Case 5 :
LOCAL VAGINAL THERAPIES

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Disclosure of Commercial Support

- This lecture has not received in kind support from any pharmaceutical companies

<u>Potential for Conflicts of Interest</u>

- I have not received any support from any pharmaceutical companies
- I do not benefit from the sale of any products that will be discussed in this program

Mitigating Potential Bias

- I have no sources of potential bias
- There is no bias as I prescribe what is most appropriate for the patient

OBJECTIVES

At the end of this presentation the participant will

- Recognize the key anatomic and physiological changes of GSM that occur as a consequence of menopausal/perimenopausal hypoestrogenism
- Appreciate the management options for GSM including nonhormonal, hormonal and new therapies on the horizon
- Formulate a therapeutic approach for this patient based on a consideration her unique needs and concerns

OUTLINE

- “CASE 5” : Our Patient Valerie
- Pathophysiology of GSM
- Management Options :
  - Non-Hormonal Treatments
  - Hormonal Therapies
- New therapies on the horizon
- Back to our patient

OUTLINE

- “CASE 5” : Introducing Our Patient Valerie

Allow me to introduce Valerie !

HISTORY:

- 48 yo G2P2 executive referred for dyspareunia & recurrent UTIs
- Avoidance of sex → problems in this new relationship
- OTC lubricants & moisturizers ineffective, some irritating
- Does not want vaginal estrogens : fears developing breast cancer .
  Mom breast Ca @ 63yo; well 10 yrs post Rx *NB she did not use any MHT)
- Non-hormonal IUCD in situ

QUESTIONS:

- What advice should she be given?
- What treatment options are available? What are their pro's & con's
- How to choose
- What about vaginal estrogens?

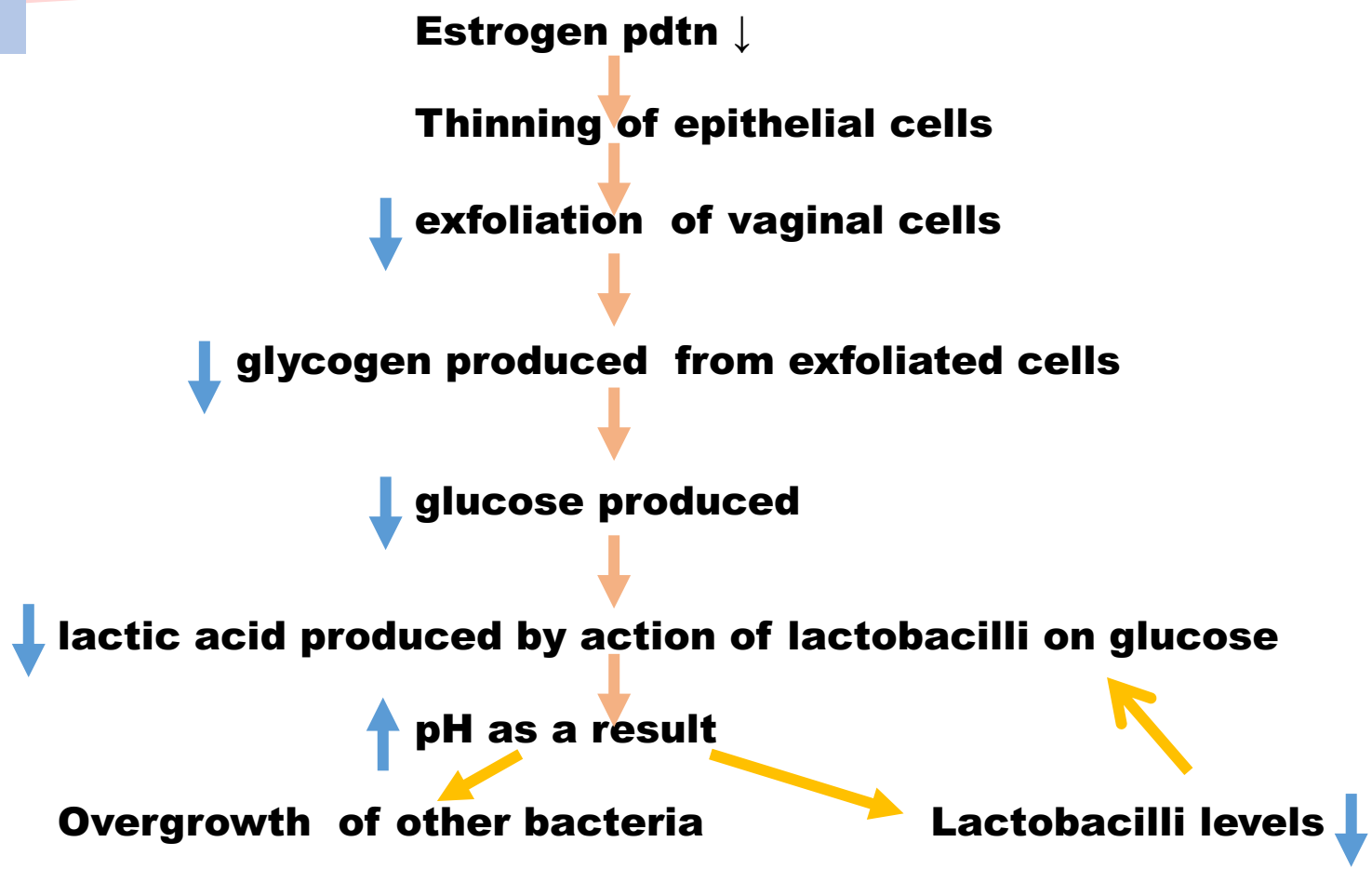
OUTLINE

- Pathophysiology of GSM

PATHOPHYSIOLOGY :

"The Cascade"

