This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist’s practice. Recognized experts in the field provide their opinions and practical advice. Gloria Bachmann, MD, the Editor of Menopause e-Consult, encourages your suggestions for future topics. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Bachmann.

**Question:**
What is the current evidence on the use of intravaginal dehydroepiandrosterone (DHEA) in urogenital atrophy and sexual function?

**Commentary by:**

![Susan R. Davis, MBBS, FRACP, PhD](image)

Sex steroids are vital for the integrity of the urogenital tract (vagina, vulva, lower urinary tract, and supporting pelvic structures). These tissues are rich in estrogen and androgen receptors. In addition, estrogen and testosterone enhance blood flow to the genital tract, which is fundamental for genital sexual arousal and lubrication.

The fall in estrogen at menopause and the gradual decline in androgen levels with age result in what is now described as genitourinary syndrome of menopause (GSM). This includes vulvovaginal atrophy (VVA) and an increase in vaginal pH. At a cellular level, there is a reduction in healthy vaginal epithelial superficial cells and an increase in parabasal cells. The increase in vaginal pH changes the vaginal microflora. Lactobacilli disappear, and as a consequence, there is increased vulnerability to vaginal infection. Symptoms of VVA include vaginal dryness, irritation, itching, infection, and dyspareunia. This in turn leads to diminished sexual desire, arousal difficulties, diminished physical and emotional sexual satisfaction, and relationship issues.

Most postmenopausal women will experience some GSM symptoms. Symptoms of VVA can be effectively treated with either vaginal or systemic estrogen therapy. Estrogenization will thicken and revascularize the vaginal epithelium, lower vaginal pH, and normalize vaginal flora. The number of vaginal epithelial superficial cells will increase. Although data show that vaginal estrogen acts locally, thus minimizing systemic exposure to estrogen, some studies have shown blood estradiol levels increase with vaginal application. A 2- to 5-fold increase in serum estradiol has been reported after 1 week of vaginal administration of a 25 µg estradiol vaginal tablet or 1 g of 0.625 mg conjugated estrogen cream. After 24 weeks of treatment, only 2% of women have estradiol levels outside the postmenopausal range.

Researchers have looked for alternative approaches for GSM management. In postmenopausal women, adrenal DHEA is an important precursor for extragonadal biosynthesis of estrone (by aromatization) and testosterone (by 5-alpha reduction).
Casson and colleagues first studied the effects of a vaginal DHEA 150 mg pessary versus placebo in five premenopausal women as a mode of hormone delivery and reported an increase in blood levels of DHEA with this approach. The daily vaginal application of three different doses of DHEA cream (6.5 mg, 13 mg, and 23.5 mg) was studied for 1 week in postmenopausal women. Labrie and colleagues reported a decrease in vaginal pH, an improvement in the vaginal cell maturation index, and restoration of DHEA levels to the range for premenopausal women at the highest dose. The circulating levels of other sex steroids remained within the normal range for postmenopausal women.

A randomized, controlled trial of the daily application of three different doses of vaginal DHEA ovules (3.25 mg, 6.5 mg, or 13 mg) was studied over 12 weeks in 218 postmenopausal women who met the entry criterion of dyspareunia. This single study has resulted in a number of publications to support the efficacy of this treatment for VVA. In these various publications, the investigators have reported an improvement in vaginal cytology and a reduction in pH. An analysis restricted to the women who fulfilled investigational criteria for a low percentage of vaginal epithelial cells and vaginal pH greater than 5 reported an increase in superficial cells and a reduction in pH, with an associated improvement in dyspareunia compared with placebo. Sexual function was assessed by three questions in the Menopause Quality of Life Questionnaire (sexual desire, vaginal dryness during intercourse, or avoiding intimacy) and by the Abbreviated Sexual Function Questionnaire. At 12 weeks, the total Menopause Quality of Life Questionnaire sexual domain score showed a significantly greater response for each treatment group versus placebo, with more mixed findings in the Abbreviated Sexual Function Questionnaire.

The main limitation in interpreting the data on DHEA as a treatment for VVA and associated sexual function is that the clinical findings to date are all from a single 12-week study. This study was analyzed as intention to treat, with the last observation carried forward for women who dropped out of the trial. Unfortunately, the publications have reported neither how many women actually completed the 12-week trial in each group nor the extent of missing data for each time point. The effects in terms of improvement in the study overall are interesting, as is the reported complete lack of absorption of the administered DHEA or change in blood levels of the metabolites. Considering how well drugs are absorbed through the vaginal mucosa, this is reassuring but also surprising.

It is biologically plausible that DHEA may alleviate VVA and hence reduce dyspareunia because the DHEA effects are likely to be mediated by local metabolism to estrone and testosterone. Thus, vaginal DHEA can be considered a promising treatment alternative, but further large studies are needed to confirm efficacy and safety. Ideally, these studies should evaluate less frequent self-administration of the DHEA ovule, because most women would find the need to self-treat on a daily basis unacceptable.

**Disclosure:** Dr. Davis reports: Consultant/Advisory Board: Trimel Pharmaceuticals. Grant/Research Support: Lawley Pharmaceuticals, Besins Healthcare.

**References**


**Case:**
A 66-year-old woman with a history of vaginal mesh placement for anterior wall (bladder) prolapse and stress urinary incontinence presents with painful intercourse, spotting, and noticeable foreign body in the anterior vault. Mesh erosion is suspected. How should you proceed?

