, it is technically not a hormone because there are no DHEA receptors in the body. Instead, DHEA works within cells by activating estrogen and testosterone receptors.

Once begun, the time it takes for estrogen or DHEA to relieve vaginal dryness and pain with sexual penetration depends on the severity of the vaginal thinning and narrowing due to menopause or radiation therapy. In mild cases, you may feel better within 6 weeks. Or, you may need grit and perseverance for as long as 1.5 years, using a dilator and hormonal product, to reach your goal. In the most severe cases of scarring due to radiation therapy, pain with penetration and vaginal narrowing may be permanent, and only partial relief of symptoms may be possible.

Once you have inserted a vaginal estrogen product, wait 6-12 hours before penetration. This will keep more of the product in you and minimize exposure of your partner. If you tend to have sex in the evening, insert the product in the morning. If you tend to have sex in the morning, insert the product at bedtime.

Once you have needed a vulvar or vaginal estrogen or DHEA product for genitourinary syndrome of menopause, it is likely you will need it indefinitely. This is particularly true if you continue to be sexually active with penetration. On the other hand, if estrogen cream is prescribed for a specific symptom, for example spotting due to a urethral caruncle, your provider will instruct you on when you can stop.

In the following notes, ‘Rx’ means a prescription is needed for these products. Instructions are based on the package insert, where available.

 **A. Estrogens**

* **Estradiol**

 -**Estrace® Vaginal Cream** (Rx) 0.01% cream.

 Instructions: Initially, 2 -4 grams vaginally once daily for 1-2 weeks; then gradually reduce over 1-2 weeks. Usual maintenance 1 gram vaginally, 1-3 times per week. Treatment is cyclic, 3 weeks on, then 1 week off.

 -**Vagifem® Tablets** (Rx); generic **Yuvafem® Tablets** (Rx) 10 mcg tablet.

 Instructions: Insert 1 tablet vaginally once daily for 2 weeks into the upper third of the vaginal vault using the supplied applicator. After 2 weeks, insert 1 tablet vaginally twice weekly, eg: every Tuesday and Friday.

 While doses as high as 25 mcg/dose were previously available, they were removed from the market because of patenting considerations. In my clinical experience, 1 in 4 postmenopausal females does not get enough relief with the 10 mcg dose.

 -**Imvexxy® Vaginal Inserts** (Rx) 4 mcg, 10 mcg inserts.

 Instructions: Insert 1 vaginal insert daily x 2 weeks, followed by 1 insert twice weekly, for example, every Monday and Thursday.

 -**Estring® Vaginal Insert** (Rx) delivers 7.5 mcg estradiol/24 hours.

 Instructions: Insert one vaginal ring deep into the upper third of the vaginal vault. Keep in place continuously for 3 months, then remove. If appropriate, insert a new ring.

 If the flexible Estring**®** is too large to insert or wear comfortably initially, try 6 weeks of a vaginal estrogen cream first. Some females who have had a hysterectomy with removal of the cervix or radiation therapy may have a vaginal vault that is too narrow for the Estring®.

* **Conjugated Equine Estrogen** The active ingredient is a mix of 11 horse estrogens derived from pregnant mare’s urine.

 -**Premarin® Vaginal Cream** (Rx) 0.625 mg conjugated estrogen per gram. Instructions depend on the indication for use. According to the package insert:

1. Insert 0.5 – 2 grams intra-vaginally, daily x 21 days then off x 7 days, for atrophic vaginitis
2. Insert 0.5 grams intra-vaginally, daily x 21 days then off x 7 days, for treatment of moderate to severe pain with penetration, a symptom of vulvar and vaginal atrophy, due to menopause
3. Insert 0.5 grams intra-vaginally, twice-weekly, eg: Monday and Thursday, for treatment of moderate to severe pain with penetration, a symptom of vulvar and vaginal atrophy, due to menopause.

 I (VK) interpret this to mean that doses higher than 0.5 grams should only be used if an examination to confirm the diagnosis has been performed, not just a report of symptoms.

* **Estriol Vaginal Cream**

 -**Estriol Vaginal Cream** (Rx) 0.5 mg per gram.

 Instructions: 1 gram vaginally twice-weekly, eg: Monday and Thursday.

 Estriol is a weak bio-identical estrogen, normally produced by the placenta. Like estradiol, it is usually derived from a plant source and purified by a complicated chemical process. A compounding pharmacy puts it in a cream base. One example of a compounding pharmacy is the Women's International Pharmacy at 2 Marsh Court, Madison, WI, 53718. Phone: 1-608-221-7800 or 1-800-699-8144. Fax: 1-800-635-1229. Another example is Towncrest Pharmacy in Iowa City, IA 1-319-337-3526.