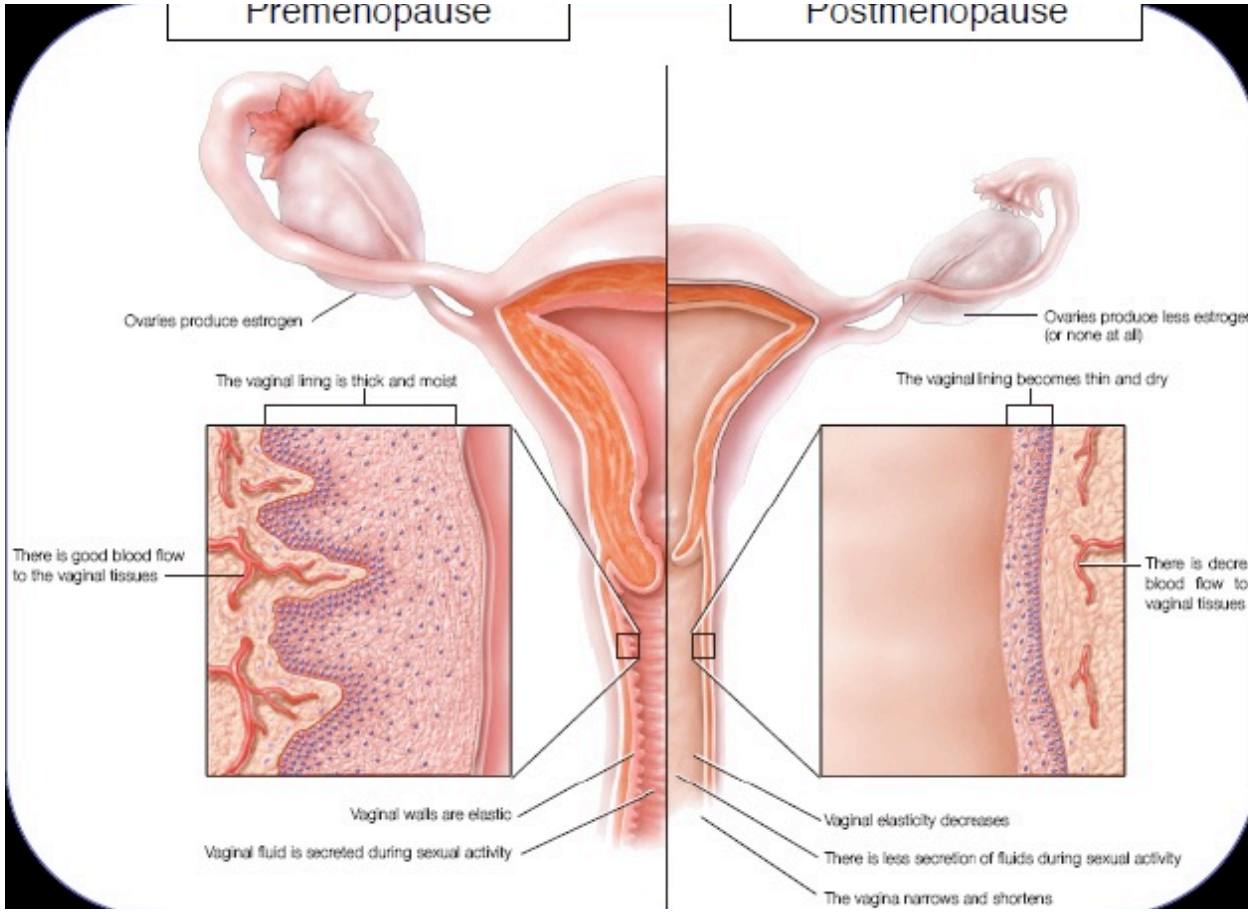
MacBride MB et al Mayo Clin Proc 2010,85:87



GSM: Clinical Presentation

Vulvo-vaginal Atrophy : Pathophysiology

Premenopause



Postmenopause

Vagina →shorter/narrower [1]

Vaginal Epithelium:
↓rugosity & elasticity

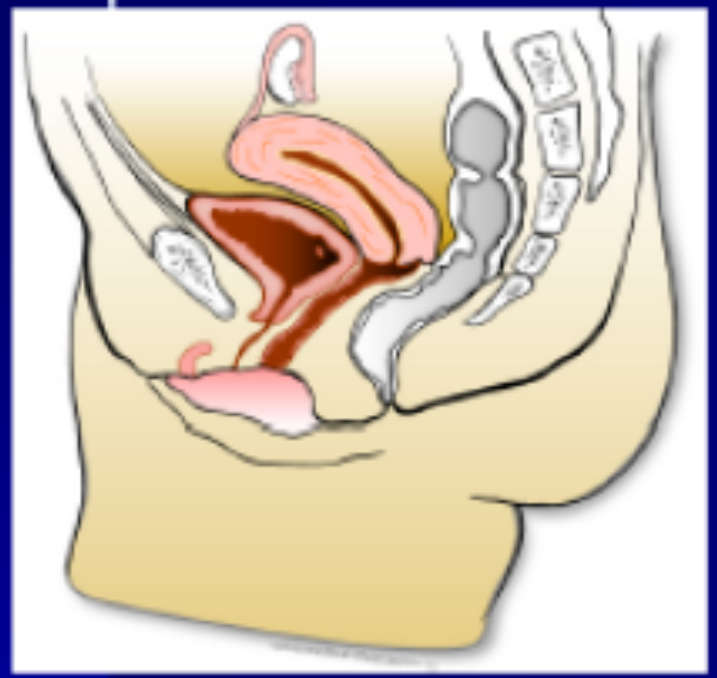
Dermis: ↑prolapse risk,
-collagen fibres fuse,
elastin fragments

Vaginal mucosa→ pale&dry [2]

Dyspareunia, a symptom of VVA,
is a medical condition that persists throughout post-menopause [3]

Johnson SL *Geriatrics & Aging 2002,5(7):9-15*

Estatrophy also affects the bladder



- Bladder urgency
- Frequency
- Recurrent UTI's

Recognizing the Symptoms of Vaginal Atrophy

- The most common vaginal atrophy symptoms reported in the IMS recommendations[1] are the same as those reported by women in the VIVA survey[2]
  - Dryness (estimated 75%)[1]
  - Dyspareunia (estimated 38%)[1]
  - Vaginal itching, irritation, discharge, pain (estimated 15%)[1]

- Urinary symptoms associated with vaginal atrophy:[1]
  - Dysuria, nocturia, and urgency
  - Urinary incontinence
  - Recurrent urinary tract infections

IMS, International Menopause Society. VIVA, Vaginal Health: Insights, Views & Attitudes.
1. Sturdee DW, Panay N. *Climacteric.* 2010;13:509-22.
2. Nappi RE, Kokot-Kierepa M. *Climacteric.* 2012;15:36-44.