**Management Issues by:**

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The use of vaginal mesh for repair of pelvic organ prolapse increased from 8% of US surgical cases in 2000 to a high of 32% of cases in 2006. An initial US Food and Drug Administration (FDA) public health notification regarding complications of vaginal mesh was released in 2008, followed by a second update in 2011 on serious complications specifically concerning vaginal mesh for prolapse. After a public hearing of the Obstetrics and Gynecology Devices Panel in September 2011 on the topic of vaginal mesh, FDA issued 522 orders requesting additional safety and effectiveness outcome data on vaginal mesh devices. Several manufacturers of trocar-guided vaginal mesh implants ceased device manufacturing, and class-action lawsuits ensued. The Pelvic Floor Disorders Registry was developed by FDA to satisfy the
requested postmarket surveillance on the remaining vaginal mesh products.

In this particular case, a careful history and physical examination is necessary. Questions to ask this patient include

1. What were your symptoms before surgery?
2. What surgery was performed?
3. Do you have the operative report, and do you know the name of the mesh used for repair of prolapse (vaginal mesh) and stress incontinence (sling)?
4. Are you experiencing any of the following symptoms:
   - **Urinary:** Stress urinary incontinence, urgency urinary incontinence, frequency, voiding difficulty, overactive bladder symptoms, urinary tract infections, blood in the urine, continuous leakage.
   - **Bowel symptoms:** Fecal urgency, fecal incontinence, diarrhea, constipation and need for manual splinting of the posterior vagina to have bowel movements.
   - **Sexual:** Pain with initial penetration or deep penetration, partner-related pain.
   - Other vaginal discharge, bleeding, and pain in the pelvis or thigh region.

The physical exam should include inspection of the thighs, perineum, vulvar vestibule, and vaginal epithelium. Be certain to carefully inspect the region of the midurethra and behind the pubic bone (retropubic sling), as well as the vaginal sulci (transobturator sling), for any exposed mesh fibers. Careful inspection of the entire anterior, apical, and posterior epithelium is necessary. Vaginal pH check and possible wet prep or culture for any abnormal discharge can also be performed. The degree of vaginal and vulvar atrophy should be assessed. If mesh exposure is clearly noted, document the location and size of the exposure(s).

Bimanual exam should then be conducted to palpate any masses and confirm the areas of exposed mesh, as well as areas of tenderness around the mesh and vaginal sidewall, especially if a trocar-based vaginal mesh delivery system was used. Palpate obturator and levator muscles and document any discreet areas of myofascial pain and mesh bands or other areas of pinpoint tenderness. Palpate any pelvic or adnexal masses and conduct a rectal examination to confirm absence of mesh erosion into the rectum or any ischioanal fossa masses or fullness. If the patient cannot tolerate a speculum or bimanual examination, then vaginoscopy using a lighted cystoscope with 30-degree lens or hysteroscope also can be very useful. In-office cystourethroscopy can be performed to ensure no mesh erosion in the urethra or bladder.

In this case, vaginal mesh exposure is noted in the mid-apex and anterior vagina. The diameter is 3 cm, and a fold or penetration of mesh is palpated. The patient has severe vaginal atrophy, and the exposed area by the vaginal cuff is tender on palpation without tenderness noted by mesh arms. Cystoscopy failed to reveal any urethral or bladder mesh erosion, no fistula is detected, and both ureteral orifices effluxed clear urine.

The patient opted for surgical excision. Review of the operative report reveals type 1 polypropylene trocar-based mesh was used for the prolapse repair, and a retropubic synthetic sling was placed. The size of the mesh exposure and the fold of mesh penetrating through the vaginal epithelium suggest that conservative management with just local estrogen and in-office trimming will not be effective, because those conservative techniques are better for small exposures (<0.5 cm). The patient was taken to the operating room and, under anesthesia, the exposed area was infiltrated with a local anesthetic with epinephrine (which helps provide hydrodissection and hemostasis). Good lighting and exposure using appropriate self-retaining or other retractors, as well as long, fine instruments, are mandatory.

The epithelium at the edge of the exposed mesh was incised with a scalpel and
undermined circumferentially using Metzenbaum scissors around the exposed mesh to provide a tension-free closure. Sharp dissection was used to completely excise the exposed mesh. Reapproximation of the vaginal epithelium with interrupted, delayed, and absorbable sutures was performed, with care taken to avoid vaginal stenosis. Cystoscopy confirmed bladder and ureteral integrity after the mesh excision. The patient was discharged the same day.

According to a 2013 Cochrane review of prolapse surgery, the vaginal mesh exposure rate is estimated to be as high as 18%, with 50% of mesh exposure cases requiring surgical correction. In one multicenter study on the management of 347 patients presenting with mesh-related complications, more than 60% of women required more than two interventions to treat the complication.

This patient has a good prognosis and should be instructed to use local vaginal estrogen and be monitored for recurrence of prolapse and mesh exposure. Excision of the entire mesh may be necessary for complete relief of symptoms in cases of large mesh exposure, recurrent mesh exposure, fistula, pain, or mesh infection.

Disclosure: Dr. Iglesia reports: none.

References

What are your clinical challenges with DHEA? Post on our Member Forum (www.menopause.org/member-login?ReturnUrl=%2fforum) to discuss this and the rest of the papers from October Menopause e-Consult.