



Managing Urogenital Atrophy

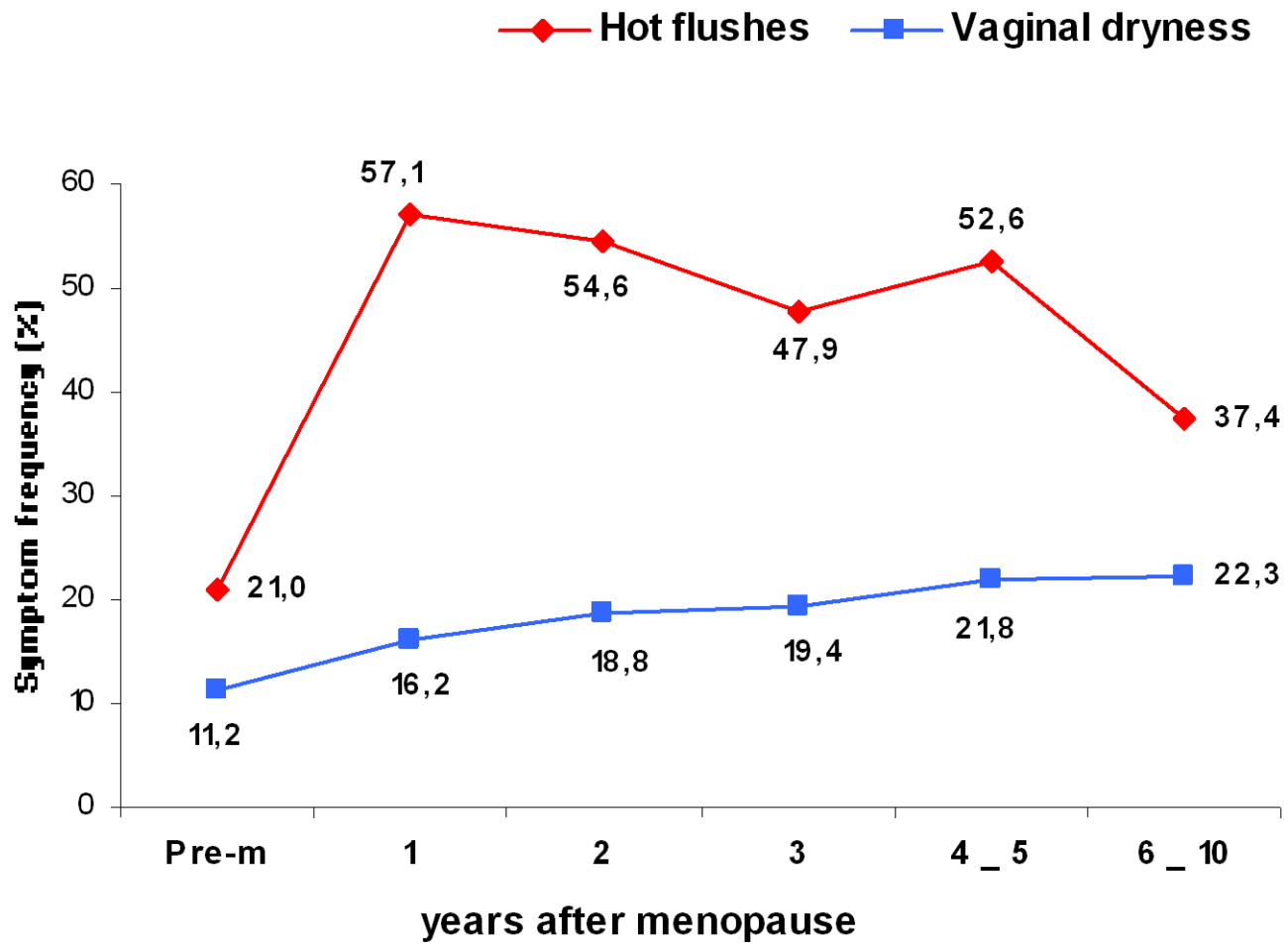
Göran Samsioe MD; PhD; Professor
Dept of Obstetrics & Gynecology
Lund university Hospital, Lund
-Sweden
E-mail: goran.samsioe@med.lu.se




FACULTY OF MEDICINE
Lund University, Sweden

Why urogenital atrophy

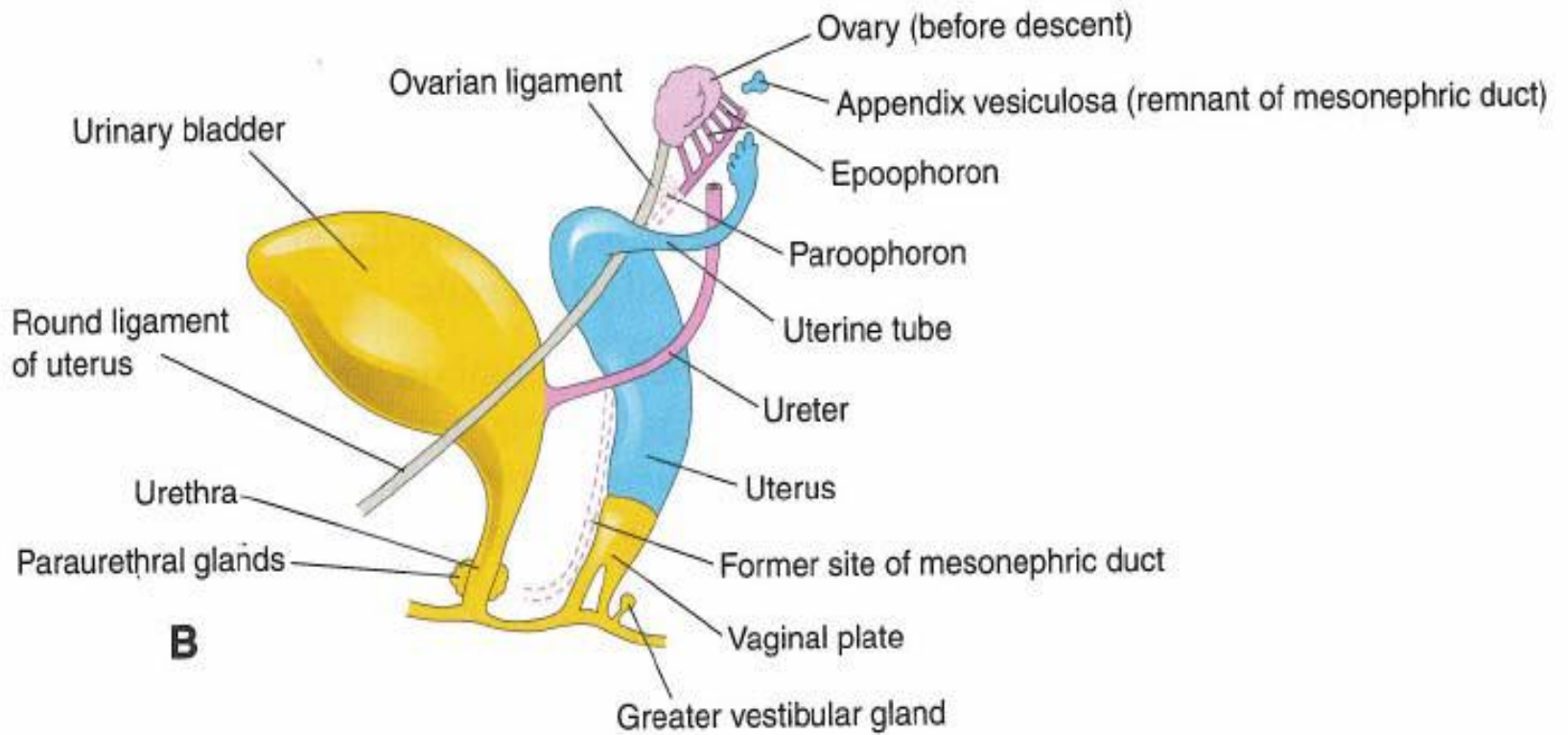
- Age
- Estrogen deprivation
- Concomitant disease
- Blood flow
- Reduced glandular function
- Obliteration of rugal folds
- Lack of a discernable basement membrane.