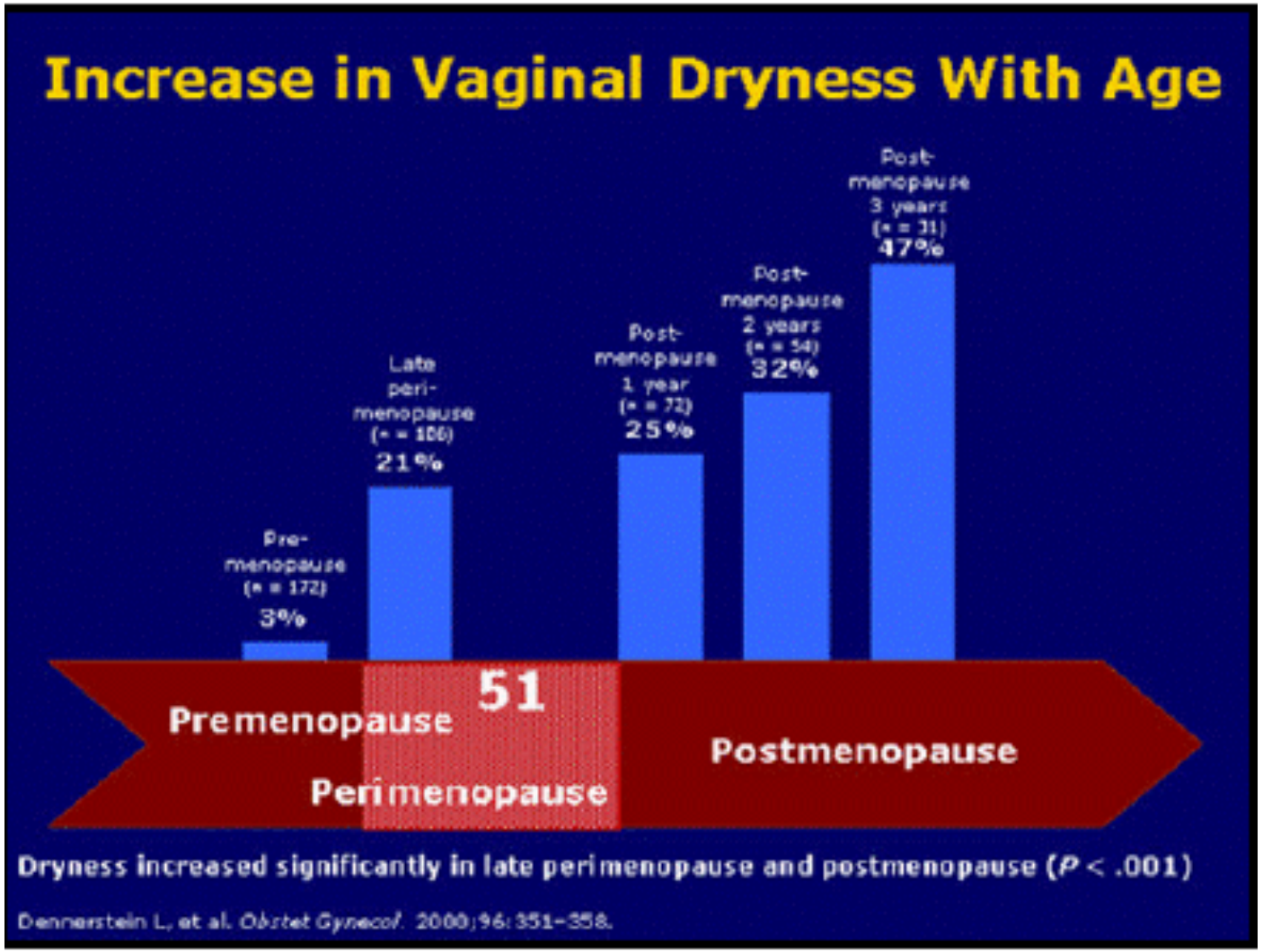
NAMS Recognizes and Commands CMS Clarification of GSM Drug Coverage (May 17, 2018)

GSM, a chronic, progressive medical condition that is the result of lowered estrogen levels in vaginal and urogenital tissue after menopause, resulting in thinning of the vaginal tissues.

At least 50% to 70% of the approximately 64 million postmenopausal women in the United States will experience symptoms of GSM.

JoAnn V Pinkerton MD, NCMP
NAMS CEO

Sheryl Kingsberg PhD
NAMS President


Increase in Vaginal Dryness With Age
Pre-menopause (n = 172) 3%
Late peri-menopause (n = 186) 21%
Post-menopause 1 year (n = 72) 25%
Post-menopause 2 years (n = 54) 32%
Post-menopause 3 years (n = 31) 47%
51
Premenopause
Perimenopause
Postmenopause
Dryness increased significantly in late perimenopause and postmenopause (P < .001)
Dennerstein L, et al. Obstet Gynecol. 2000;96:351-358.

