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## Treating Vulvovaginal Atrophy/Genitourinary Syndrome of Menopause: Lubricants, Moisturizers, and Vaginal DHEA

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 Past Chairman, British Menopause Society  
 Immediate Past Co-Editor in Chief, Climacteric

With thanks to Dr David Edwards

### Disclosures

- I have lectured and acted as an advisor for a number of pharma companies including
- Abbott
- Bayer
- Besins
- MSD
- Mithra
- Mylan
- Novo Nordisk
- Pfizer
- SeCur
- Shionogi

**VVA is a tale of neglect!**

CLIMACTERIC 2014;171-2

Editorial

**Vulvovaginal atrophy – a tale of neglect**

*Nick Panay and Anna Ferrus*

EDITORS-IN-CHIEF

The impact of vulvovaginal atrophy (VVA) on quality of life continues to be underestimated according to an expert review published in this issue of *Climacteric*<sup>1</sup>. The reasons for this are multiple and complex. Women are reluctant to complain about the problem for risk of personal embarrassment and for social and cultural reasons. Health-care providers are reluctant to bring the problem up in consultation because they are uncomfortable discussing sexual issues and for fear of triggering extensive complex dialogue with limited time to deal with the consequences; they also lack knowledge as to the available effective treatment options, both hormonal and non-hormonal. Even though we have an aging population adaptation of a dermatology quality-of-life scale<sup>2</sup>. However, by the admission of the authors of the paper, there is considerable work still to be done. The ultimate goal must be to devise a practical, validated questionnaire which accurately assesses the impact of VVA symptoms on personal, social and professional aspects of quality of life.

Despite guidelines issued by the International Menopause Society and other societies<sup>3,4</sup>, there continues to be confusion regarding key issues in the use of local oestrogen therapy, particularly in primary care. Unfounded concerns are often raised, despite these issues having been clarified by the society recommendations. The most commonly raised concerns include:

GSM, genitourinary syndrome of menopause  
VVA, vulvovaginal atrophy

**NICE** National Institute for  
 Health and Care Excellence

**NEW MENOPAUSE GUIDELINES – NG23**

**Nick Panay**  
 Menopause - Guideline Development Committee Member

- In the recently published NICE Guidelines for menopause, one of the recommendations for the treatment of urogenital atrophy is:

**“Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen”**

## Vaginal health: practical recommendations

- A practical guide: effective management of vaginal health in postmenopausal women with VA
- Reflecting a global consensus of independent experts - the 'Who's Who' of vaginal health
- Each section is accompanied by a key practice point
- [http://www.imsociety.org/ims\\_recommendations.php](http://www.imsociety.org/ims_recommendations.php)\*



\*Accessed September 2017

Sturdee DW, Panay N et al. *Climacteric* 2010;13(6):509-522

VA, vaginal atrophy

## Vaginal dryness

- Vaginal dryness can affect women of all ages, but is very common during and after the menopause
- Dryness is one of many symptoms reported as a result of VA or VVA

Edwards D and Panay N. *Climacteric* 2016;19(2):151-161  
Sturdee DW et al. *Climacteric* 2010;13(6):509-522

## What causes vaginal dryness?



## Estrogen

- Plays a key role in maintaining the normal vaginal environment
- Stimulates proliferation of *Lactobacilli*, reduces pH and prevents colonisation of Enterobacteriaceae
- The menopause can reverse this situation with decreasing estrogen levels

Edwards D and Panay N. *Climacteric* 2016;19(2):151-161  
Sturdee DW et al. *Climacteric* 2010;13(6):509-522

### Vaginal dryness

- Is associated with painful intercourse
- Affects about half of all women at some point in their lives
- Inadequate lubrication is a common cause of dyspareunia: recurrent or persistent pain with sexual activity causes marked distress, but...