 Urogenital sinus

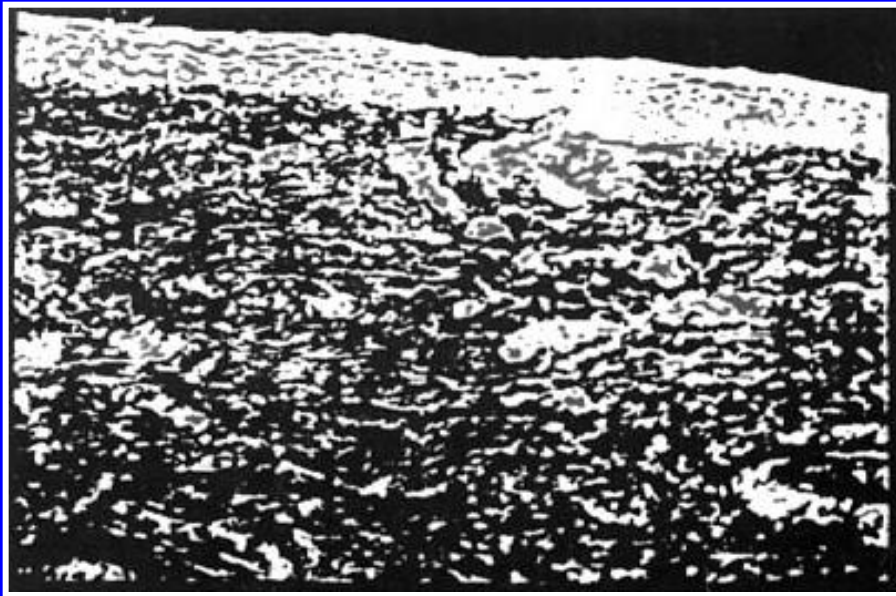
 Mesonephric duct

 Paramesonephric duct

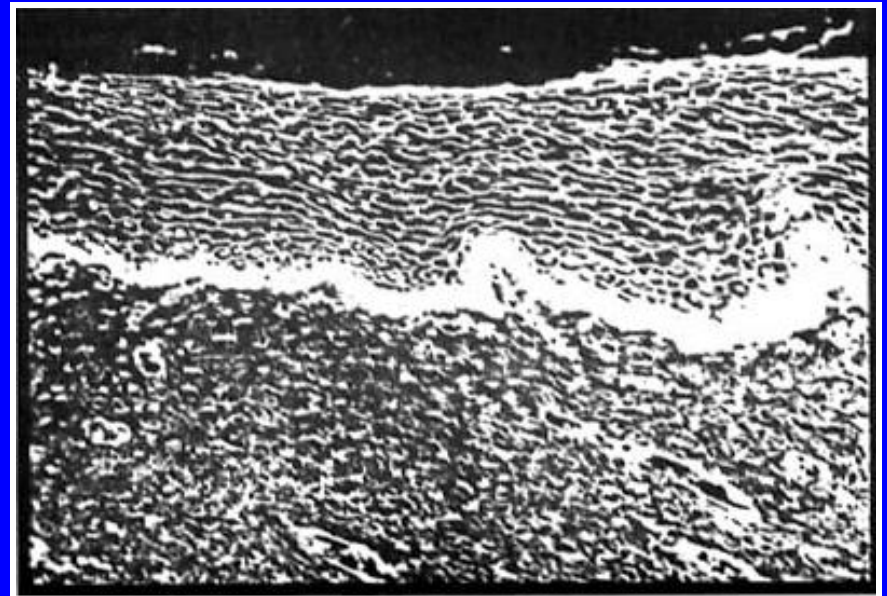


Vaginal Biopsies

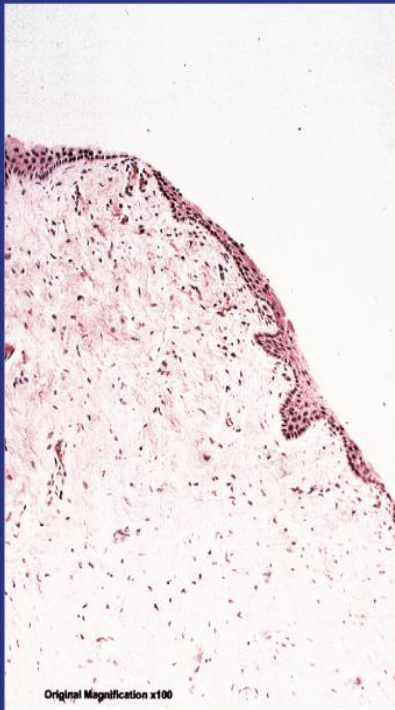
Postmenopausal, atrophic



Same patient, local ET (one month)



Vaginal Epithelium



Without estrogen – atrophic

6 weeks of
estrogen



With estrogen¹

- ▶ Vagina/urethra highest concentration of estrogen receptors²
- ▶ Most efficient response with local application^{3,4}

1. Freedman unpublished data.

2. Iosif et al. *Am J Obstet Gynecol.* 1981;141:817.

3. Elia et al. *Obstet Gynecol Surv.* 1993;48:509.

4. Weinberger. *Clin Obstet Gynecol.* 1995;38:175.

Physiology of Vulvovaginal Changes: Structure and Histology

Vulva

- loss of collagen (elastin) and adiposity ¹

Clitoral glands

- lose protective covering²

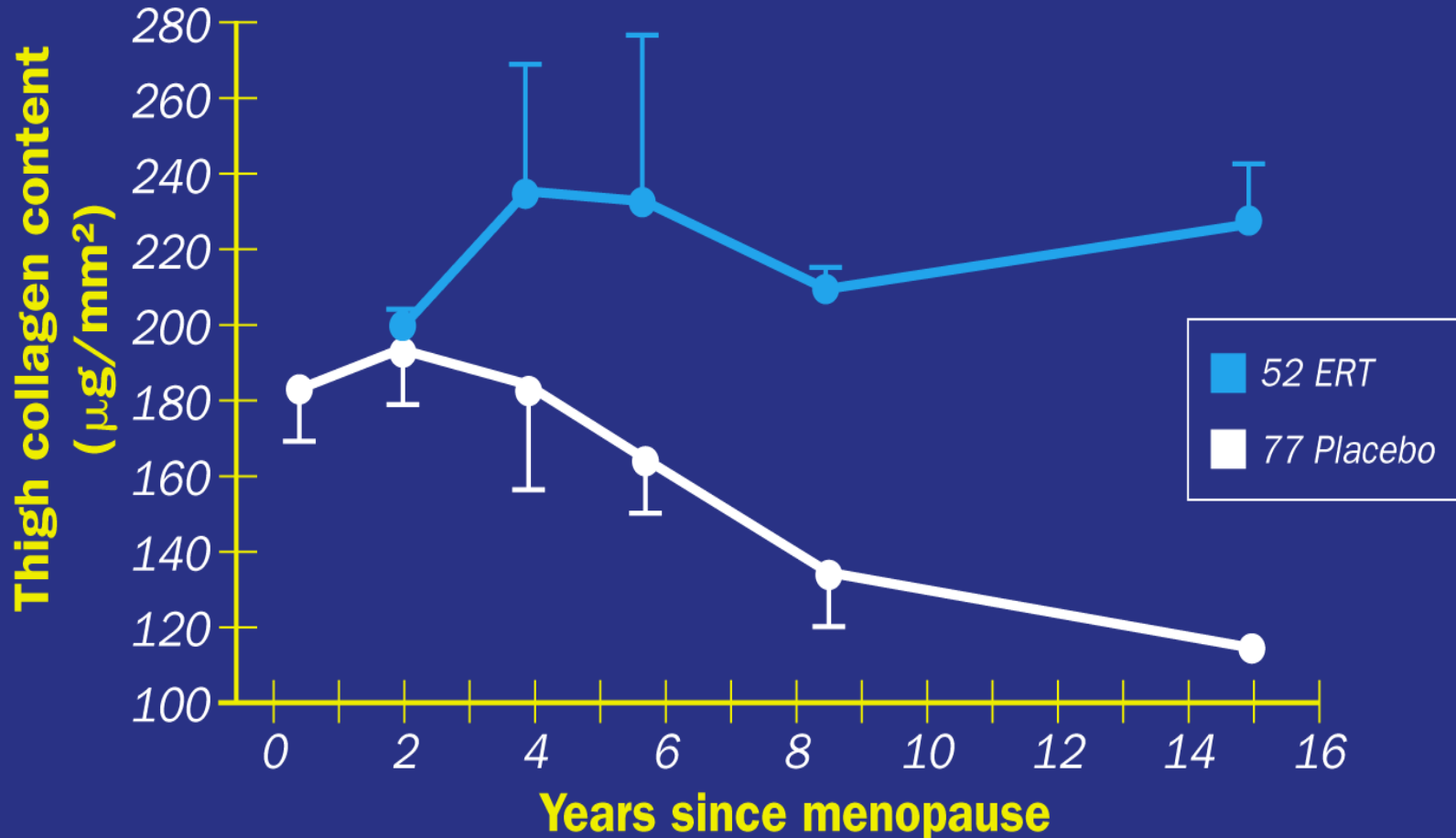
Vaginal surface

- thinner, less elastic; more friable²

¹Oriba HA, Maibach HI. *Acta Derm Venereol.* 1989;69:461-5.

²Bachmann GA, et al. In: *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects.* 2nd ed. 1999:195-201.

Collagen Content and Menopausal Age



$P < 0.001$

Adapted from Brincat. *Br J Obstet Gynaecol.* 1985;92:256.

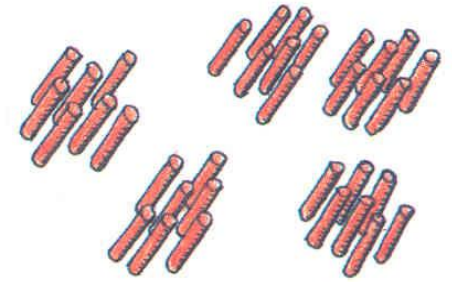
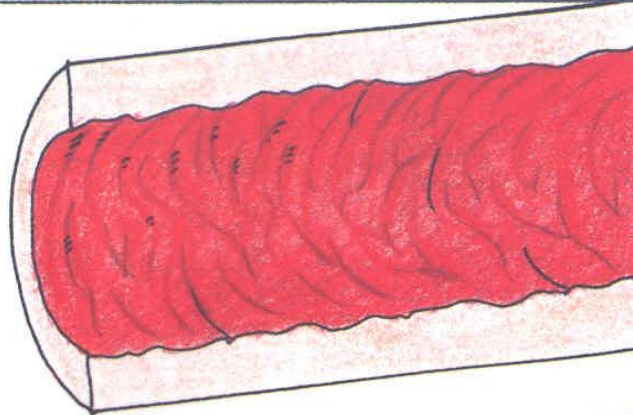
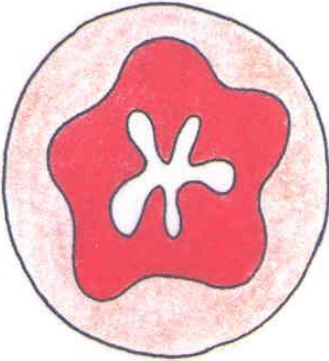
Collagen hypothesis

- Estrogen deprivation
 - **decreases** collagen synthesis and turnover
- Newly formed collagen molecules
 - have **few** secondary bridges between protein chains such as disulfuric and other secondary bridges
- "Old" collagen
 - has **a huge** number of secondary bridges and is therefore more rigid
- Stress incontinence
 - **decreases** by estrogen loss and HT will enhance it
- Urge incontinence
 - **increases** by estrogen decline due mainly to atrophy which leads to increased susceptibility of nerve endings