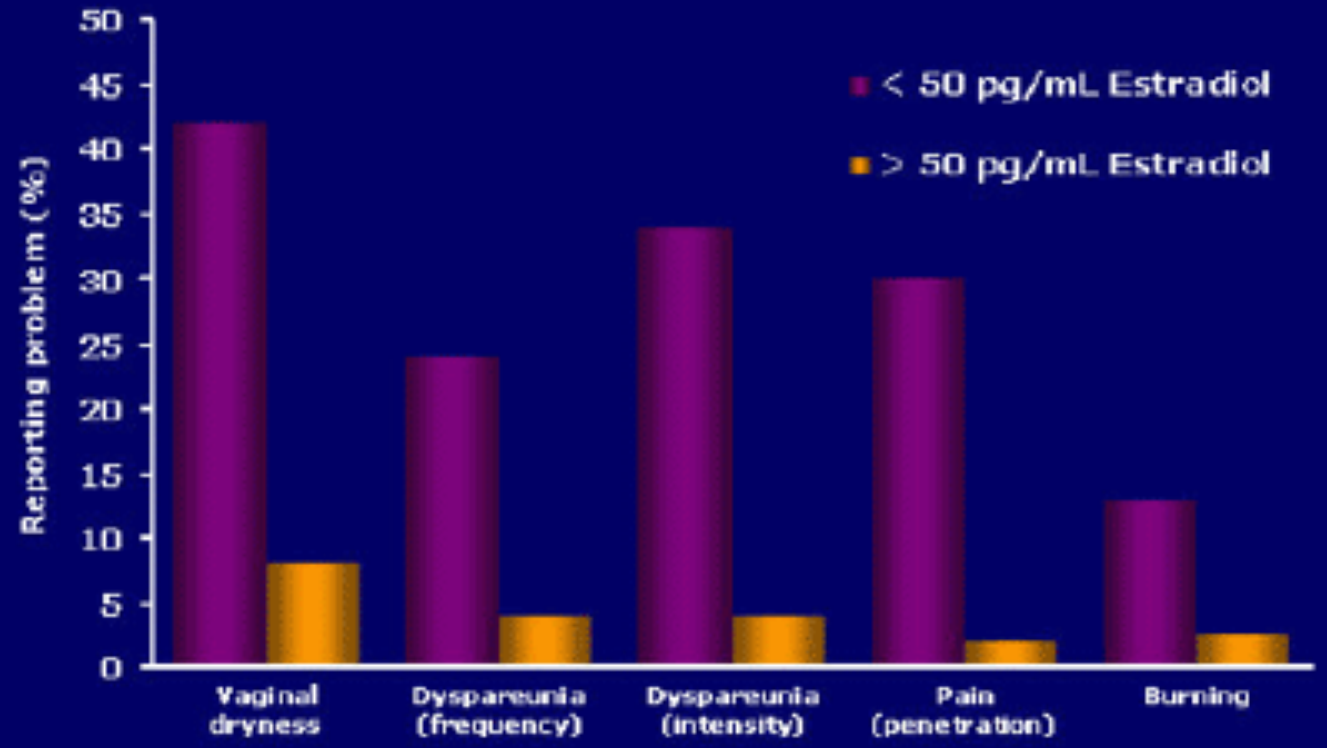
FEMALE SEXUAL DYSFUNCTION *In Menopause ….*

Vaginal Atrophy Symptoms (dryness, dyspareunia)

Secondary Low Libido

Sexual Dysfunction (Arousal Disorder)

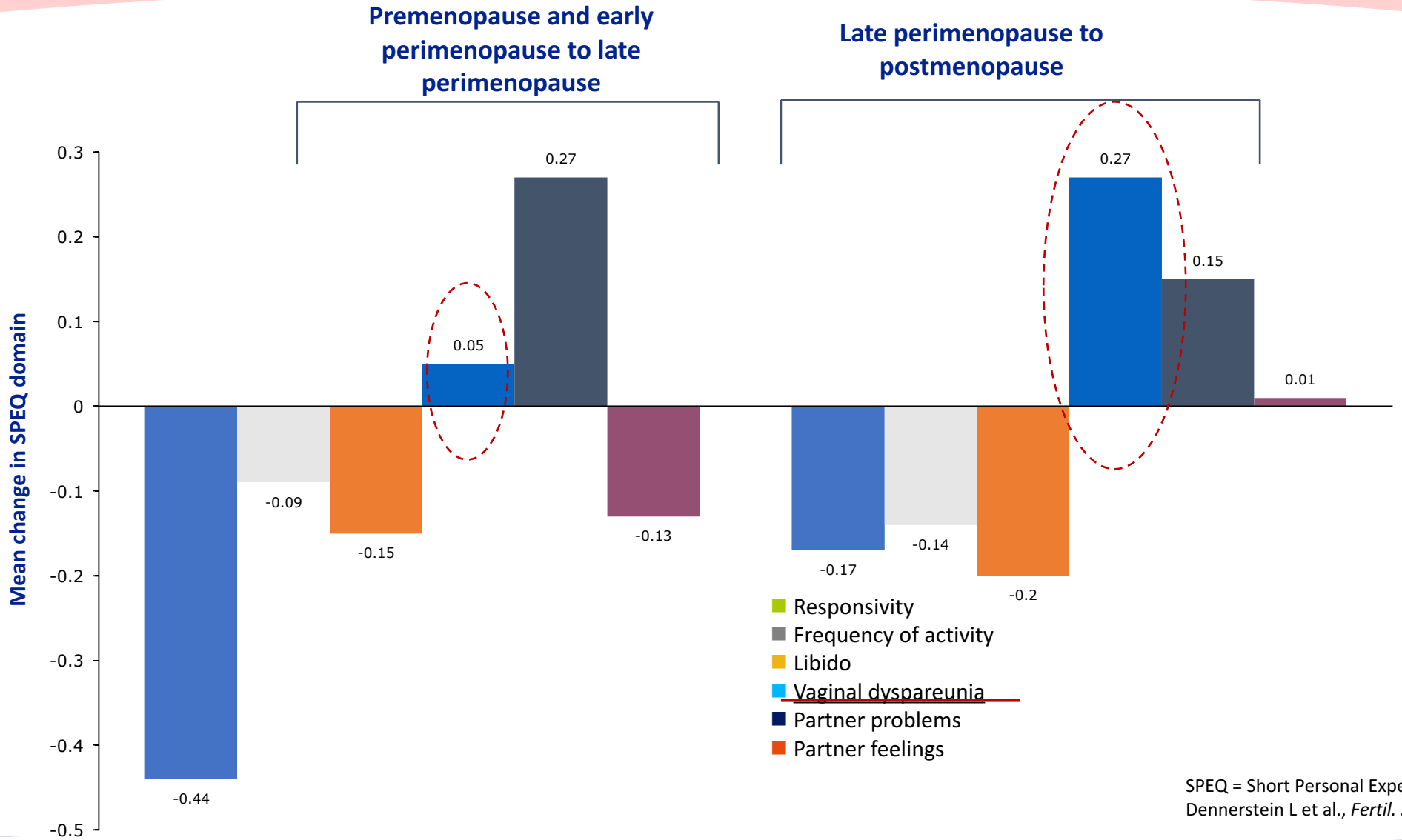
Lower Estrogen Levels Increase Prevalence of Sexual Problems



Significance not reported (n = 93).