Sutton KS et al. *J Sex Med* 2012;9(1):240-250  
Jamieson DJ and Steege JF. *Obstet Gynecol* 1996;87(1):55-58

### Vaginal dryness

- ...many women, who are not sexually active, can also benefit from using vaginal moisturizers in addition to or instead of estrogen, when estrogen is contraindicated or not desired<sup>1</sup>
- Can be a factor associated with erectile dysfunction in the sexually active couple<sup>2</sup>

1. Edwards D and Panay N. *Climacteric* 2016;19(2):151-161  
2. Nappi RE et al. *J Sex Med* 2013;10(9):2232-2241

### Expectations

- Women are expected, and in general expect themselves, to produce a moderate amount of vaginal lubrication during sex
- Women themselves report that they prefer vaginal-penile intercourse to feel wetter
- Women are more easily orgasmic when sex is wetter
- Women believe their partner prefers sex to feel more wet than dry

Edwards D and Panay N. *Climacteric* 2016;19(2):151-161

### The importance of reduced or lack of lubrication

- Can affect many women some of the time
- Ask about drug history
- There are many types of lubricants
- Beware of 'stimulating lubricants' which may contain irritating ingredients
- If you don't ask, women often won't volunteer the information!

## Composition of moisturizers and lubricants varies – so does efficacy!

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http://dx.doi.org/10.1111/clm.12107



REVIEW

OPEN ACCESS

Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition?

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### ABSTRACT

Vaginal dryness is a common condition that is particularly prevalent during and after the menopause, and is one of the symptoms of vulvovaginal atrophy/genitourinary syndrome of menopause. The impact of vaginal dryness on interpersonal relationships, quality of life, daily activities, and sexual function can be significant, but is frequently underestimated. Furthermore, barriers exist to treatment seeking, and this condition is often underreported and undertreated. Greater education about vaginal dryness and the range of available treatments is essential to encourage more women to seek help for this condition.

Personal lubricants and moisturizers are effective at relieving discomfort and pain during sexual intercourse for women with mild to moderate vaginal dryness, particularly those who have a genuine contraindication to estrogen, or who choose not to use estrogen. However, there is a distinction between lubricants and moisturizers, and notable differences between commercially available products. Women should be advised to choose a product that is optimally balanced in terms of both osmolality and pH, and is physiologically most similar to natural vaginal secretions. A series of recommendations for the use of vaginal lubricants and moisturizers, either on their own or in combination with systemic or topical hormone replacement therapy, is presented.

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Edwards D and Panay N. *Climacteric* 2016;19(2):151–161

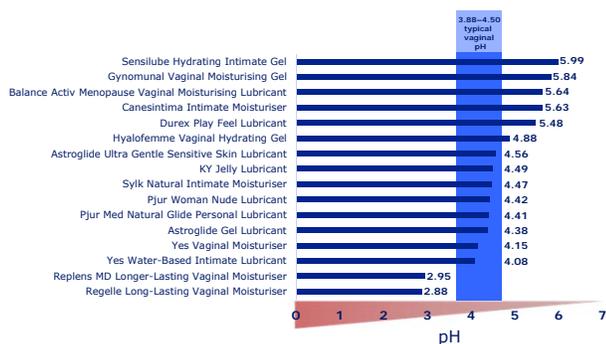
## pH

- In healthy women vaginal pH is 3.8–4.5
- Vaginal environment, altered by lubricants with pH>4.5, may lead to recurrent UTIs, thrush and BV
- Animal studies suggest that pH≤3 are unacceptable for human use

