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Time to advocate for better science, and better treatments for women

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As women's health researchers and care providers we enthusiastically support the goal of having multiple effective, well-tolerated, affordable treatment options for genitourinary syndrome of menopause (GSM). We also advocate that there be strong evidence as a basis for recommendations for individual treatments, and a better understanding of the pathophysiology underlying symptoms. Topical vaginal hormonal therapies like estrogen or prasterone, selective hormone receptor agonists such as ospemifene, and vaginal moisturizers and lubricants all work for some women some of the time. However, data show the majority of women do not continue to use topical estrogen medications after an initial trial.¹ In the recent Vaginal Health Trial completed by the MsFLASH network, we found that neither a low dose vaginal estrogen tablet nor a vaginal moisturizer had greater efficacy than dual placebo (gel and tablet) in reducing the severity of the most bothersome symptom (MBS),² though on average symptoms improved in all 3 arms. Only 50% of women in our study reported "mild" or "no" symptoms at the end of the trial, suggesting significant room for improvement. New therapies are needed that target the pathophysiologic process responsible for symptoms.

What is the underlying pathophysiology of GSM?

An assumption in the field is that because symptoms occur after the menopause-associated drop in systemic estrogen, and because topical estrogen reduces symptom severity in some women, that lack of estrogen stimulation of the epithelium is the source of GSM symptoms. However, all postmenopausal women have a decrease in systemic estrogen and only half have GU symptoms. Why? There is little evidence to support a consistent biologic phenotype in women with vulvovaginal symptoms versus those without.³ In cross-sectional studies, the vaginal microbiome composition has not correlated with the presence of moderate-severe vulvovaginal symptoms,^{4,5} though *physical findings* of vaginal "atrophy" (pallor, loss of rugae, and friability) have been associated with lower prevalence of vaginal *Lactobacillus*.⁶

An objective measure of vaginal estrogenization, the vaginal maturation index (VMI), a weighted score of superficial, parabasal and intermediate vaginal epithelial cells in a vaginal wall scraping, has long been considered an important outcome measure for studies of

medications to treat postmenopausal vaginal discomfort.⁷ This measure increases with topical estrogen treatment,^{7,8} but also after treatment with vaginal oxytocin,⁹ vaginal hyaluronic acid,¹⁰ and oral ospemifene.¹¹ In many studies, changes in physical findings, vaginal symptoms and VMI occur concurrently, which has led to an assumption of causal association.^{8,10,11} However, VMI is not correlated with report of pain with sex,⁷ and physical findings of “atrophy” are also poorly correlated with report of vaginal symptoms in general cohorts of postmenopausal women.^{3,12}

What is the appropriate outcome measure for efficacy of GSM interventions?

One critical question is: what is the appropriate outcome, the “objective” findings of pH and VMI or the “subjective” findings of symptom severity? The FDA has chosen symptom severity – either whichever symptom is most bothersome for a given woman,¹³ or the severity of a common symptom such as dyspareunia or dryness.¹⁴ We agree that since the treatment goal is to improve quality of life, symptom severity is the most meaningful outcome. In the recent MsFLASH Vaginal Health Trial, we asked separately about general vaginal or vulvar pain/soreness and pain with any type of vaginal penetration (we did not specifically assess introital pain). We also asked about severity of dryness, discharge, irritation, and itching. Participants chose pain with sex or vaginal dryness as the two most common bothersome symptoms over all the other options. The magnitude of decrease in most bothersome symptom severity was similar to previous trials of topical vaginal estrogen, ospemifene and prasterone, whether the trial evaluated any MBS or specifically an MBS of dyspareunia (Table 1). The biggest difference between the MsFLASH trial and other trials that showed benefit for vaginal estrogen in the most bothersome symptom is the magnitude of the placebo effect, suggesting that the hydroxyethylcellulose gel placebo may have had some therapeutic benefit – and that there was no additional benefit from vaginal estrogen beyond the placebo gel effect.

What is a clinically meaningful benefit?

Another important question to be answered is: what difference on a scale of 0–3 is clinically meaningful? The MsFLASH Vaginal Health Trial was powered to see a 0.5 point difference in the change in symptom severity between arms, a difference we deemed clinically meaningful. Most previous trials, regardless of agent or dose (outlined in Table 1), showed an average 0.3–0.4 point difference between active and placebo arms. Although each showed statistical significance, is this small difference clinically valuable to patients? Perhaps small magnitude changes are functionally important – secondary findings from the MsFLASH trial show that more women in the estradiol arm felt that they had a “meaningful benefit.” Although FSFI (which asks about arousal, orgasm, satisfaction, lubrication and pain) was not statistically different between arms, the MENQOL sexual function domain (which asks about dryness and desire) showed a small but significantly better improvement in the estradiol arm vs. placebo. Perhaps a categorical measure is a better way to assess functional improvement? Over half of women in each arm had a decrease in MBS severity of 50% or more: 70% in the estradiol arm, 54% in the moisturizer arm, 65% in the dual placebo arm.

However, even if a therapy provides relief initially, data show that 12 months after receiving a prescription for low dose vaginal estrogen fewer than half (42%) of women prescribed vaginal tablets and a dismal 10–14% of those prescribed vaginal creams were still using them,²¹ suggesting that whatever the initial benefits, other considerations loom larger in determining long term patient preferences and adherence.

When do GSM intervention effects typically plateau, i.e. how long does the trial have to be?