 **B. DHEA** (Prasterone)

 Although technically a prohormone, not a hormone, DHEA is produced by the adrenal glands and found in large amounts in the blood. When inserted in the vagina or applied to the vaginal entrance, small amounts of DHEA do not raise blood levels of estrone, estradiol, or testosterone. Some females who don’t get enough pain relief from vaginal estrogen products alone, will get relief when a medication that also works at testosterone receptors is added or substituted.

* **Intrarosa® Vaginal Inserts** (Rx), 6.5 mg insert.

 Instructions: Insert one insert vaginally daily at bedtime.

 Twenty-eight inserts cost $207 at most retail pharmacies. Coupons are available. For those with insurance, tier of coverage can sometimes be improved by submitting a Prior Authorization request based on personal or family history of breast, genetic risk of breast cancer, or the fact that Intrarosa® does not have a black box warning, whereas vaginal estrogen products do.

* **Julva® Cream**, available online without a prescription, 1 ounce tube costs $70 at [www.amazon.com](http://www.amazon.com). Here are my suggestions related to Julva® Cream. If you and your medical provider feel this is a good option for you, I suggest you first get the 7-day trial pack available for $4.95 shipping at [www.drannacabeca.com](http://www.drannacabeca.com). Julva® Cream has a somewhat unique smell, probably due to the imu oil (bird fat, non-vegan). If you find the smell acceptable, apply the cream to the vulva as directed using 1/8th of a teaspoon once a day. If you do not experience irritation, order the 1 ounce tube at [www.amazon.com](http://www.amazon.com). This tube will last about 1.5 months. Some Walmart stores also carry Julva® Cream. Apply 1/8th of a teaspoon (spoon comes with tube) starting above the clitoris and including the hymenal ring (the narrowest part of the vaginal opening) and inner labia minora daily. If not effective after 6-8 weeks, increase to twice-daily application. If that is not effective within another 6-8 weeks, Julva® Cream will not work for you. Please note, Julva® Cream will not give you elasticity or comfort inside the vagina. It does not come with a vaginal applicator and the dose is for vulvar use, not deep vaginal use (dose may be too high for vaginal use). You may need to use Julva® Cream together with a daily vaginal moisturizer or vaginal estrogen product.

Please see Appendix A, page 10, for more information on vulvar and vaginal hormonal products.

**III. Systemic Estrogen, Estradiol & Progesterone, and Ospemifene**

Hormone therapy that is given to control hot flashes, improve sleep, reduce aches and pains, or prevent or treat osteoporosis is called ‘systemic’ hormone therapy. This is because it relies on absorption into the blood to have its effect. It can be given by mouth (oral hormone therapy) or through the skin in the form of a patch or gel (transdermal hormone therapy). Females with a uterus who take systemic estrogen also need to take some form of progesterone. Natural progesterone or a synthetic progestin will prevent overgrowth of the uterine lining, and reduce the risk of cancer of the uterus. Females without a uterus who take systemic estrogen do not need progesterone or a progestin.

There are too many systemic estrogen options to list here, but you can learn more at [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Providers, 2014 Menopause and Sexual Health Clinic Protocols. Ospemifene® is an oral medication prescribed to treat genitourinary syndrome of menopause. Testosterone is sometimes compounded in doses appropriate for females and applied to the skin to treat low sexual interest. Generally, it should only be considered once any sexual pain problems have been treated.

Please see Appendix B, page 12, for more information on systemic estrogen, estradiol & progesterone, and ospemifene.

**IV. Surgical treatment of vaginal stenosis after pelvic radiation therapy**

Dr. Emily Hill (UIHC Gynecologic Oncologist) and Dr. Cate Bradley (UIHC Urogynecologist) have agreed to collaborate in the evaluation and possible surgical care of patients with vaginal stenosis after pelvic radiation therapy. Surgical treatment may be possible when patients are referred early, before scarring is permanent. Call (319) 356-2294 to schedule an appointment or speak with a nurse.

**V. Navigating the pharmacy payer system**

Here is a summary of my (VK) clinical experience in trying to get insurance to cover hormonal therapies, along with references in the footnotes that can be used to support Prior Authorization or Change of Tier requests.