Edwards D and Panay N. *Climacteric* 2016;19(2):151–161

BV, bacterial vaginosis  
UTI, urinary tract infection

## pH of products available in the UK

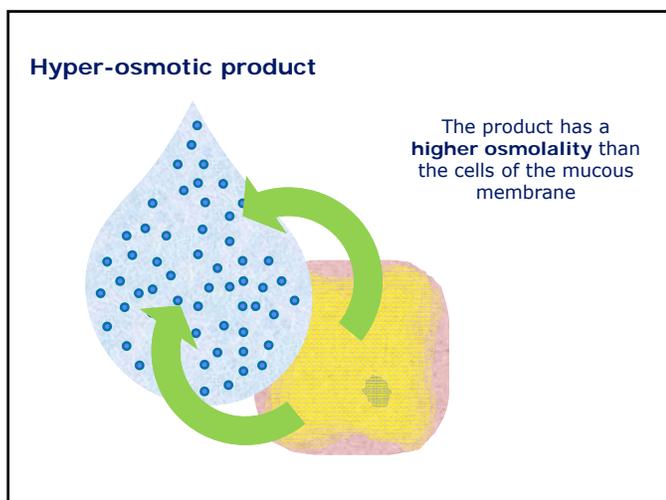
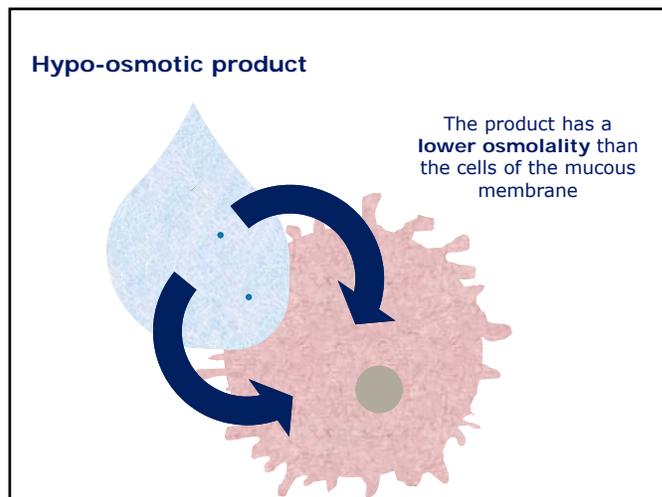
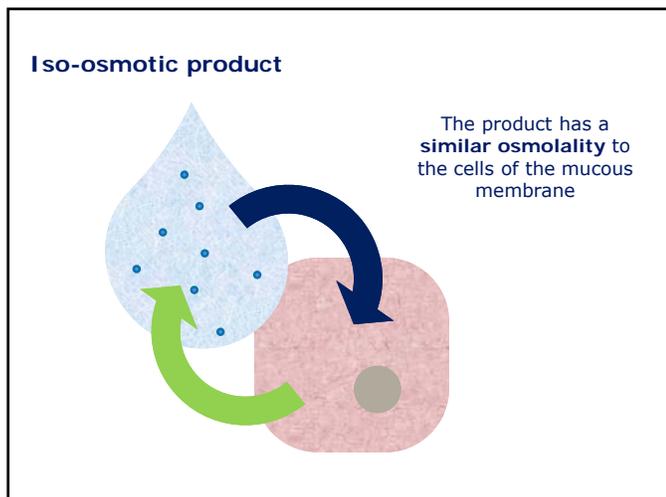


Edwards D and Panay N. *Climacteric* 2016;19(2):151–161

Not all products available  
over the counter

## Osmolality

- The measure of dissolved particles per unit of water in a solution, measured in mOsm/kg
- The osmolality of a lubricant is important because the epithelial layer and the body's natural mucus are constantly trying to maintain an equilibrium of water pressure; water flows freely through the cell walls of non-keratinised epithelium and mucus



#### Links between osmolality, pH and cytotoxicity of lubricants

- Some lubricant ingredients are associated with detrimental biological effects
- Hence, care needs to be taken when choosing lubricants, especially in specific situations such as women trying to conceive or those at risk of STIs

### *Arion lusitanicus*



### Slug mucosal irritation assay

- Is a sensitive measure of mucous membrane's tolerance to vaginal preparations
- Slugs were tested with lubricants over 5 days to quantify mucus production and tissue damage
- Each product could then be assigned an irritant potency category: none, mild, moderate and severe

Adriaens E and Remon JP. *Sex Transm Dis* 2008;35(5):512-516

### So what... that's in slugs! What about humans?

- *In vitro* incubation of sperm with hyperosmolar lubricants led to loss of motility and DNA integrity
- Also caused damage to epithelial cell lines and cervical and colorectal cultures<sup>1</sup>
- In humans, hyperosmolar lubricants applied rectally cause significant damage and denudation of the epithelium<sup>2</sup>
- Research has shown the following results...