Urethra

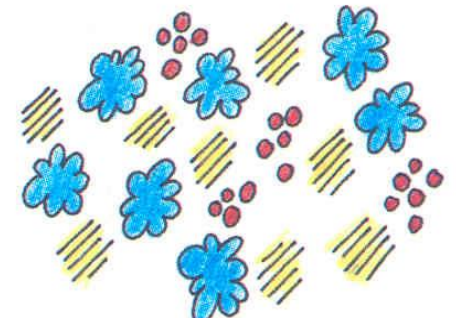
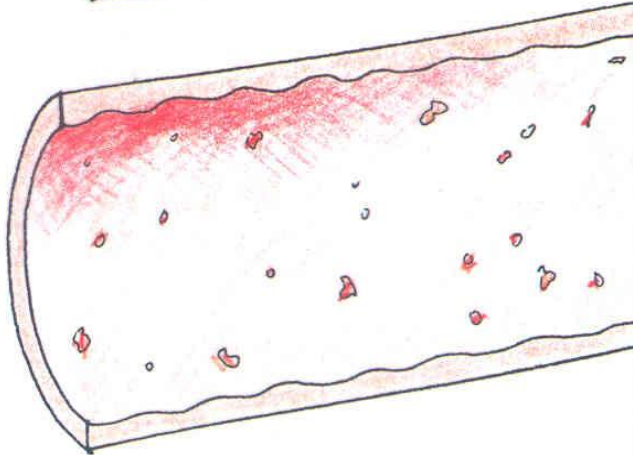
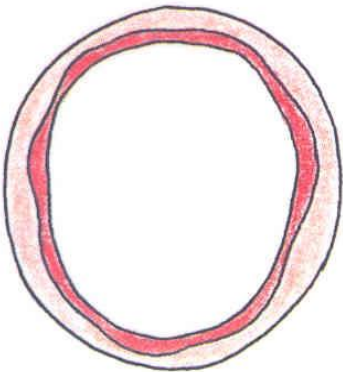
Vagina

Younger



Lactobacillae
pH 4

Elderly



Mixed Germ flora
pH 6-7

Uro-Genital Symptoms

Vaginal:

- Dry vagina,
- Dyspareunia,
- Vaginitis,

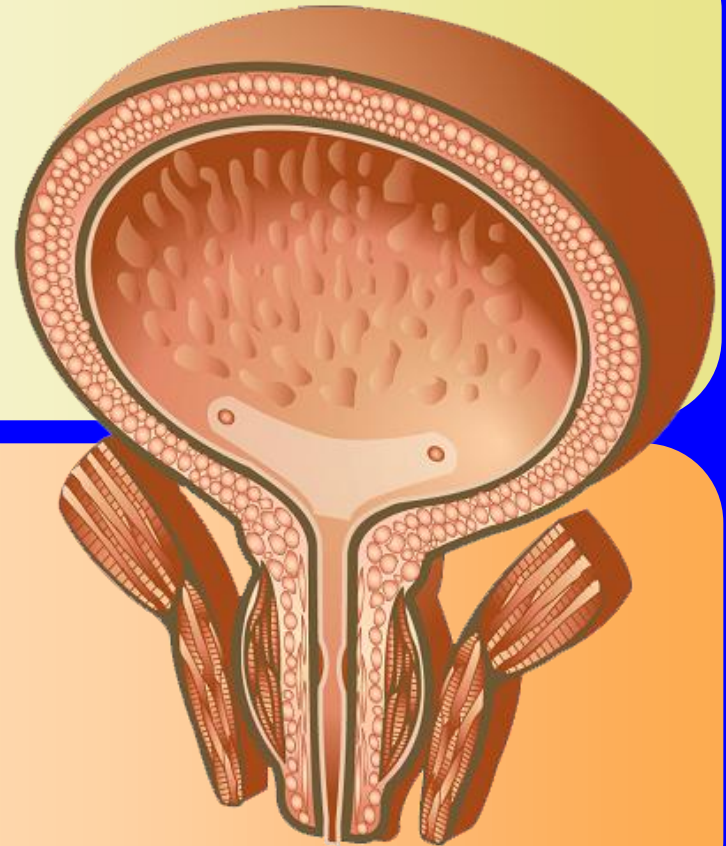
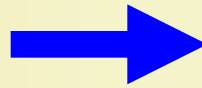
Urologic:

- Incontinence,
- Dysuria,
- RUTI,
- Urethritis

Difference between stress and urge urinary incontinence

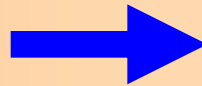
Urge

urinary incontinence
*result of involuntary
BLADDER contractions*



Stress

urinary incontinence
*result of insufficient
URETHRAL closure*



UI types

Stress

urinary incontinence
(SUI)

Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing

Urge

urinary incontinence
(UUI)

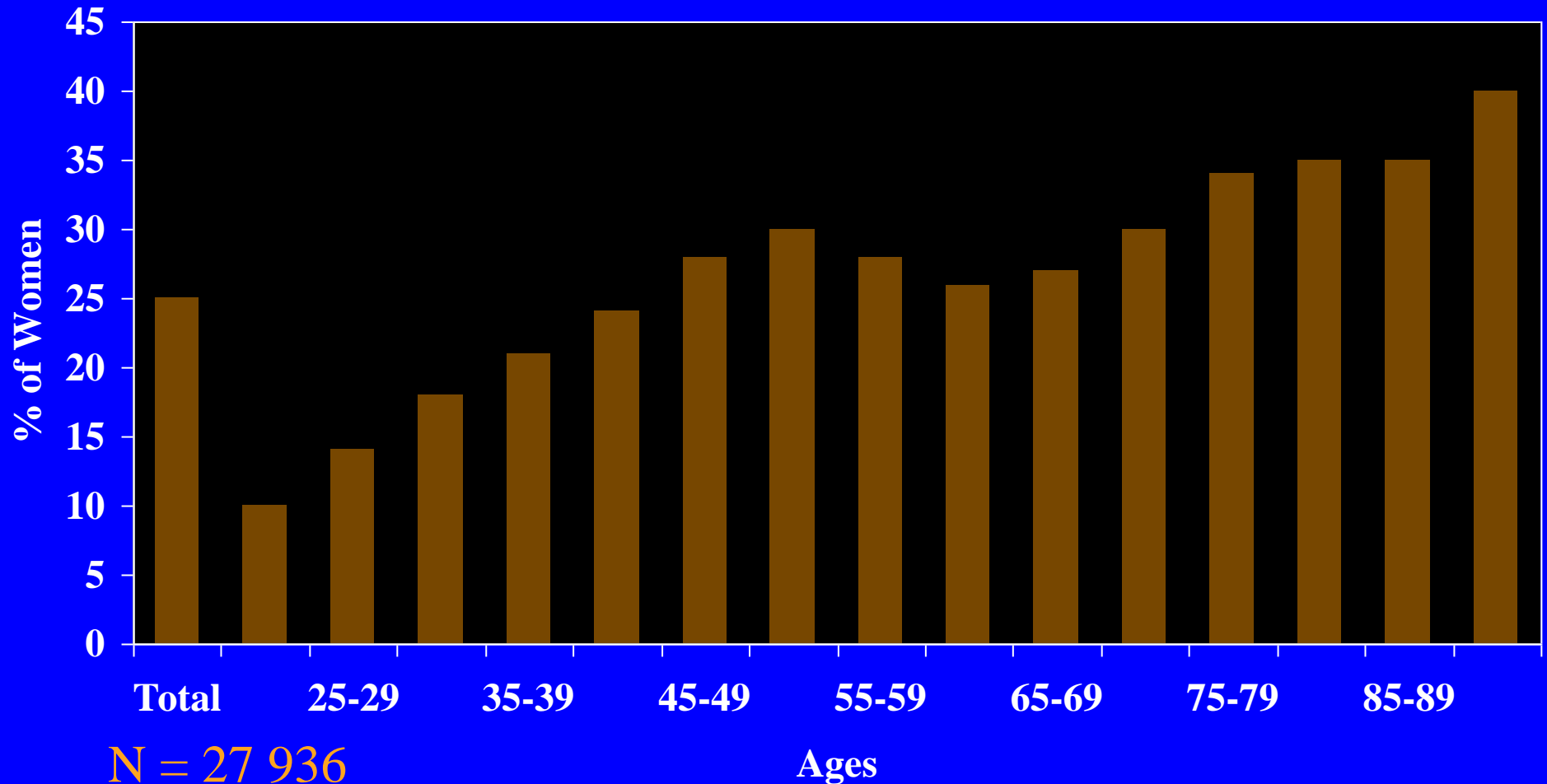
Complaint of involuntary leakage accompanied by or immediately preceded by urgency