Sarrel PM. *J Womens Health Gend Based Med.* 2000;9:S25–S32.
Sarrel PM. *Obstet Gynecol.* 1990;75:26S–30S.

Menopause-related changes in female sexual dysfunction (FSD)

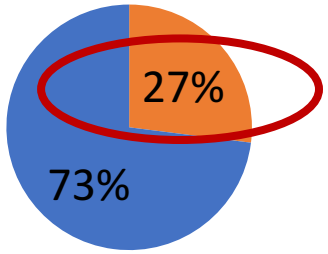


SPEQ = Short Personal Experiences Questionnaire
Dennerstein L et al., *Fertil. Steril.* 2001; 76:456–460

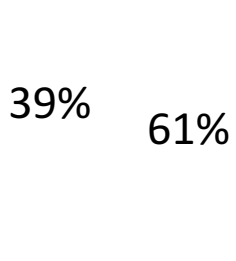
Menopausal women suffering from atrophic vaginitis

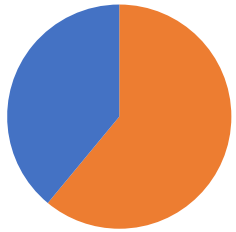
SYSTEMIC HORMONE THERAPY IS NO GUARANTEE THAT VVA/GSM WILL NOT OCCUR

Women taking systemic HRT



Women NOT taking systemic HRT





Patients suffering from AV
Patients not suffering from AV

HRT Market Understanding, *TNS EMNID* 2002

- Over half of postmenopausal women will have urogenital discomfort associated with oestrogen deficiency
- Although many women use oral hormone replacement therapy, urogenital symptoms persist

Notelovitz M et al., *Obstet Gynecol.* 2002; 99:556–562

GSM Reduces the Quality of Life

Atrophic Vaginitis

- Decreased Vaginal mucosal thickness
- Decreased Vaginal acidity
- Decreased Vaginal secretions
- Pain, irritation, infection
- Dyspareunia
- Decreased sexuality

Urogenital Estatrophy

- Atrophy urethral mucosa, bladder
- Frequency, urgency, nocturia
- Urinary incontinence
- Recurrent Cystitis

Estrogen corrects them all

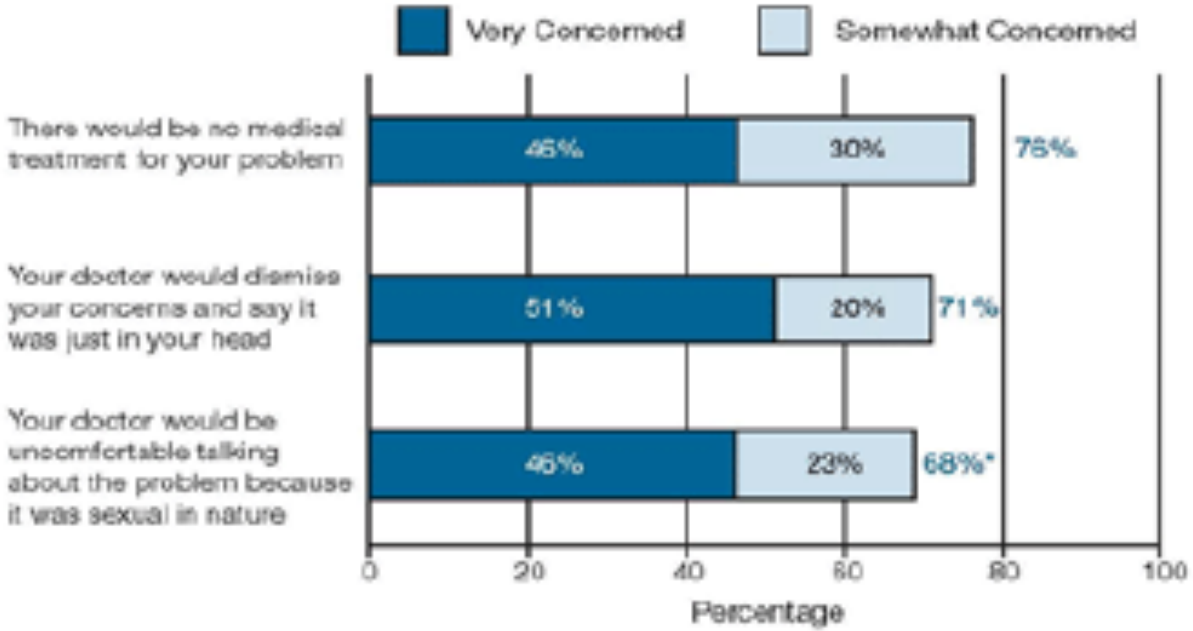
OUTLINE

- Management Options :
  - Non-Hormonal Treatments
-

Communicating With Your Patients About Vaginal and Sexual Health Issues

Physician-Patient Communications Concerning Sexual Problems May Not Be Optimal

If you wanted to talk to your doctor about a sexual problem you were having, how concerned would you be that each of the following might happen during your doctor's visit?



*Numbers do not add up because of rounding.

Marwick C. *JAMA*. 1999;281:2173-2174.

Medscape

Nonhormonal Options for the Treatment of Atrophic Vaginitis

Nonhormonal therapy:

- Water-based vaginal lubricants
  - Eases penetration during intercourse
- Vitamin E oil for lubrication
  - Eases penetration
- Vaginal moisturizers
  - Replenishes and maintains water content in the vaginal vault
- Regular sexual activity
  - Increases the vascularity of the vagina

Nonhormonal therapy does not stop the progression of involutional change

The North American Menopause Society. Menopause Practice: A Clinician's Guide, 3rd Edition.