1. Dezzutti CS et al. *PLoS One* 2012;7(11):e48328  
2. Fuchs EJ et al. *J Infect Dis* 2007;195(5):703-710

### Osmolality of products available in the UK



Edwards D and Panay N. *Climacteric* 2016;19(2):151-161

Not all products available over the counter

## Excipients in lubricants

- Are paraben preservatives associated with breast tumours? ...relevance?
- Glycols and glycerine act as humectants/emollients, but can be mucosal irritants at higher concentrations (WHO advises below 9.9%)
- Both can kill *Lactobacilli*, and at low concentration glycerine/glycerol can act as a food source for *Candida*
- Microbicides can cause epithelial damage, inflammation of genital mucosa, alterations in microbiome and increased susceptibility to STI

Edwards D and Panay N. *Climacteric* 2016;19(2):151-161

## Efficacy of hyaluronic acid (HA)

Study	Treatment	Outcomes and study conclusions
Bohbot et al. (2015)	Liposomal HA	<ul style="list-style-type: none"> <li>• ↓ vulvo-vaginal dryness and pain</li> <li>• ↑ vaginal health index</li> </ul>
Chen et al. (2013)	HA gel vs estriol cream	<ul style="list-style-type: none"> <li>• <b>Both HA and estriol improve symptoms of vaginal dryness</b> (improvement rates: 84% and 89%)</li> </ul>
Ekin et al. (2011)	HA tablets vs 25µg estradiol tablets	<ul style="list-style-type: none"> <li>• Both HA and estradiol ↓ VA symptoms, atrophy and pH; ↑ VMV</li> <li>• <b>Estradiol provides greater improvement of symptoms and VMI</b></li> </ul>
Grimaldi et al. (2012)	High-molecular weight HA vs placebo	<ul style="list-style-type: none"> <li>• Both HA and placebo ↓ dryness, atrophy and erythema; well-tolerated</li> <li>• HA more effective than placebo: ↓ itchiness, burning, atrophy and erythema</li> </ul>
Morali et al. (2006)	HA + liposomes, phytoestrogens, vitamin E	<ul style="list-style-type: none"> <li>• ↓ VA symptoms: ↓ dryness, itching, burning, dyspareunia</li> <li>• Confirmed safety and patient acceptability</li> </ul>
Karaosmanoglu et al. (2011)	HA	<ul style="list-style-type: none"> <li>• ↓ VA symptoms: ↓ dryness, itching, irritation, dyspareunia</li> <li>• <b>HA effect on VMI is similar to estrogen</b></li> </ul>
Quaranta et al. (2014)	HA	<ul style="list-style-type: none"> <li>• ↓ VA symptoms: ↓ burning, dyspareunia, itchiness, dryness</li> <li>• ↑ secretion and moisture</li> </ul>
Tersigni et al. (2015)	HA + collagen, isoflavones, vitamins	<ul style="list-style-type: none"> <li>• ↓ itching, dryness, dyspareunia, dysuria, colposcopic score</li> <li>• <b>No effect on VMI</b></li> </ul>

VMI, vaginal maturation index; VMV vaginal maturation value

## Efficacy of Replens

Study	Treatment	Outcomes and study conclusions
Biglia et al. (2010)	Replens vs estradiol tablets 12.5µg or estriol cream 0.25mg	<ul style="list-style-type: none"> <li>• Estrogen: <ul style="list-style-type: none"> <li>• Improved VSS/VHI/sexual function; ↓ pH, small ↑ KI/VMI</li> <li>• No change in endometrial thickness</li> <li>• Small ↓ serum estrogen levels</li> </ul> </li> <li>• <b>Replens: transient improvement in VSS; no change in VHI/pH/KI/endometrial thickness/sexual function</b></li> <li>• <b>Both estrogen and Replens: ↓ lubrication and ↓ dyspareunia</b></li> <li>• Low-dose estrogen provides effective relief for VA symptoms; <b>Replens provide only transient benefit</b></li> </ul>
Brygdeman et al. (1996)	Replens vs Dienestrol cream	<ul style="list-style-type: none"> <li>• Both treatments: ↓ itching, irritation and dyspareunia</li> <li>• Greater ↓ dryness with Dienestrol</li> <li>• <b>No change in pH</b>, no adverse events</li> </ul>
Nachtigall et al. (1994)	Replens vs Premarin vaginal cream	<ul style="list-style-type: none"> <li>• Both treatments: ↓ VA symptoms; ↑ elasticity and moisture</li> </ul>
van der Laak et al. (2002)	Replens	<ul style="list-style-type: none"> <li>• ↓ VVA symptoms</li> <li>• Effect on vaginal cytology (↑ mean cellular area)</li> <li>• <b>No change in vaginal maturation index/value</b></li> </ul>