Mixed

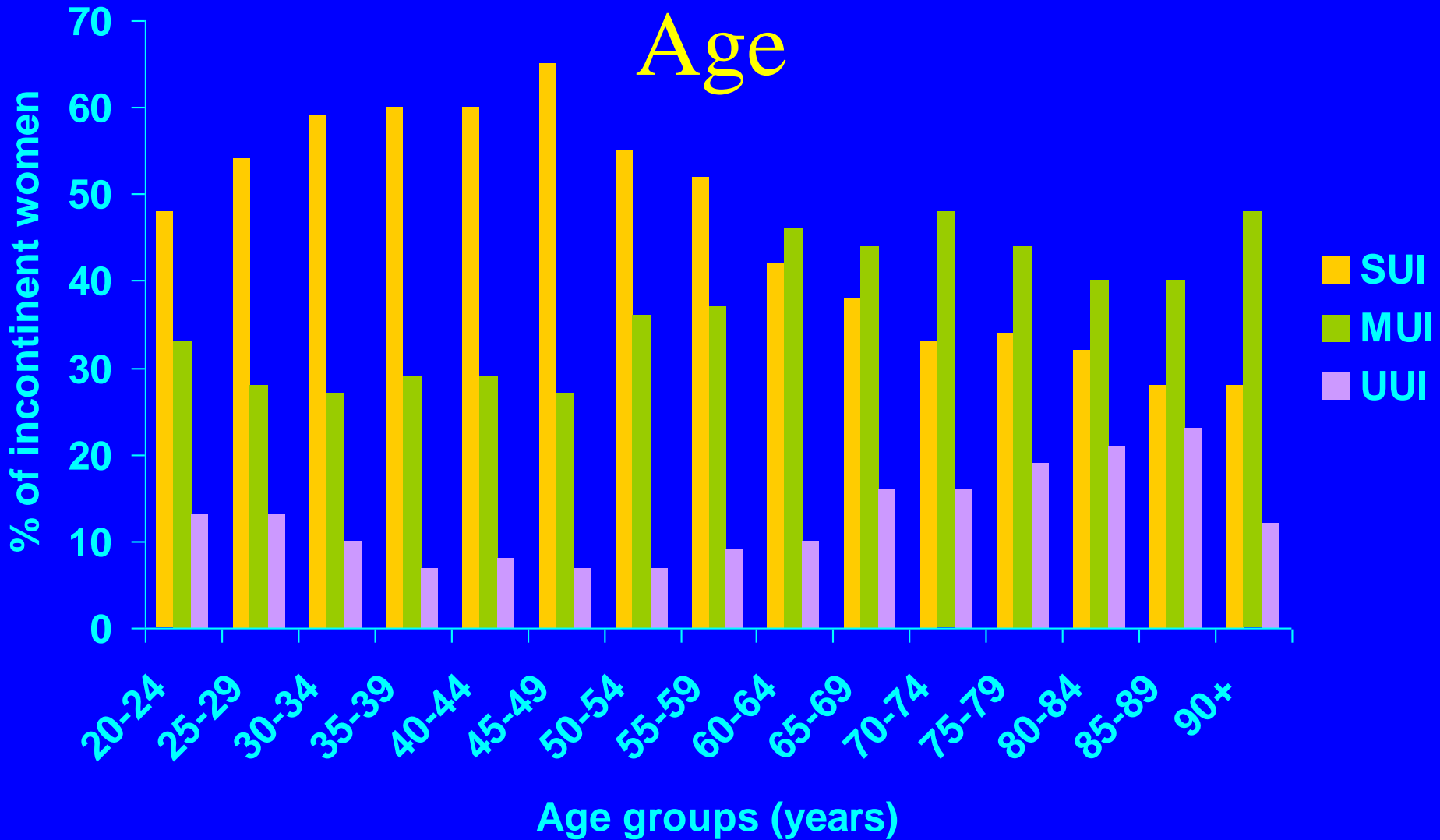
urinary incontinence
(MUI)

Complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing and coughing

Urinary incontinence in women increases with age



Community based survey in > 25.000 women



Urge incontinence

- Bladder training
- Pelvic floor exercise
- (Low dose topical) Estrogens
- Anticholinergics
- (Surgery)

Overactive bladder – risk factors

	Odds Ratio	Confidence Interval	P value
Stress incontinence	3.0	2.3 – 3.9	P<0,001
BMI>30	1.6	1.2-2.3	P<0,01
Diabetes heredity	1.5	1.04-2.3	P<0,05

Over Active Bladder

Germany, Italy, Spain, Sweden and UK (=USA)

- 20.2 million above 40 had symptoms in 2000
- Expected to rise to 25.5 million by 2020
- Total costs in 2000 €4.2 billion
- Expected to rise by 26% to €5.2 billion in 2020
- Major cost: Incontinence pads (63%)

Over Active Bladder

- Antimuscarinic drugs (M2) and M3 specific:
 - darifenacin, solifenacin
- Tolterodin
- Calcium channel blockers still under debate
- Oxybutunin transdermal patch may widen its therapeutic window
- Botulinum toxin type A
- Surgical procedures
- **Low dose (topical) estrogen**

Estrogens & RUTI

- RCTs only **Nine** studies (n=3345)
- Vaginal but **NOT** oral estrogen reduced RUTI
 - effect enhanced by duration
- Vaginal estrogen also more effective than antibiotics in reducing no of UTI

Pelvic floor muscle training: Cochrane review

- Studies up to December 1 2004
- Huge heterogeneity prevented formal meta analysis
- 13 trials but only 6 contributed to data analysis (n=403)
- Support for widespread recommendation that PFMT be included as first line intervention for all female incontinence