Reduced lubrication and dryness are important and need to be addressed!

What drugs is she taking? : many drugs reduce lubrication

Which *lubricant /moisturizer is* she using? :

--could it be a cause of irritation ? Infection?

a chemical sensitivity to a stimulating/"warming " lubricant?

Check **products composition** :

should have a **pH 3 - 4.5**

& an **osmolality < 380mOsm/kg**

Outside these limits
Could be cytotoxic

Check **excipients** eg parabens, glycols & glycerine

Composition of moisturizers & lubricants varies –so does efficacy
Edwards D and Panay. Climacteric 2016; 19(2): 151-161

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

Symptom or situation	Recommendation	Rationale
• Urogenital atrophy • Elevated vaginal pH • Pain due to dryness	**Vaginal moisturizer** • Acidic pH (≥3) • Osmolality <380 mOsm/kg	• Rehydrate vaginal tissues • ↓ vaginal pH to minimise infection
• Dyspareunia caused by urogenital atrophy	**Vaginal lubricant** • Acidic pH matched to vaginal pH • Osmolality <380 mOsm/kg	• Lubricate dry vaginal tissues without causing irritation • ↓ or maintain vaginal pH
• Urogenital atrophy as a result of cancer treatment • HRT contraindicated • In combination with topical estrogen	**Paraben-free vaginal moisturizer** *(daily comfort)* • Acidic pH (≥3) • Osmolality <380 mOsm/kg **Paraben-free vaginal lubricant** *(sexual intercourse, vaginal dilators)* • Acidic pH matched to vaginal pH • Osmolality <380 mOsm/kg	• Rehydrate vaginal tissues • ↓ vaginal pH to minimise infection • Lubricate dry vaginal tissues without causing irritation • ↓ or maintain vaginal pH • Avoid paraben preservatives

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

HRT, hormone replacement therapy

HYALURONIC ACID PRODUCTS

1. HA is a **natural component** in vaginal lining and other body tissues.
   --body's reservoir for water & **maintaining hydration** in moisture sensitive areas

Bohot J-M et al Gynecologie Obstetrique & Fertilite 43 (2015),437-442

2. "enhances the ability of vaginal epithelial cells to **reseal an epithelial wound**

Immunology and Cell Biology (2011) 89, 630–639;
doi:10.1038/icb.2010.140

3. Induces **self-defense mechanisms** in vaginal epithelium and secretion of an antimicrobial peptide.

Immunology and Cell Biology (2011) 89, 630–639;
doi:10.1038/icb.2010.140

PELVIC PHYSIOTHERAPY : GOALS

Increase awareness and proprioception of pelvic floor muscles

Improve muscle relaxation

Normalize muscle tone

Increase elasticity at the vaginal opening

Desensitize painful areas

Decrease fear of penetration

OUTLINE

- Management Options :
  - Hormonal Therapies

Vaginal Estrogens

Effective Treatment for Vulvovaginal Atrophy

Ring

Cream

Pellet

VAGINAL ESTROGEN THERAPY "SAFER"

Limited systemic absorption –

- very small serum increase ;

- remains in normal postmenopausal range

- 30% lower serum level than some dose taken orally

Avoids enterohepatic metabolism

Minimizes adverse **systemi**c effects

-minimal bleeding / mastalgia

No changes in lipids, clotting or fibrinolytic factors or globulins

Al-Assawi F.. Menopause 2005

TREATING GSM : SUMMARY

•Regular **sexual activity or stimulation** (promotes vaginal health and blood flow)

•**Vaginal lubricants** (for temporary relief of dryness before and during sex)

•**Vaginal moisturizers** (for longer-term relief from dryness)

•**Low-dose vaginal estrogen** therapy in cream, ring, or vaginal tablet form (reverses underlying atrophy and dryness)

•**Higher-dose /systemic hormone therapy** with pills, patches, gels, (reverses underlying atrophy and dryness; preferred choice for women with troublesome VMS)

OUTLINE

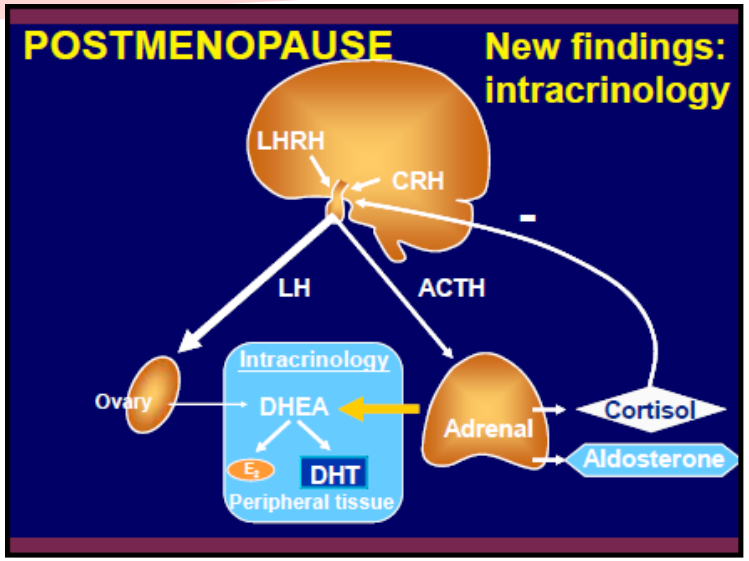
- New therapies on the horizon

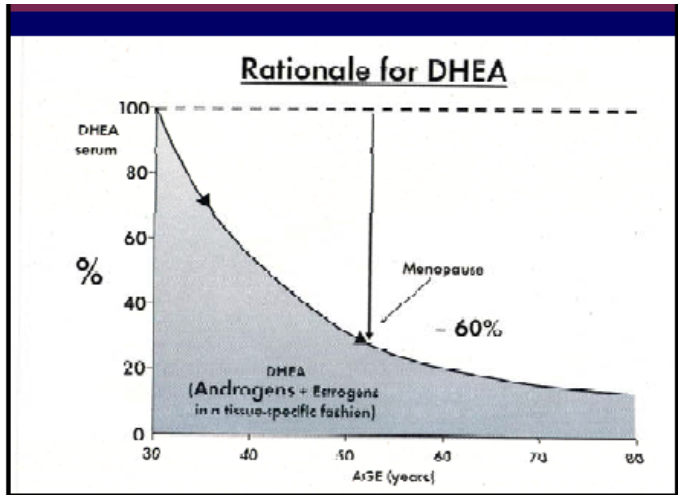
OSPEMIPHENE (oral)