KI, karyopycnotic index; VHI, vaginal health index; VSS, vaginal symptom score

## Efficacy of moisturizers and lubricants

- Data on efficacy of moisturizers and lubricants suggest at least transient symptomatic relief from VA symptoms
- Moisturizers and lubricants do have a role for pre-coital lubrication and may be an alternative treatment of VA for women who do not wish to/cannot use MHT

Edwards D and Panay N. *Climacteric* 2016;19(2):151-161  
Sturdee DW et al. *Climacteric* 2010;13(6):509-522

MHT, menopausal hormone therapy

## What about topical estrogens?

- Some women do not want to use topical estrogens, especially women who have had estrogen receptor positive cancers<sup>1</sup>
- When women use topical estrogens, it is a good idea to add vaginal moisturizers and/or lubricants<sup>2,3</sup>
- Some women find that using a regular 'base coat' with an oil-based preparation and then add a water-based preparation, prevents friction and re-application of the water-based product

1. Edwards D and Panay N. *Climacteric* 2016;19(2):151-161
2. Lumsden MA. *Climacteric* 2016; 19(5):426-429
3. Sturdee DW et al. *Climacteric* 2010;13(6):509-522

## Is it ever too late to start local estrogen?

- **2016 IMS recommendations on women's midlife health and menopause hormone therapy:**
  - "Treatment should be started early, before irreversible atrophic changes have occurred, and needs to be continued to maintain the benefits"
- **Poster presentation:** The age at start of treatment for vaginal atrophy predicts response to vaginal estrogen therapy.
- (*IMS congress Prague 2016: Christine Derzko, Sebastian Rohrich, Anita Chudecka, Nick Panay*)

## Recommendations on vaginal lubricants and moisturizers, used alone or with HRT

Symptom or situation	Recommendation	Rationale
<ul style="list-style-type: none"> <li>• Urogenital atrophy</li> <li>• Elevated vaginal pH</li> <li>• Pain due to dryness</li> </ul>	<b>Vaginal moisturizer</b> <ul style="list-style-type: none"> <li>• Acidic pH (<math>\geq 3</math>)</li> <li>• Osmolality &lt;380 mOsm/kg</li> </ul>	<ul style="list-style-type: none"> <li>• Rehydrate vaginal tissues</li> <li>• ↓ vaginal pH to minimise infection</li> </ul>
<ul style="list-style-type: none"> <li>• Dyspareunia caused by urogenital atrophy</li> </ul>	<b>Vaginal lubricant</b> <ul style="list-style-type: none"> <li>• Acidic pH matched to vaginal pH</li> <li>• Osmolality &lt;380 mOsm/kg</li> </ul>	<ul style="list-style-type: none"> <li>• Lubricate dry vaginal tissues without causing irritation</li> <li>• ↓ or maintain vaginal pH</li> </ul>
<ul style="list-style-type: none"> <li>• Urogenital atrophy as a result of cancer treatment</li> <li>• HRT contraindicated</li> <li>• In combination with topical estrogen</li> </ul>	<b>Paraben-free vaginal moisturizer</b> ( <i>daily comfort</i> ) <ul style="list-style-type: none"> <li>• Acidic pH (<math>\geq 3</math>)</li> <li>• Osmolality &lt;380 mOsm/kg</li> </ul> <b>Paraben-free vaginal lubricant</b> ( <i>sexual intercourse, vaginal dilators</i> ) <ul style="list-style-type: none"> <li>• Acidic pH matched to vaginal pH</li> <li>• Osmolality &lt;380 mOsm/kg</li> </ul>	<ul style="list-style-type: none"> <li>• Rehydrate vaginal tissues</li> <li>• ↓ vaginal pH to minimise infection</li> <li>• Lubricate dry vaginal tissues without causing irritation</li> <li>• ↓ or maintain vaginal pH</li> <li>• Avoid paraben preservatives</li> </ul>