Presenting Genital Symptoms and Physical Signs of Vaginal Atrophy

Symptoms

Dryness

Itching

Burning

Dyspareunia

Burning leukorrhea

Vulvar pruritus

Feeling of pressure

Yellow malodorous discharge

Signs on Physical Exam

Pale, smooth, or shiny vaginal epithelium

Loss of elasticity or turgor of skin

Sparsity of pubic hair

Dryness of labia

Fusion of labia minora

Introital stenosis

Friable, unrugated epithelium

Pelvic organ prolapse

Rectocele

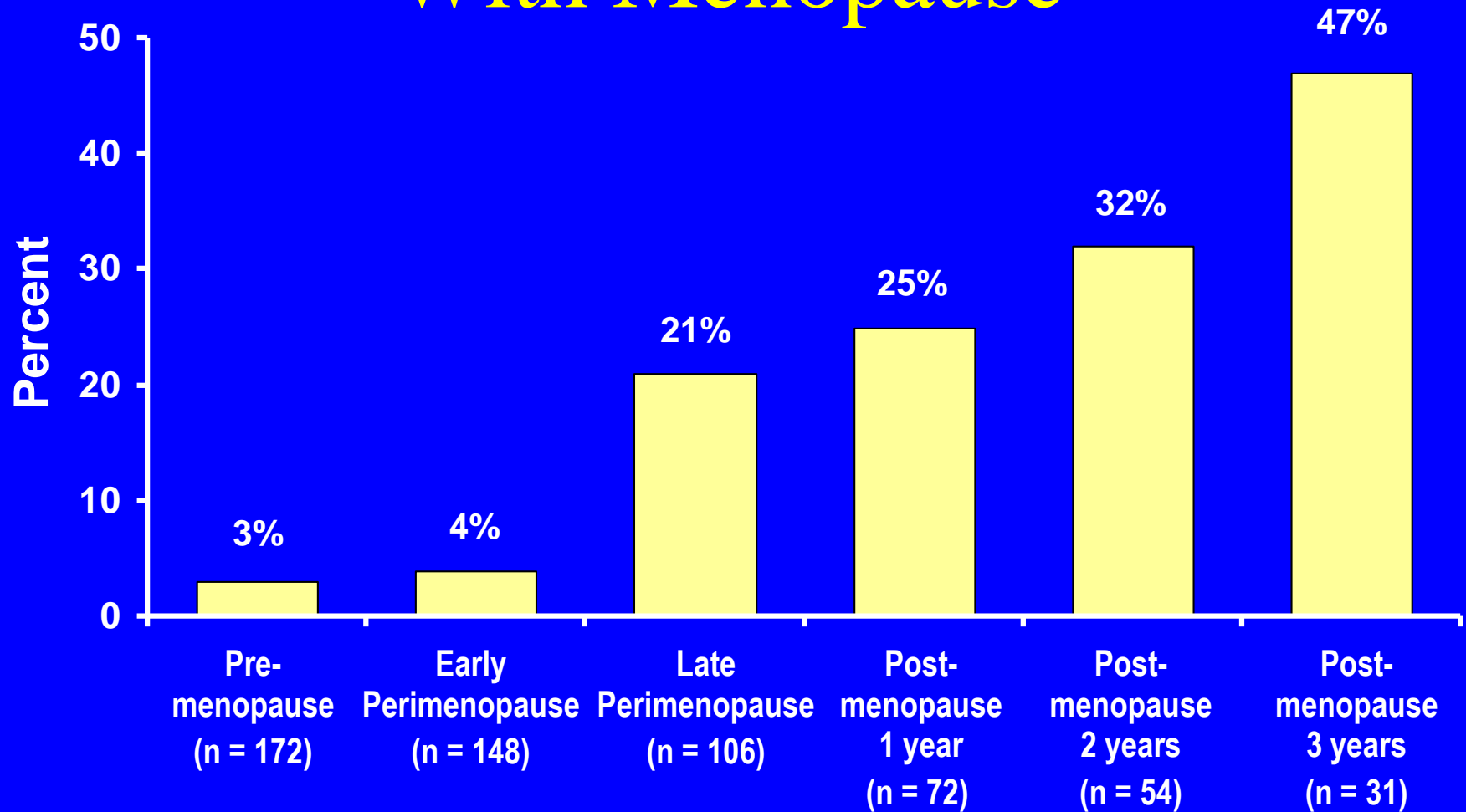
Vulvar dermatoses

Vulvar lesions

Vulvar patch erythema

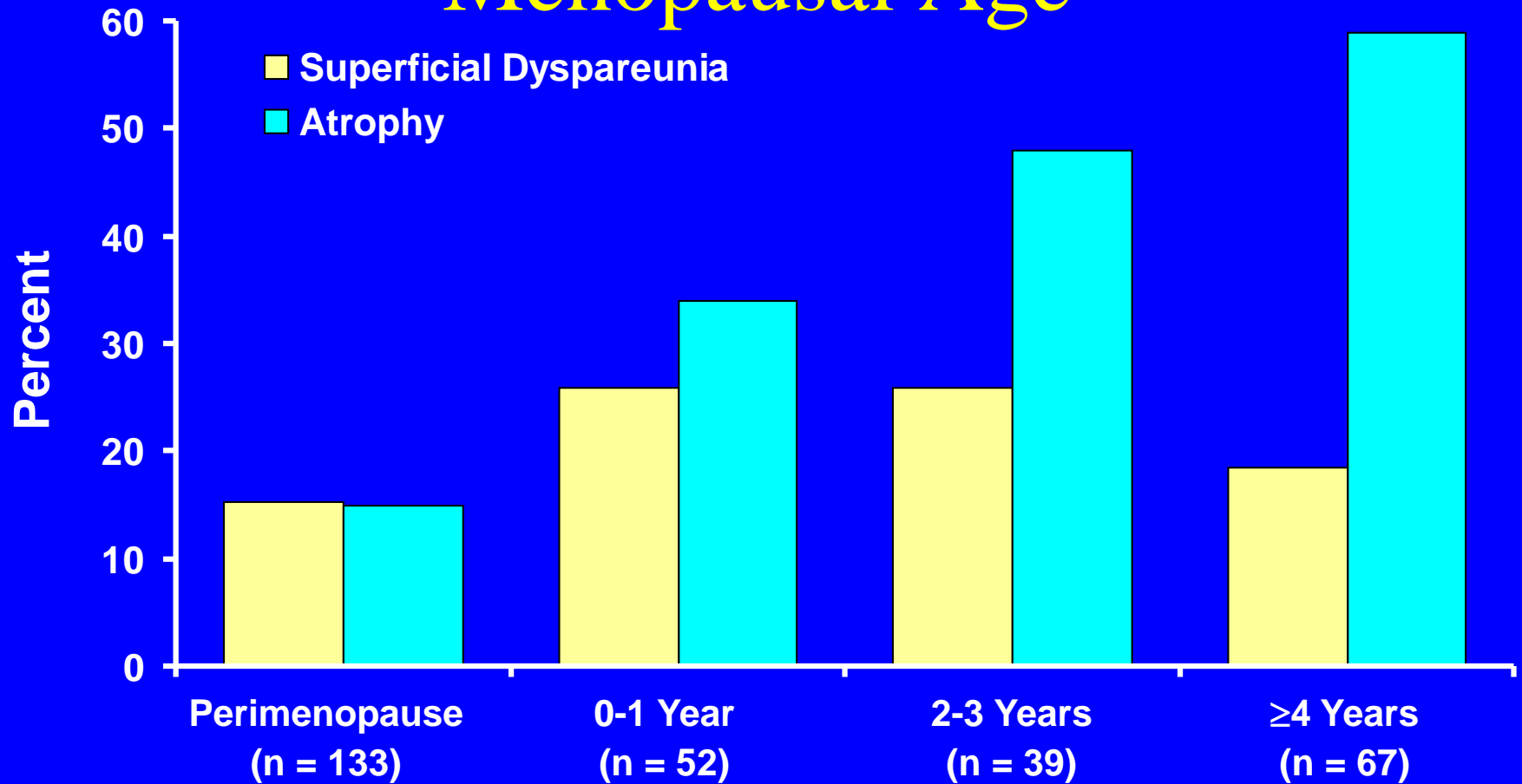
Petechiae of epithelium

Increase in Vaginal Dryness With Menopause



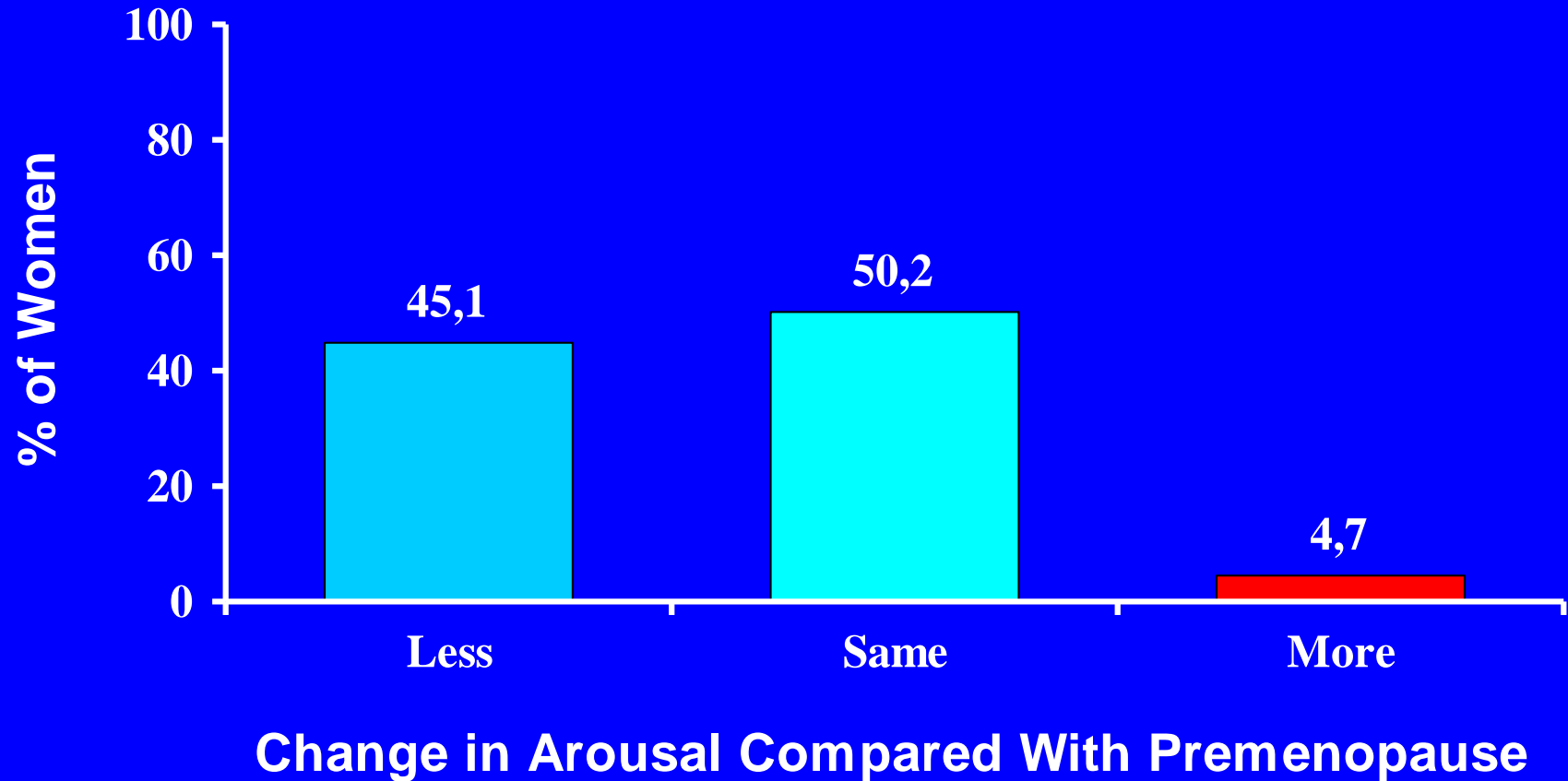
Dryness increased significantly in late perimenopause and postmenopause ($P < .001$).
Dennerstein L, et al. *Obstet Gynecol.* 2000;96:351-8.

Prevalence of Superficial Dyspareunia and Vulvovaginal Atrophy by Menopausal Age



Atrophy increased significantly with increase in menopausal age ($P < .001$).
Adapted from Versi E, et al. *Int Urogynecol J*. 2001;12:107-10.

Changes in Sexual Arousal After Menopause*



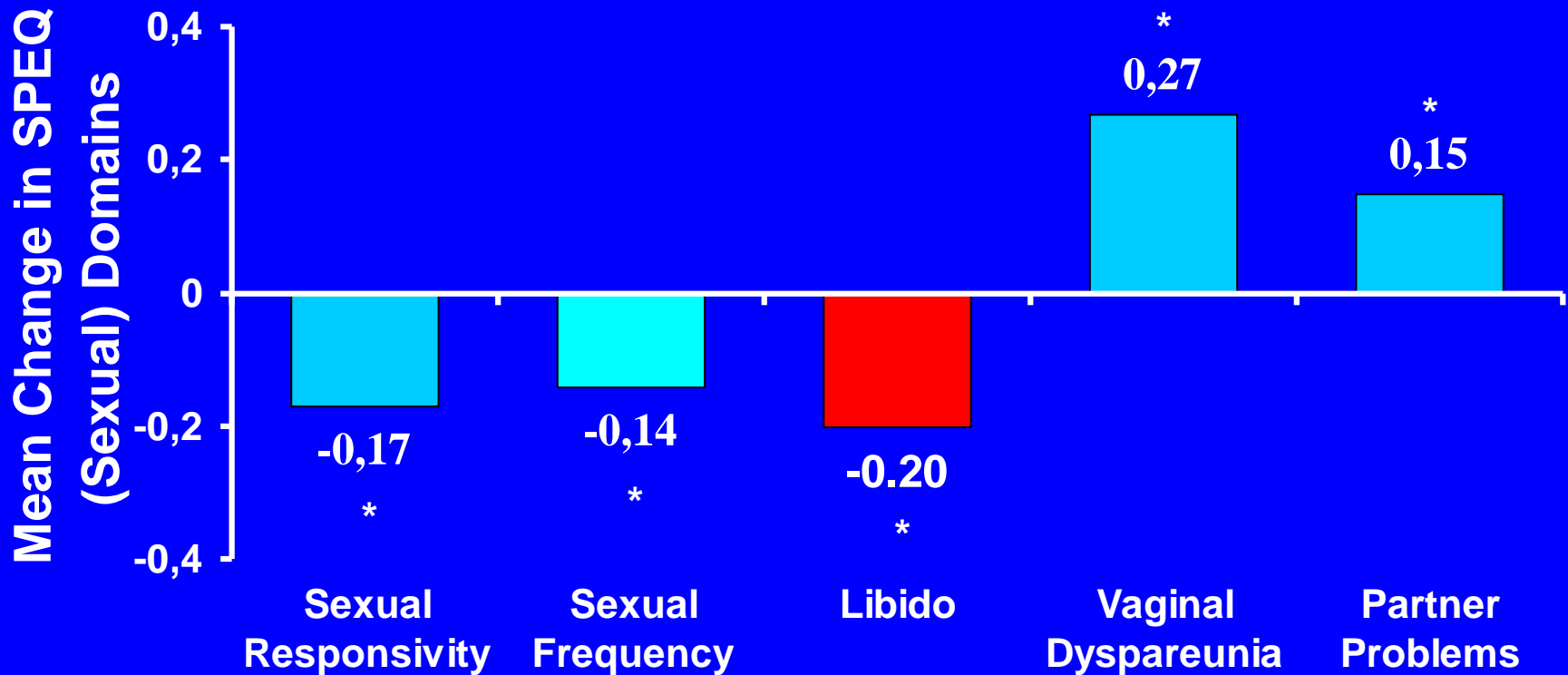
*As measured by the Sexual Activity Questionnaire. This scale has not been validated. n = 79.
Avis NE, et al. *Menopause*. 2000;7:297-309.