- **SERM** with predominantly estrogenic effects on the vulvovaginal tissues; ---
  ---antagonistic to endometrium and breast **
- Indications (1) treatment of **GSM/VVA**
  & (2) **dyspareunia** due to GSM
- Taken **orally**; 60 mg tab/day
  12 mo effectiveness & safety studies (S/E = VMS 7% vs 2% pbo)
- Available in the USA & Europe, but not in Canada

VAGINAL DHEA Rx FOR VAGINAL ATROPHY

LABRIE HYPOTHESIS : "INTRACRINOLOGY of DHEA"





Vaginal DHEA Rx : ↑ mucin; ↑collagen , stimulates muscularis

INDICATIONS for DHEA Rx :

1. ***VVA***
2. ***LIBIDO***

Vaginal DHEA (Prasterone) Available in US, Europe
Not yet in Canada

VAGINAL CO2 LASER Rx

- Theoretical explanation for its use is interesting
- Not adequately studied RCT's
- No long term efficacy or safety data available
- Cost limits its wide use
- Endorsement from our academic bodies awaits more data

- Available in the USA & Europe, but not in Canada

OUTLINE

- Back to our patient : What should we advise?

……BACK TO CASE

LOCAL VAGINAL THERAPIES

Christine M Derzko MD

HISTORY:

- 48 yo G2P2 executive referred for dyspareunia & recurrent UTIs
- Avoidance of sex → problems in this new relationship
- OTC lubricants & moisturizers ineffective, some irritating
- Does not want vaginal estrogens : fears developing breast cancer .
  Mom breast Ca @ 63yo; well 10 yrs post Rx *NB she did not use any MHT)
- Non-hormonal IUCD in situ

QUESTIONS:

- What advice should she be given?
- What treatment options are available? What are their pro's & con's
- How to choose
- What about vaginal estrogens?

Hormone Rx in Women with a Family Hx Breast Ca

- Family history has no additive impact on breast cancer risk with HRT use[1,2] although women with gene mutations are at vastly increased lifetime risk of breast cancer
- HRT use and family history had independent and non interacting risk factors for breast cancer in WHI[3]
- Long term observational studies have reported no extra risk for those with a family history of breast cancer using HRT
- HRT following risk reduction surgery appears not to increase risk[4,5]
- HRT in such women should use minimal progestrogen and ideally progesterone or dydrogesterone

1. Rippy L Marsden J Climacteric 2006;9:404-15
2. Sellars T et al Ann Intern Med 1997;127:973-80
3. Gramling R et al Epidemiology 2009;20:752-6
4. Rebeck T et al J Clin Oncol 2005;23:7804-10
5. Eisen J et al J Nat Cancer Inst. 2008;100:1361-67

Family Hx Breast Cancer & LET

- No evidence that vaginal estrogen Rx increases Breast Ca Risk
- Absorption of estrogen is minimally increased for a few days initially from atrophic vagina (to early follicular levels) –but no evidence that this would be risky
- After loading dose systemic E2 levels return to normal postmenopausal levels

GSM : Management Strategies SUMMARY (1)

- Regular sexual activity or stimulation promotes vaginal health and blood flow

- Vaginal lubricants for temporary relief of dryness before and during sex) and
  Vaginal moisturizers (for longer-term relief from dryness) are useful
  Product pH, osmolality and excipient content is important.

- Low-dose vaginal estrogen therapy in cream, ring, or vaginal tablet form reverses underlying atrophy and dryness and addresses bladder/urethral issues

Faubion SS, Sood R, Kapoor E Mayo Clin Proc 2017 (92(12),1842

GSM : Management Strategies SUMMARY (2)

- *Systemic hormone* Rx oral, transdermal gels patches, and other preparations, (i.e a higher dose than LET) also reverses underlying atrophy and dryness, but generally is recommended for women with bothersome VMS; LET preferred for GSM
- BUT
- Estimated that as many as 1/3 women taking adequate doses of systemic estrogen experience some degree of GSM and should be considered for additional local Rx

Faubion SS, Sood R, Kapoor E Mayo Clin Proc 2017 (92(12),1842

GSM : Management Strategies SUMMARY (3)

- Consider adding Pelvic Physiotherapy and/or Sexual Counselling when appropriate

- NEW TREATMENTS on the horizon:

  SERM – Ospemifene - oral;
  "INTRACRINOLOGY" –Vaginal DHEA Rx Vaginal CO2 Laser (Limited data)

Faubion SS, Sood R, Kapoor E Mayo Clin Proc 2017 (92(12),1842

THANK YOU!

Case 6: Progestogens and Progestogen Intolerance

Michel Fortier, MD, FRCSC

Thanks to Dr Elaine Jolly for sharing didactic material

DISCLOSURE STATEMENTS

Speakers Honoraria: Merck, Pfizer

Advisory Boards:

Pfizer, Allergan

Participation in research projects as Sub-investigator:

Inovio, Endoceutics, Myovant, Bayer, Estetra

Case 6

- 51 yr old lawyer, G2 P2, vaginal deliveries
- Partner: vasectomy
- Symptomatic for the past 8 months with hot flashes 10 per day, sleep disruption and fatigue
- Abnormal uterine bleeding for the past 8 months
  - Cylcles 28 – 40 days / 7 days duration / heavy bleeding for 2 days; 2 episodes of intermenstrual bleeding for 5 days
- Personal History: no particular illness or surgery
- Family History
  - Mother : Breast DCIS age 55; no recurrence
  - Maternal Aunt: Breast cancer age 60