Edwards D and Panay N. *Climacteric* 2016;19(2):151-161

HRT, hormone replacement therapy

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### POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

#### Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of both vasomotor VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer duration of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic reevaluation. For bothersome GSM symptoms not relieved with over-the-counter

- "Non-estrogen therapies that improve vaginal VVA and are approved for relief of dyspareunia in postmenopausal women include ospemifene and **intravaginal DHEA**"

### Effect of intravaginal dehydroepiandrosterone (DHEA) Prasterone on VVA / Dyspareunia

#### SUMMARY

- Prasterone is a steroid indicated for Rx of moderate to severe dyspareunia, a symptom of vulvar & vaginal atrophy, due to menopause.
- Dose: One vaginal insert 6.5mg at bedtime
- Effectiveness: in moderate to severe dyspareunia, was demonstrated in two 12 week placebo-controlled efficacy trials
- ARs: Four 12-wk placebo RCTs the most common adverse reaction ( $\geq 2$  percent) was vaginal discharge.
- CI: Vaginal bleeding / Caution: Breast Cancer

### Effect of intravaginal dehydroepiandrosterone (DHEA) Prasterone on VVA / Dyspareunia

- 12/52 placebo controlled RCT 0.5 % DHEA (157) v placebo (352)
- **4 co primary endpoints**
- % parabasal cells decreased by 27.7% v placebo ( $p < 0.0001$ )
- % superficial cells increased by 8.44% v placebo ( $p < 0.0001$ )
- vaginal pH decreased by 0.66 v placebo ( $p < 0.0001$ )
- pain at sexual activity decreased by 1.42 severity score from BL or 0.36u v placebo ( $p = 0.0002$ )

### Effect of intravaginal dehydroepiandrosterone (DHEA) on the female sexual function in postmenopausal women: ERC-230 open-label study.

- Long-term effect of 52-week treatment with daily intravaginal 0.50% (6.5 mg) DHEA was evaluated
- Various domains of female sexual function using the FSFI questionnaire at baseline, Week 26 and Week 52.
- FSFI domains desire, arousal, lubrication, orgasm, satisfaction and pain were increased by 28%, 49%, 115%, 51%, 41% and 108%, respectively ( $p < 0.0001$  for all parameters) at 52 weeks vs. baseline

Bouchard C, Labrie F, Derogatis L et al Horm Mol Biol Clin Investig. 2016 Mar;25(3):181-90.

### Effect of intravaginal dehydroepiandrosterone (DHEA) on the female sexual function in postmenopausal women: ERC-230 open-label study.

- Serum levels of DHEA and all its metabolites, including estradiol and testosterone, showed no meaningful change
- Possible stimulatory effect of intravaginal DHEA through a local action, in agreement with the preclinical data
- ?Androgens made locally from DHEA in the vagina induce an increase in local nerve density.

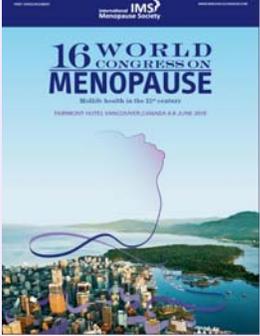
Bouchard C, Labrie F, Derogatis L et al Horm Mol Biol Clin Investig. 2016 Mar;25(3):181-90.

## Conclusions

- **Vaginal moisturizers and lubricants are not merely a quick fix ... but not a cure for VVA!**
- Moisturizers and lubricants can provide relief from the symptoms, but local estrogen therapy can address the underlying pathology of VVA
- Intravaginal DHEA (Prasterone) provides an effective option for women with dyspareunia due to VVA and can improve Female Sexual Function according to clinical trials
- It is important to educate women about VVA, to ensure they can make informed treatment choices
- Women should be encouraged to report symptoms early, to avoid unnecessary suffering

International Menopause Society **IMS**  
 Promoting education and research on healthy women's lives

**Thank you for listening!**



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