Pain during sexual intercourse

	WHILA- incontinent	WHILA- continent	
Sexually active	53.6 %	57.3 (NS)	p<0.001
Not at all	65.6 %	75.3 %	
A little	28.5 %	21.4 %	
Somewhat+ A lot	5.9 %	3.3	

Effect of Menopausal Transition on Parameters of Sexual Functioning

Cross-sectional Data Reported From a Longitudinal, Population-based Cohort of Australian Women, 45–55 Years of Age

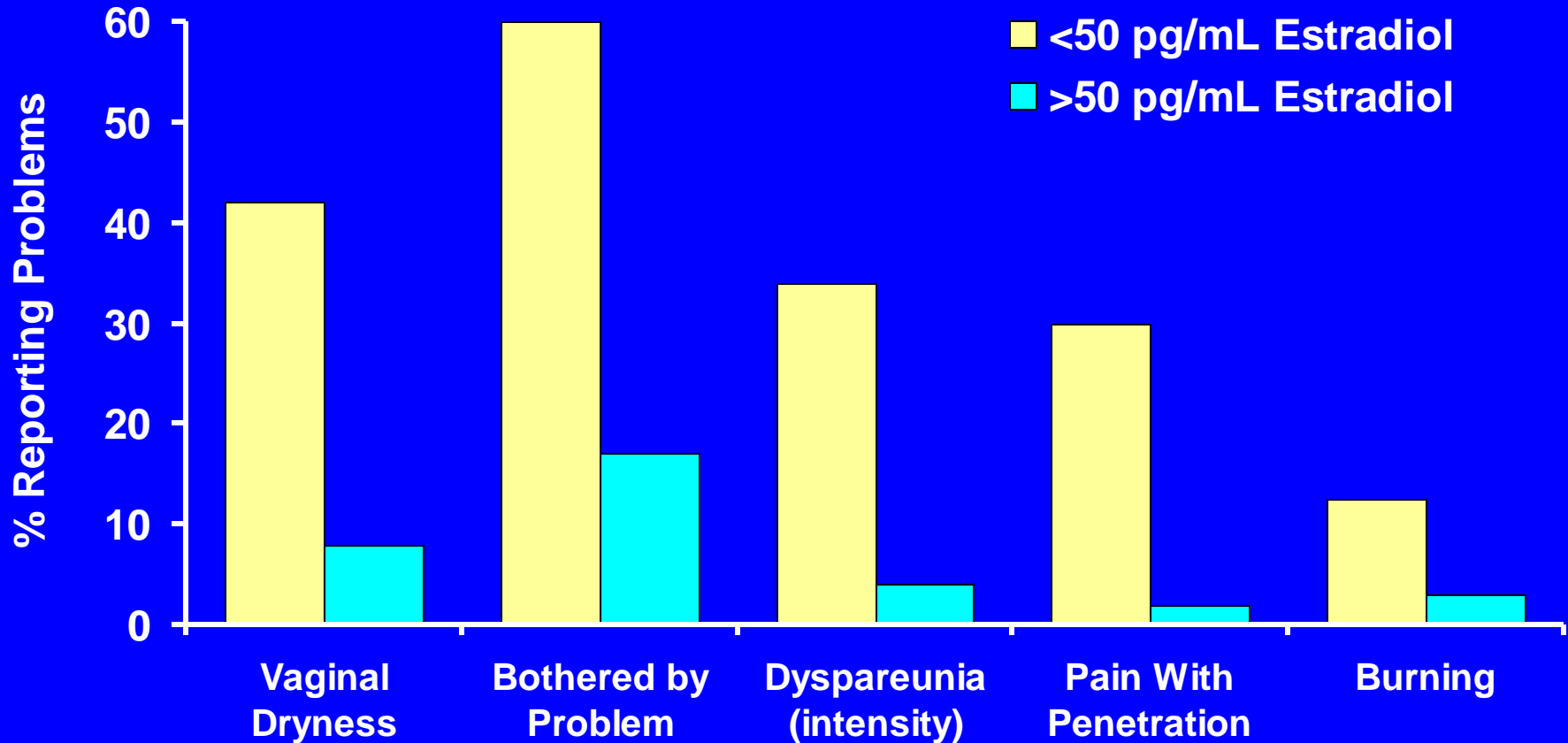


n = 438; SPEQ = Shortened version of the Personal Experiences Questionnaire.

*P < .05 for postmenopausal compared with perimenopausal women.

Dennerstein L, et al. *Fertil Steril*. 2001;76:456-60.

Lower Estrogen Levels Are Associated With Increased Prevalence of Sexual Problems



n = 93; significance not reported.

Sarrel PM. *J Womens Health Gen Based Med.* 2000;9:S25-S32.

Adapted from Sarrel PM. *Obstet Gynecol.* 1990;75:26S-30S.

Treatment Options for Sexual Dysfunction/Complaints

- Sex therapy/couples' therapy
- Hormone therapy
 - Topical estrogen
 - Systemic estrogen
 - Estrogen ± progestin
 - Estrogen/androgen*
 - Androgens*
- Lubricants/moisturizers

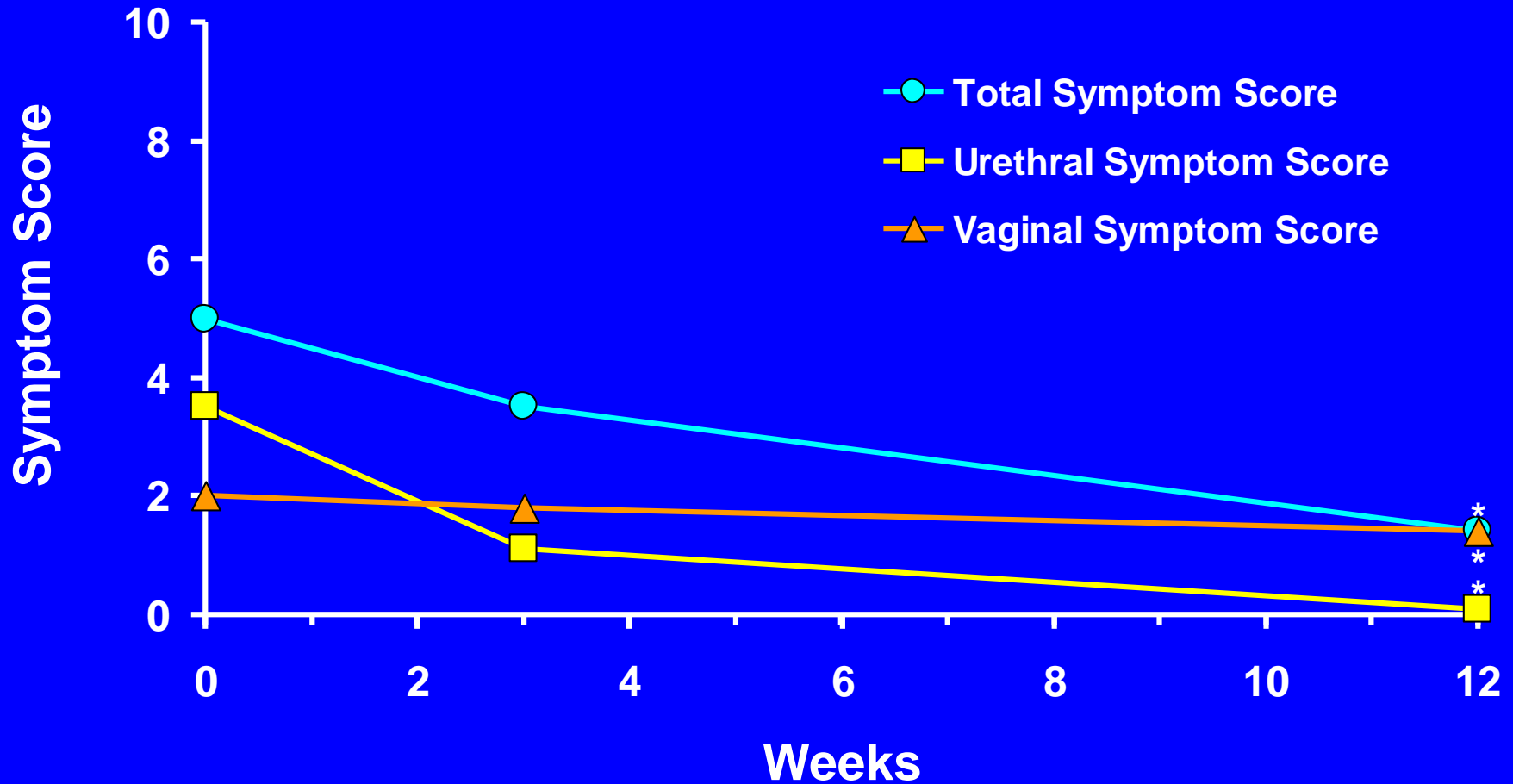
***Not FDA approved for treatment of sexual complaints.**

Vaginal Lubricants and Moisturizers

- Multiple vaginal moisturizers and lubricants are available over the counter
- Selection of product is based on individual preference