* For **vaginal estrogen** products, if the female had a very narrow vaginal opening, that is too small for insertion of the plastic applicator that comes with Estrace® and Premarin® Vaginal Creams, a letter from the medical provider to your insurance company can sometimes get a better tier of coverage for the comparatively narrower Vagifem® or Yuvafem® applicator and might work for the Imvexxy® Vaginal Inserts.
* For **females impacted by breast cancer**, some insurance companies will cover Intrarosa® at a better tier, if provided with a letter of supporting rational and a Prior Authorization form. This approach sometimes works for female carriers of BRCA mutations who prefer Intrarosa®, too.
* For **transdermal hormone therapy** (HT), I always prescribed the generic first. If the adhesive is poor or you have an adverse skin reaction, I would get a Prior Authorization form from your pharmacy, fill it out, send back to pharmacy, and they will forward it to your insurance company. Alternatively, a nurse would fill out the form and I would dictate a letter of support regarding why a specific brand name patch is needed. This was the best way to get the smaller patches with better adhesives, like the Vivelle-Dot® or Sandoz brand patch.
* For females wishing to continue **hormone therapy beyond age 65**, who receive a notification from their insurance that hormone therapy will no longer be covered (due to Beer’s Criteria List), I send letters stating that both NAMS[[1]](#footnote-1) and ACOG[[2]](#footnote-2) have come out with statements indicating that the decision regarding continuation of HT should be between the patient and her provider. If the patient is on estrogen alone (without a progestin or progesterone), I describe the better safety profile related to breast cancer risk for estrogen-only therapy[[3]](#footnote-3).
* If the patient’s insurance does not cover **oral micronized progesterone** (Prometrium®), sometimes a letter outlining the benefits of oral micronized progesterone over synthetic progestins (eg: medroxyprogesterone acetate (Provera®) and norethindrone acetate (Aygestin®) will cause the insurance company to improve tier of coverage for oral micronized progesterone. Position statements from national academic organizations can be used to support coverage requests.6, 7
* I (VK) have not had luck getting insurance to cover compounded medications, like a 50mg dose of oral micronized progesterone or the estriol vaginal cream. Neither of these products is commercially available at standard retail pharmacies. However, the price of compounded products is usually fairy reasonable, especially when compared to over-the-counter options or if you need to meet a high deductible. For example, a 90-day supply of oral micronized progesterone, 50 mg, costs $72 at Towncrest Pharmacy in Iowa City, IA, and the prescription can be mailed out. Just because insurance is unlikely to cover compounded medications, doesn’t mean it is pointless to try to get a Prior Authorization, as insurance decisions about coverage might change in the future.

Here are some suggestions I (KD) have found helpful.

* Copay cards and patient assistance programs provided by the medication manufacturer can be used alone or in combination with insurance. These are typically a good starting point for patients with insurance who have a high deductible or high copays, as they can save more money than a generic discount card. However, it is important to note the restrictions on these offers. Some cannot be used with government sponsored insurances like Medicare, and some have specific benefit limits. These are typically only available for brand-name only medications.
* Current manufacturer savings options (in alphabetical order by product brand name)

 -Estrace® cream patient assistance program: <https://www.abbvie.com/patients/patient-assistance/allergan-patient-assistance-program.html>

 -Estring® copay card: <https://www.estring.com/save-on-estring?gclid=57ec1652a43d1ae4f363760ce4fa64e4&gclsrc=3p.ds>. Patient assistance program is also available: <https://www.pfizerrxpathways.com/>

 -Imvexxy® inserts copay card: <https://www.imvexxy.com/savings-information>

 -Intrarosa® inserts copay card: <https://us.intrarosa.com/savings-and-support>

 -Osphena® copay card: <https://www.osphena.com/savings>

 -Premarin® cream copay card: <https://www.premarinvaginalcream.com/savings-and-support>

* Discount cards, like GoodRx, may make medication more affordable. They are a good option for patients who do not have prescription insurance coverage, or who do not have insurance coverage for specific products. Unfortunately, these cannot be used in combination with insurance. Medication price will vary by pharmacy. The best way to find the lowest price is to go to the discount card’s website (ex: goodrx.com) and search by the specific medication to see a list of available pharmacies and their contracted prices.
* Sometimes price checking at different pharmacies can also result in a more economical price. This is especially true for a cash paying patient. A cash paying patient can call the pharmacy with the specific medication, strength, and quantity to get a quote. If a patient has insurance and wants to find the best cost, usually the best strategy is to call the Member Benefits number listed on the back of the insurance card. The insurance company can list preferred contracted pharmacies and their copay structures.