Most trials of medication to treat postmenopausal vaginal dryness or dyspareunia randomize women to 12 weeks of treatment, and measure primary outcomes at 12 weeks. However, many argue that with low dose vaginal estradiol, longer use leads to greater benefit, and thus trial duration should be extended to see maximum benefit. There are few data supporting this assertion. In an open label follow-up studies of 102/230 (44%) participants in 12-week randomized trial of a 25mcg vaginal tablet there was no additional improvement between 12 and 52 weeks (Figure 1).²² In the single one year randomized trial of 25mcg vaginal estradiol tablets vs. placebo in 1612 women, the most benefit was seen between 0 and 16 weeks, while additional decrease in symptom severity between 16 and 52 weeks is similar in both placebo and active arms (Figure 1).²³ Comparative efficacy studies with two different estrogen arms that evaluate outcomes at 12 and 24 weeks also demonstrate no additional improvement in symptom severity between those time points.^{24–26} Alternatively, some suggest more frequent, off-label dosing of the 10mcg vaginal estradiol tablet to increase local exposure. The few, low-quality comparative studies assessing relative efficacy of different estrogen formulations and dosages (reviewed by Lethaby et al.) demonstrated minimal variation in efficacy between very low dose treatments such as tablet or ring, and higher dose treatments such as vaginal creams.²⁷

Cost – it matters to the patient and to our health care system

Finally, we come to the (literally) million-dollar question: cost. When women are asked to pay higher and higher out of pocket costs for vaginal estrogen products, is there a respectively greater benefit to these therapies than non-hormonal options? Here, data are scarce. Prior to the MsFLASH Vaginal Health Trial, few studies had evaluated the efficacy of vaginal moisturizers like Replens^{28–30}; two of these, including one randomized crossover trial in breast cancer survivors, demonstrated no difference between placebo and moisturizer products, though both decreased symptom severity.^{31,30} One non-randomized study showed no difference between estrogen cream and moisturizer at 4 weeks, though symptoms decreased further by 12 weeks in women using estrogen but not those using vaginal moisturizer.²⁸ Manufacturers of vaginal moisturizing products promote “mucoadhesive” properties due to proprietary ingredients, but our data showing no difference between Replens and simple hydroxyethylcellulose gel suggest these claims are not scientifically based. In a recent Cochrane Review, the bulk of the data for vaginal estrogen products demonstrated a significantly greater decrease in symptom severity compared to placebo.²⁷ No trials had a placebo gel like that used in the MsFLASH trial, thus few conclusions can be drawn about the relative benefit of estrogen creams or rings vs. a vaginal gel placebo. Since

the magnitude of symptom severity reduction in our estradiol arm was comparable to that in many other trials, one might hypothesize that the larger placebo response seen with the hydroxyethylcellulose gel might have rendered those trials non-significant as well.

Conclusions

Our goal as women's health providers should be to provide safe, cost-effective treatment to our patients. The conclusion we draw from our results is that for many women, a cheap over-the-counter gel might provide as much symptom relief as a \$200/month prescription medication. However, as clinicians we know that one must treat the individual patient in the office – and that not all products are right for all patients. This holds as true for estrogen as it does for non-hormonal options. In the editorial accompanying the MsFLASH results, Drs. Huang and Grady state: "...this longstanding therapeutic focus on vaginal estrogenization may be misplaced given the absence of clear data to support the superiority of estrogen-based treatments in symptom control. While decline in estrogen levels is an established contributor to the development of vulvovaginal atrophy, multiple studies have shown that tissue-specific markers of vaginal estrogenization such as vaginal cellular maturation or pH are only modestly correlated with the severity, bothersomeness, and impact of vulvovaginal symptoms." The results of the MsFLASH Vaginal Health Trial should serve as a call to action: we need more and better studies of the pathophysiology underlying postmenopausal vaginal discomfort, and we need well designed clinical trials to guide choices for cost effective targeted therapies with substantial clinically meaningful benefit for GSM.

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Figure 1.

Change in symptom severity of a composite score of vulvovaginal symptoms (dryness, dyspareunia, itching, soreness) after treatment with 25mcg vaginal estradiol tablet over 52 weeks.

Table 1

Comparison of magnitude of symptom improvement between active and placebo arms of treatments for postmenopausal vaginal discomfort.

	Agent	Outcome	Active arm	Placebo arm	Statistically significant?
Mitchell 2018 (n = 302) ²	10 mcg vaginal estradiol tablet ^a	MBS (any)	-1.4	-1.3	No
Kroll 2017 (n = 550) ¹⁵	0.003% vaginal estradiol cream	MBS (dyspareunia)	-1.5	-1.2	Yes
Constantine 2017 (n = 764) ¹⁶	10 mcg vaginal estradiol softgel	MBS (dyspareunia)	-1.69	-1.28	Yes
Labrie 2016 (n = 558) ¹⁷	Prasterone 0.5% vaginal suppository	MBS (dyspareunia)	-1.42	-1.06	Yes
Bachmann 2010 (n = 826) ¹⁸	60mg ospemifene oral tablet	MBS (dyspareunia)	-1.19	-0.89	Yes
Freedman 2009 (N = 305) ¹⁹	1g vaginal estrogen cream	MBS (any)	-1.71	-1.1	Yes
Simon 2008 (n = 309) ²⁰	10 mcg vaginal estradiol tablet	MBS (any)	-1.23	-0.87	Yes

^aPlacebo arm in this trial included both twice weekly vaginal placebo tablet and three times a week vaginal hydroxyethylcellulose gel