Examples of over-the-counter lubricants include Astroglide® and Replens.®

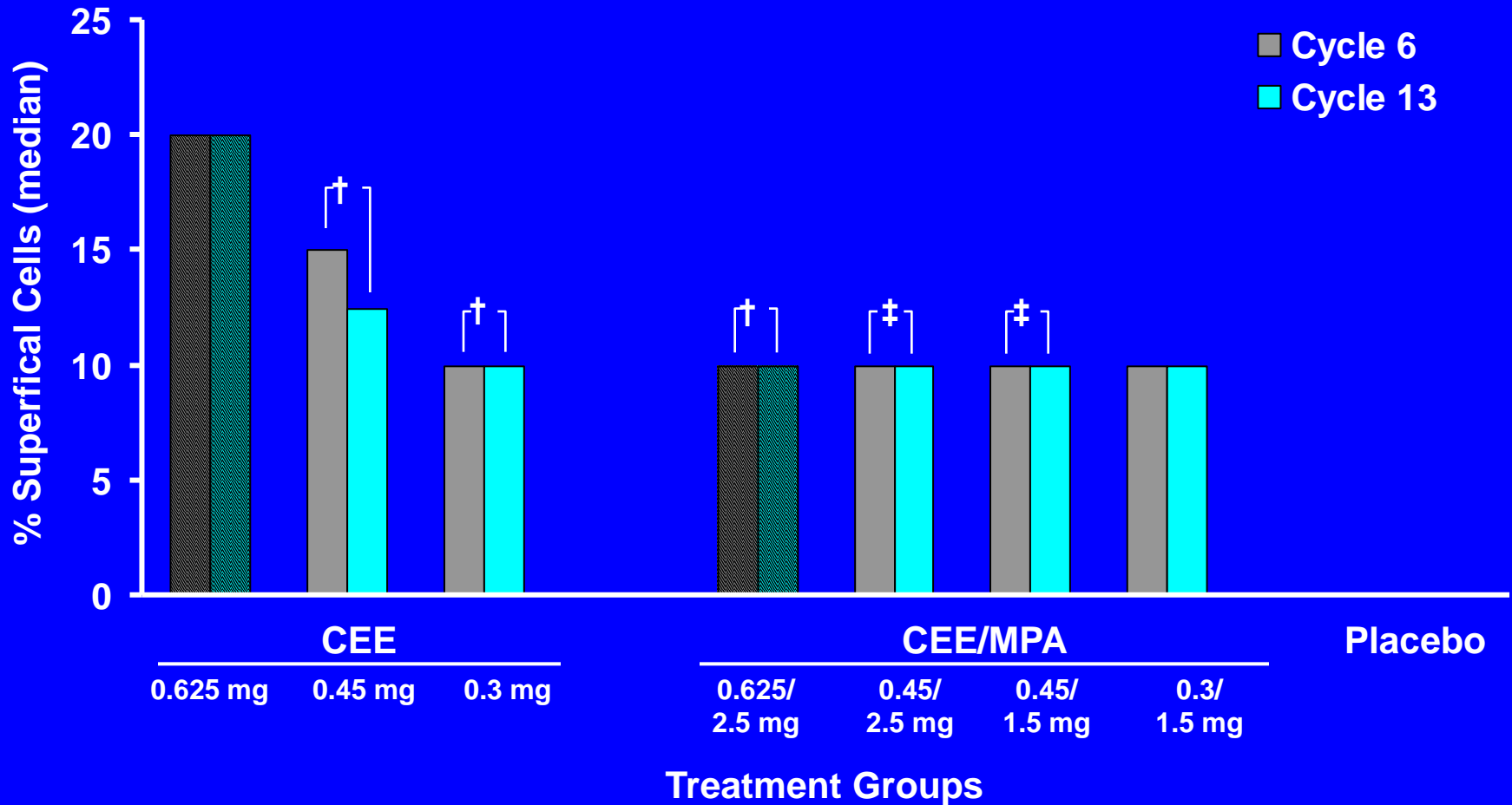
Estradiol Administered Vaginally Treats Urogenital Symptoms



* $P < .05$ compared with baseline

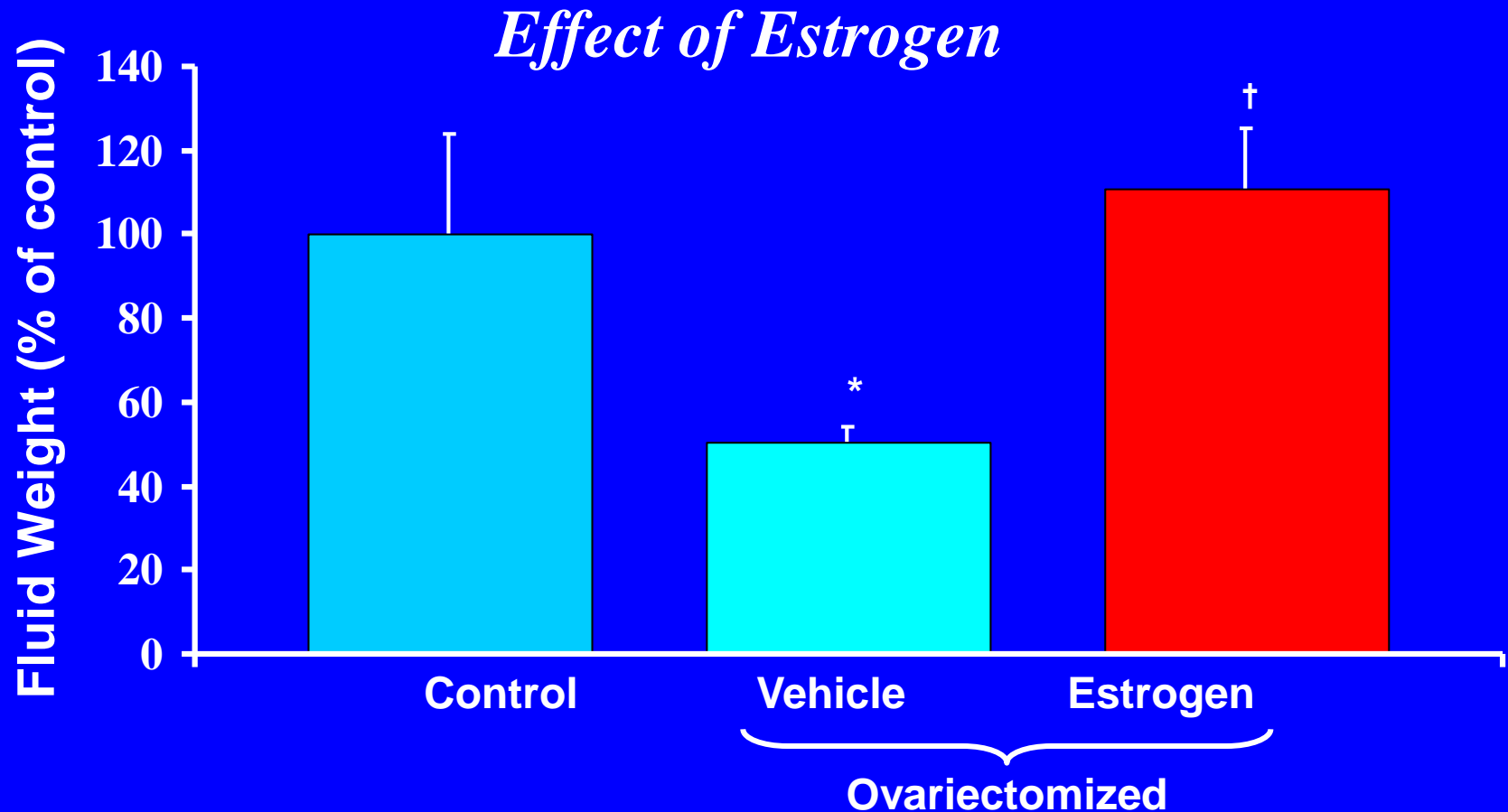
Women's HOPE Study

*Effect of CEE, CEE/MPA on Vaginal Maturation**



* $P < .05$ vs baseline and placebo for all active treatment groups; † $P < .05$ vs CEE 0.625; ‡ $P < .05$ vs CEE 0.3/MPA 1.5.

Vaginal Lubrication (Weight of Vaginal Tampon) Following Pelvic Nerve Stimulation in an Animal Model