**Appendix A**

**More Information on Vulvar & Vaginal Hormonal Products**

1. Vaginal estrogen products are all absorbed into the blood to varying degrees. This is important for a number of reasons. First, if you have had an estrogen-dependent tumor, like most breast cancers, you may be taking medication to keep your blood estrogen level as low as possible. This is because estrogen may increase the risk of cancer recurrence. Second, if you have a uterus, too much estrogen without enough progesterone (the other main female hormone produced by the ovaries), can cause the lining of the uterus to thicken abnormally, increasing the chance of abnormal bleeding, overgrowth of the uterine lining (endometrial hyperplasia), and uterine cancer. While the amount of estrogen absorbed from vulvar and vaginal products is almost never a problems, generally, the goal is to use the lowest effective dose.[[4]](#footnote-4),[[5]](#footnote-5)
2. Although Premarin® Vaginal cream and Estrace® Vaginal Cream are equally effective on vaginal tissues, Premarin® Cream is not approved by the equivalent of the Australian FDA, because of the mix of 11 horse estrogens in the product; it is derived from pregnant mare’s urine and is not vegan. The actual estrogenic effect of Premarin® products can’t be measured by blood levels. I prefer to prescribe estradiol vaginal products, for which serum levels have been measured, reported, and compared. This difference is especially important for females with breast cancer who are trying to use the lowest effective dose.
3. The vaginal entrance and vagina have different embryologic tissue origins. The vaginal entrance and bladder have estrogen and testosterone receptors. The vagina has mostly estrogen receptors. This provides theoretical support for a possible advantage of DHEA over estrogen alone, specifically at the vaginal entrance and for urethral and bladder tissues. DHEA can be delivered to these tissues with either vaginal inserts (Intrarosa®) or vulvar application (Julva® Cream).
4. Early studies of low dose vaginal estrogen (Vagifem® equivalent) use in females impacted by breast cancer who were also taking an aromatase inhibitor (AI) (eg: Tamoxifen, Anastrozole, Letrozole, Exemestane) raised concern. This was because a few females who were on both an AI and the equivalent of Vagifem® had blood levels of estradiol that were too high. More recent studies of vaginal DHEA in females taking AIs, done with better hormone tests, do not show any worrisome elevations of blood estrogens.[[6]](#footnote-6) Blood DHEA-S and testosterone levels were elevated at the 6.5 mg/day dose (the dose in Intrarosa®), but not at a 3.25 mg/day dose. Further research on vaginal DHEA is needed in females with hormone dependent cancers.
5. Females with cardiovascular disease can use standard vaginal estrogen products for painful penetration. This is because the low amounts of hormone absorbed from the vagina with standard dosing are not enough to cause production of the liver proteins that increase risk of blood clots in the circulation (thromboembolism).
6. Some patients with a history of breast cancer or BRCA genetic risk use daily vaginal moisturizers and daily Julva® Cream at the hymenal ring and vaginal entrance to increase elasticity.
7. The high cost of medications is the reason that some medical providers prescribe compounded vaginal Estriol (E3) cream, which costs about $40 per month through the Women's International Pharmacy in Wisconsin and $30 per month through Towncrest Pharmacy in Iowa City, IA. Estriol is a low potency estrogen normally produced by the placenta. It has the possible advantage that it can’t be metabolized into higher potency estradiol.
8. A vaginal estradiol insert/suppository (Imvexxy®) is now commercially available. It’s a welcome improvement in delivery system over reusable, but difficult to clean, plastic vaginal applicators (Premarin® and Estrace® creams) and the single-use plastic applicator (Vagifem® tablets). The inserts are still under patent, so cost may be a concern.
9. Studies have looked at the possible benefits of vaginal testosterone. I have some experience with prescribing a compounded vulvar estrogen plus testosterone cream for vulvar pain (vulvodynia), but stopped recommending this after commercial products like vaginal and vulvar DHEA became available, as these also work at testosterone receptors.