Case 6

- Medications: none, refuses OCs for fear of breast cancer
- Smoking: social, 5 cigarettes per week
- BMI 28
- BP 125/80 mm Hg
- Hb: 100 g/l
- Pap smear: normal
- Endometrial biopsy: simple hyperplasia, no atypia
- Vaginal ultrasound: normal uterus, no adnexal masses

Case 6

- What are the issues for this symptomatic subject in late perimenopause?
  - Control AUB
  - Control hot flashes
  - Control anemia and fatigue
  - Control fear of breast cancer

Treatment Options

Treatment options

- Status quo, information
- Medical
  - Iron +/- tranexamic acid
  - Cyclic progestogens
  - Continuous progestogens
  - Levonorgestrel IUS-52mg
- Surgical
  - Endometrial ablation

Progestogens

- Induce secretory endometrium to support gestation
- Prevent uterine cancer and endometrial hyperplasia
- May act as a neurosteroid and may improve sleep (progesterone)
- Minimal thrombogenic activity when used alone
- May treat VMS independently

Classifications of Progestogens

Progestogen	Example
Progesterone	Natural progesterone
Retroprogesterone	Dydrogesterone
17 α hydroxyprogesterone derivatives	Pregnanes: MPA, cyproterone Norpregnanes: nomegestrol
19 nortestosterone derivatives	Estranes: NETA (norethindrone) Gonanes: LNG, desogestrel
Spironolactone derivative	Drospirenone

Recommended Progestogen Doses for Endometrial Protection

Progestogen	Cyclic 12-14 days	CT daily
MPA	5 -10 mg	2.5 – 5 mg
Norethindrone	.35 - 0.7 mg	0.35
Northindrone acetate	2.5 mg - 5 mg	0.5 - 1 mg
Micronized Progesterone	200 – 300 mg	100 mg
IUS-levonorgestrel		20µg/day
Progesterone gel (vaginal)	45 mg (4-8% gel)	45 mg

Progestins and Progesterone are different

- Side effects may differ between progestins (synthetic) and progesterone:
  - MP has a soporific effect and may help with sleep
  - MP has been associated with fewer bleeding days than MPA
  - Available MP is prepared with sunflower oil, so a compounded preparation may be considered for those with a peanut allergy

Curr MedChem. 2006;13(29):3575-82
Lindfield and Langer (2002) Obstet Gynecol. Nov; 100(5 Pt1):853-63
De Lignières (1999) Clin ther. Jan;21(1):41-60;discussion 1-2

Case 6

- After 12 months on MP 300 mg 14 days / 28 days
  - No bleeding for 6 months
- Feels awful on progesterone
  - Dizzy, depressed
  - Increased hot flushes in the last month
  - Decreased concentration at work
- Wants another solution…more open to HT
- Normal exam and repeat endometrial biopsy is normal

Significant progestogen side effects

- Psychological effects
  - Anxiety, irritability, depression
- Mineralcorticoid-like effects
  - Breast discomfort
  - Edema
  - Abdominal bloating
- Sedative effects - related to pregnenolone metabolites and GABA receptors may cause dizziness or nausea in up to 20%
- Progesterone has mild diuretic effect 100 mg=25mg spironolactone

Options for P intolerant patient

- Start unopposed E with monitoring of endometrium (Goldstein)
- Long cycle HT
- Switch route-vaginal progesterone
- LNG IUS – 52 mg with E
- **New TSEC: CE 0.45 mg / BZA 20 mg OD**
  - One pill; no progestogen required
  - Insurance needed, unique dosage
- Stop hormones and try alternative therapies, SSRI, gabapentin or clonidine

Bazedoxifene/CE: SMART Trials

- Reduction in # (80%) + severity (54%) hot flashes
- Increase LS and total hip BMD at year 1 and 2
- Endometrial hyperplasia < 1%
- Amenorrhea similar to placebo, lower than CE/MPA
- Decreased dyspareunia
- Improved sexual domain on MENQOL
- Improvement of sleep and QOL over 1 yr

Pinkerton JV et al, *Climacteric*, 2012; Bachmann G, et al, *Climacteric*, 2010; Lobo et al, *RA Fertil Steril*, 2009; Kagan R et al, *Menopause*, 2010

Effects on Breast

Breast tolerability profile similar to placebo following up to 2 years of treatment with CE/BZA[1-3]

Pooled analysis of SMART clinical trials	CE 0.45/BZA 20 (n=1585)	CE 0.625/BZA 20 (n=1583)	Placebo (n=1241)
Breast cancer incidence up to 2 years (per 1000 woman-years)	1.00 (CI 0.00-3.21)	0.00 (CI 0.00-1.54)	1.40 (CI 0.00-4.17)
Incidence of reported breast pain/tenderness up to 12 wks	9.8-11.5%	9.8-10.2%	8.1-11.2%
Incidence of abnormal mammogram at month 12	2.58%	2.60%	3.16%
Mean change in breast density at month 12 (SMART-5)*	–0.38%	–0.44%	–0.32%

1. Pfizer Inc. CDS. Page 21, Table 7; 2. Pickar J, et al. Abstract presented at NAMS 2013; 3. Pinkerton JV, et al. *Obstet Gynecol.* 2013;121:959-968; 4. Pfizer Inc. Data on file. *n= 186, n=191 and n=182 for DUAVIVE 0.45 mg, 0.625 mg and placebo respectively.

Estrogen + LNG IUS–52mg Benefits

- Good endometrial protection (off label in Canada)
- Provides simultaneous contraceptive effect
- Good symptom control
- Insertion may be more difficult in menopausal uterus
- After initial spotting, high rate of amenorrhea, even during perimenopause
- Well tolerated; comparable safety profile to that in premenopausal women using the LNG-IUS 52 mg
- No clinically relevant effects on plasma lipids or other cardiovascular risk factors. When used in combination with transdermal estrogen high continuation rates

Depypere H, *Climacteric*, 2015
Somboonporn W, *Menopause*, 2011

Conclusions

Currently the main purpose of the progestogen component of HT is protection against endometrial cancer

- Different progestogens have different risks and benefits related to their derivation
- Alternative doses, regimens and routes are available to improve compliance

Discussion