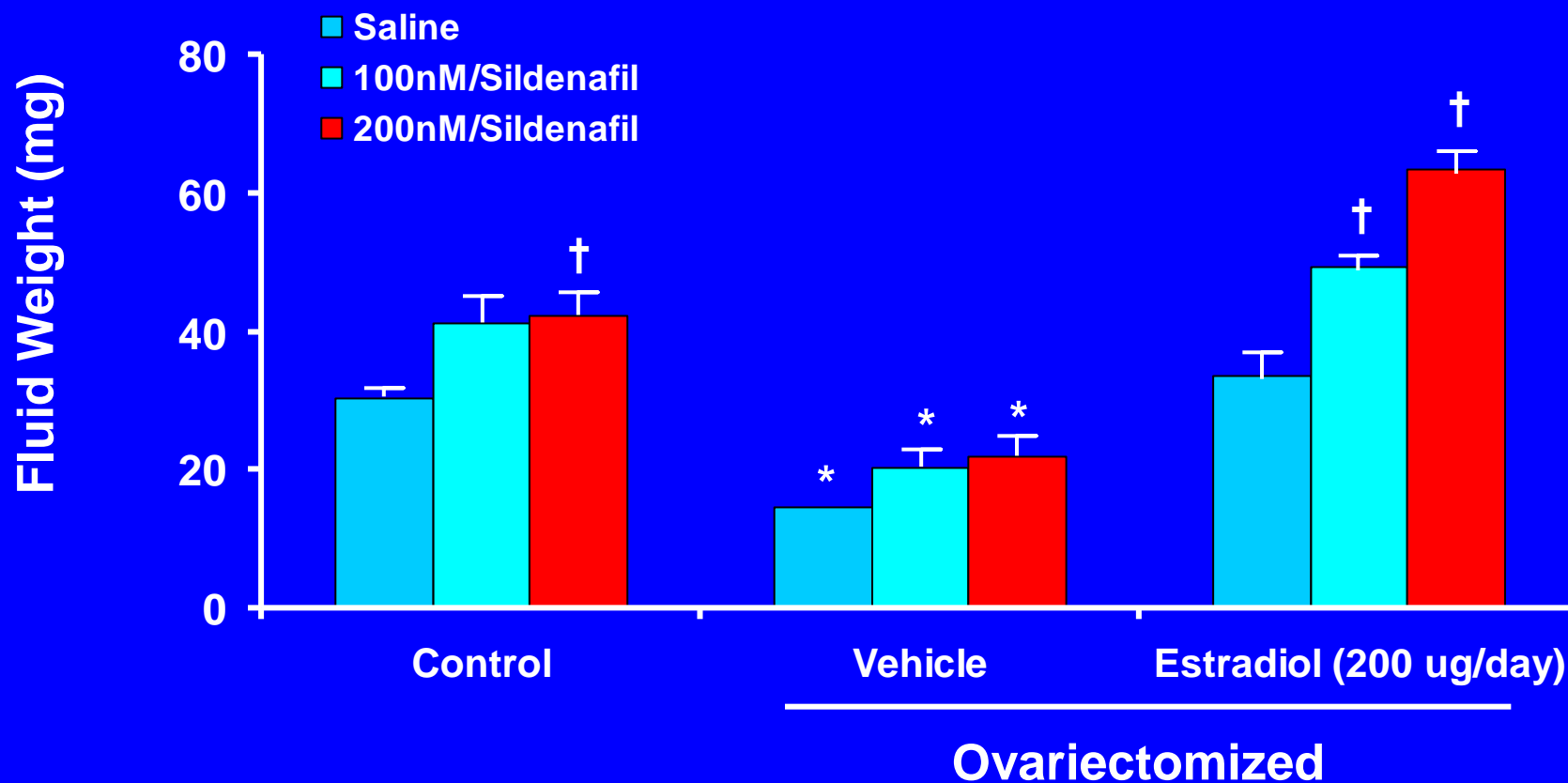
After ovariectomy, pelvic nerve stimulation resulted in reduced vaginal lubrication.

Estrogen therapy after ovariectomy restored vaginal lubrication.

* $P < .0001$ relative to control; † $P < .01$ relative to ovariectomy

Vaginal Lubrication (weight of vaginal tampon) Following Pelvic Nerve Stimulation in an Animal Model

Effect of Estrogen and Sildenafil



* $P < .05$ vs control at same sildenafil concentration.

† $P < .05$ vs saline within each treatment group.

Pelvic floor exercise

- Estrogens increase blood flow
- Less risk of exhaustion
- TRAINING MORE EFFICACIOUS

Oral vs vaginal administration

- Both equally effective
- Vaginal ring may offer support to bladder neck
- Preference for one or the other
- Parkinsons and other diseases could be obstacles to vaginal administration
- Different pharmaco-kinetics & -dynamics

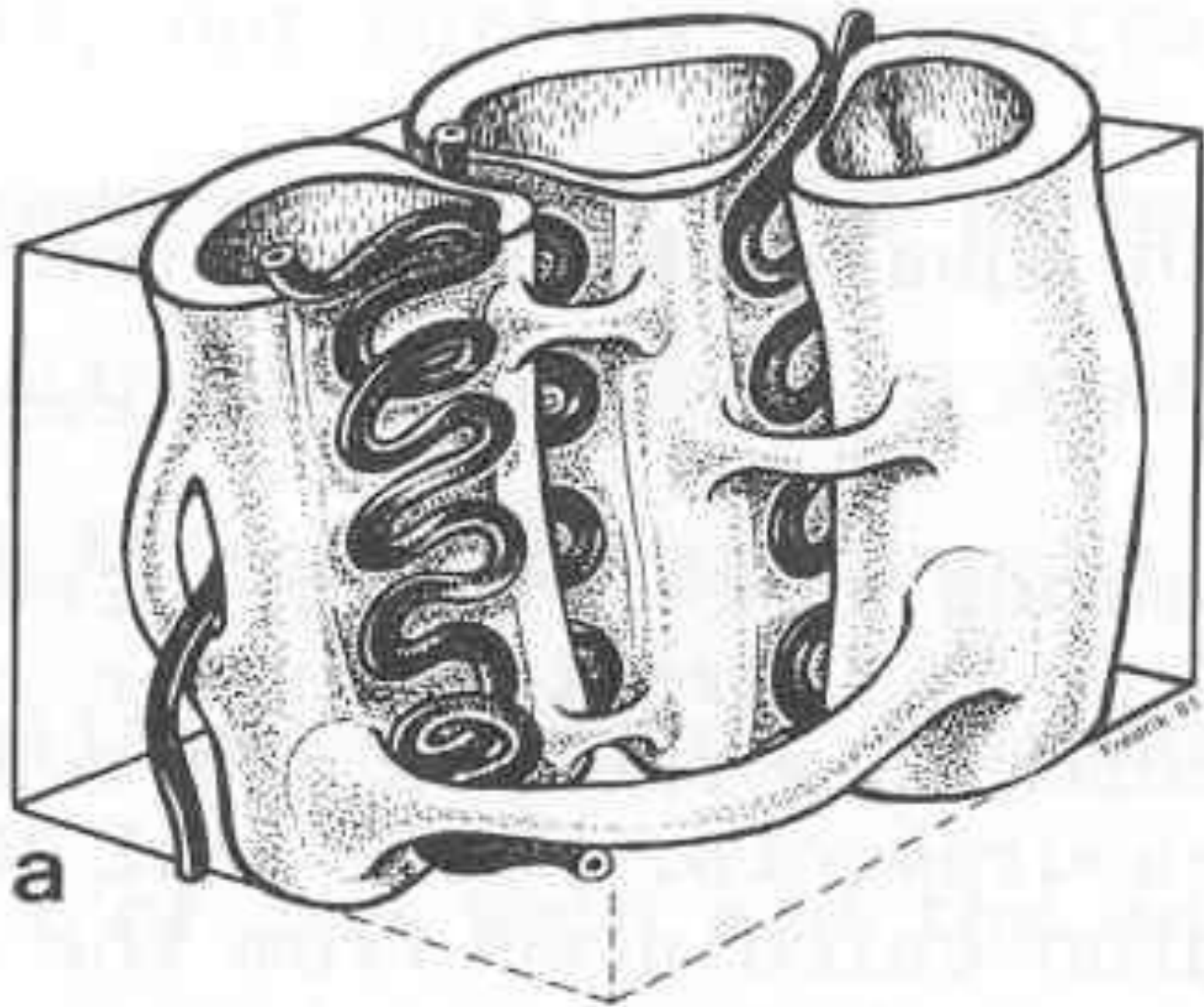
Serum E2 levels by Vagifem

24 women 10 microg or 25 microg Vagifem

- Significant increase on day 1
- Small insignificant increase by day 14
- Equally effective on vaginal variables
- 25 microg superior on maturation index

Counter current mechanisms

- A common physiologic principle
- Loop of Henle
- Uterine-ovarian direct communication
- Branches of uterine vein and artery
- Local concentrations remain local
- Local metabolism and excretion



Counter-current transfer from vagina to urethra

- 30 postmenopausal women
- Cold saline tubes vaginally
- Temperature in bladder vs urethra
- Significantly quicker and more pronounced cooling of the urethra

Accumulation of pc in vaginal fluid

- 1 g penicillin to 5 women b.i.d for 10 days
- Steady increase in vaginal fluid but
- Not in serum or saliva
- 15 hours after intake vag.fluid > 1 mg/L with no activity in serum or saliva.
- Drug not eliminated until 2nd day after adm

Countercurrent mechanisms & Vaginal absorption

- Not of significance in atrophic conditions
- Will develop as a response to estrogen
- At low doses drug retained urogenitally
- Slow elimination hence (twice) weekly administration.

Local estrogens

- Enhance blood flow
- Augment counter current mechanisms
- Facilitates pelvic floor muscle training
- Increase sensitivity to drugs by up to 4 times allowing lower doses and hence less systemic (side) effects

Local estrogens

- Void of systemic side effects after 2weeks
- Exception the old elderly due to poor counter current status and poor hepatic clearance.

Vaginal symptoms and Vagifem

- 1357 pm (10 yrs) women mean age 61.1 yrs
- 6 months
- Marked reduction of ALL vaginal symptoms

Vagifem 10 and 25 ug

- RCT 230 pm women.12 weeks then all on 25 ug for 52 weeks
- Both regimens effective but 25 ug superior on several symptoms of atrophic vaginitis

Low dose estrogens and endometrial cancer

17822 postmenop women ,15.5 yr follow-up

Questionnaire data

166 cases with Endometrial cancer

Combined oral HT RR 0.3 (0.1-0.8)

Oral estriol 1-2 mg RR 2.0 (1.1-3.6)

Vag E2 or E3 RR 1.5 (0.4-6.2)

Local estrogens:efficacy

Cochrane review

- 19 trials with 4162 women
- Endometrial hyperplasia 2-4%
- All products equally effective

Vaginal estrogens & serum E2 and E1 levels

- 20 postmenop. women aged 44-72 yrs
- FSH > 40IU. Mod or severe vaginal sympts
- Ransomized to Vagifem or Premarin Cream
- 1 w treatment GLC/MS determ. of E1 & E2
- Significant increase of both E1 and E2
- Some on Vagifem remained low

Vaginal E2 & breast cancer

- Does not increase risk of breast cancer
- May intervene with mechanism of action in breast cancer patients on aromatase inhibitors
- If severe vaginal atrophy ensues-shift to tamoxifen

Conclusion

- Estrogens ameliorate the majority of all symptoms
- Low dose topical estrogens exert no systemic effects.
- Very low doses required for the old elderly
- Can be used by breast cancer patients
- Not to be used in conjunction with aromatase inhibitors but OK with Tamoxifen

THANK YOU
for
Your Attention!