**Appendix B**

**More Information on systemic estrogen, estradiol & progesterone, and ospemifene.**

1. Transdermal estradiol products at or below the 0.05 mg dose are not associated with increased risk of venous thromboembolism (VTE) risk while all doses of oral estrogens increase VTE risk.
2. Transdermal products at or below 0.05 mg dose usually are not enough to relieve genitourinary syndrome of menopause, the vaginal dryness and irritation, and pain with penetration associated with low estrogen levels. In order to have the lowest effective systemic levels of estrogen and relief of vaginal symptoms, some females use systemic and vaginal estrogen products, eg: A 0.0375 mg. estradiol patch, 100 mg oral micronized progesterone, plus Juvafem® tablets or the Estring®.
3. There is no advantage to blood testing to determine hormone therapy dose for relief of hot flashes and body aches; use the lowest-effective dose.
4. When starting to treat hot flashes in naturally menopausal females, I have noticed the following approximate clinical dose-dependent response. Similar information for females who reach menopause due to cancer treatment is not available.

|  |  |
| --- | --- |
| **Dose of transdermal estradiol (mg)** | **Percent of new start patients who will get relief** |
| .05 | 75% |
| .0375 | 50% |
| .025 | 25% |
| .014 (Menostar®) | 15% (a published study claims 50%) |

1. A typical start doses for systemic hormone therapy for moderate to severe hot flashes in a female with a uterus would be 0.0375 mg estradiol patch plus 100 mg of oral micronized progesterone at bedtime.
2. Oral micronized progesterone, 300 mg at bedtime, has been shown to decrease hot flashes and improve sleep. It also reduces anxiety in some females. It can be considered in females whose cancer is not hormone sensitive, but will not improve genitourinary syndrome of menopause/vulvovaginal atrophy.
3. There is no advantage to compounded oral hormone therapy over prescription oral hormone therapy, as all oral hormone therapy ends up as predominantly Estrone (E1) in the blood, once it passes through the liver in what is called first pass metabolism. Estrone is a low potency estrogen that is the main estrogen in post-menopausal females. In such females, estrone levels are directly proportional to body mass index (weight). If you want to increase estradiol (E2), the most potent estrogen during the reproductive years, use transdermal doses of 0.05 mg or less.
4. The free Menopro™ app, created by the North American Menopause Society at www.menopause.org, provides a risk calculator for initiation of systemic hormone therapy for the management of hot flashes. It does not address specific cancer types. Most breast cancers, adenocarcinoma of the cervix, and uterine cancer are hormonally sensitive, so if you have one of these cancers, systemic hormone therapy may not be appropriate for you.
5. There is good evidence for not starting systemic hormone therapy more than 10 years out from menopause. This is because of increased cardiovascular risk.
6. There is no evidence that systemic estradiol improves libido, however, if serum levels are at or above 60 mg/mL, vaginal atrophy and resultant pain will be relieved. Unfortunately, this is also the blood level where risk of venous thromboembolism (blood clot to the leg or lung) increases.
7. There is little data regarding the risks or benefits of discontinuing long-term low or ultra-low dose hormone therapy at or after age 65.
8. **Ospemifene** (Osphena®) 60 mg daily, get 30 pills for $248 at retail pharmacies, coupons available. Ospemifene is a synthetic estrogen receptor agonist/antagonist and is taken by mouth once a day to treat genitourinary syndrome of menopause/vulvovaginal atrophy. There are not many females who are good candidates for this medication. It is intended for use in postmenopausal females without a uterus who are at low-risk for blood clots to the leg or lung (known as venous thromboembolism (VTE)). Females at low-risk for VTE are slender, non-smokers with normal blood pressure and an active lifestyle. If such a female can’t or won’t use vaginal or transdermal estrogen or DHEA products for genitourinary syndrome of menopause/ vulvovaginal atrophy, she might want to consider ospemifene. However, ospemifene increases the risk of VTE, while the other options listed above don’t increase VTE risk.

For corrections and additions, please contact Erin Sullivan Wagner using the contact tab at [www.allofmeiowa.org](http://www.allofmeiowa.org).

1. North American Menopause Society Position Statement on Continued use of Systemic HT after age 65. Menopause 2015;22:693 [↑](#footnote-ref-1)
2. American College of Obstetrics and Gynecology, Committee Opinion 565, June 2013, reaffirmed 2020, Hormone therapy and heart disease. [↑](#footnote-ref-2)
3. Stuenkel CA et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(11):3975-4011 [↑](#footnote-ref-3)
4. See tables in University of Iowa Menopause and Sexual Health Clinic Protocols 2014, at [www.allofmeiowa.org](http://www.allofmeiowa.org), Resources for Providers, Best Practices, or comparison of various products. [↑](#footnote-ref-4)
5. Santen RJ, et al. Systemic estradiol levels with low dose vaginal estrogens. Menopause 2020;27(3):361-70. [↑](#footnote-ref-5)
6. Barton DL, et al. Systemic and local effects of vaginal DHEA: NCCTG N10C1 (Alliance). Support Care Cancer 2018;26(4):1335-43. [↑](#footnote-ref-6)