

# CONSEQUENCES AND MANAGEMENT OF UROGENITAL ATROPHY

## UROGENITAL ATROPHY

1 UG changes in menopause

2 Prevalence of vaginal atrophy

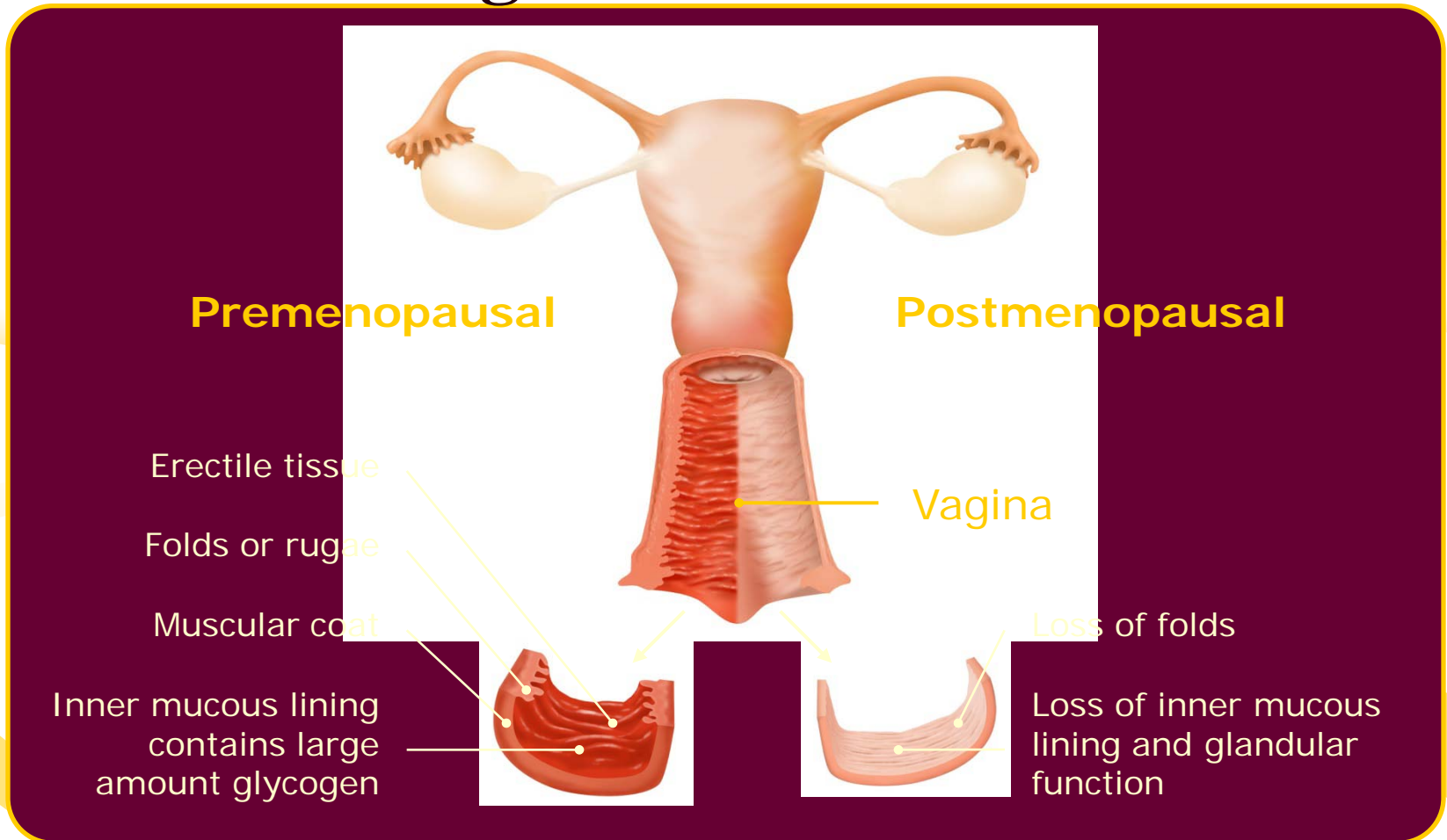
3 Management options

4 Hormone therapy. Vaginal route

5 Potential barriers to management UGA

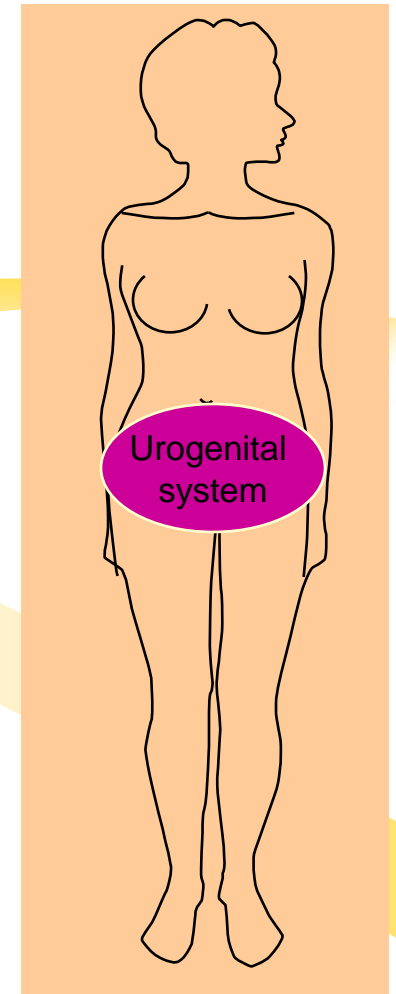


# Postmenopausal changes in the vaginal mucosa



# Vaginal Changes in Menopause

- Before menopause
  - Vaginal epithelium is thick and nonkeratinized
  - Glycogen is abundant
  - Normal acidic pH is 3.5 to 4.5
- Impact of menopause on the urogenital system
  - Estrogen declines
  - Vaginal epithelium loses rugae
  - Tissues grow thin and pale
  - Vaginal secretions decrease
  - Glycogen diminishes
  - Vaginal pH increases



Pandit and Ouslander. *Am J Med Sci* 1997; 314:228-231.



# Compared to premenopausal women, postmenopausal women with estrogen deficiency have

## **FEWER:**

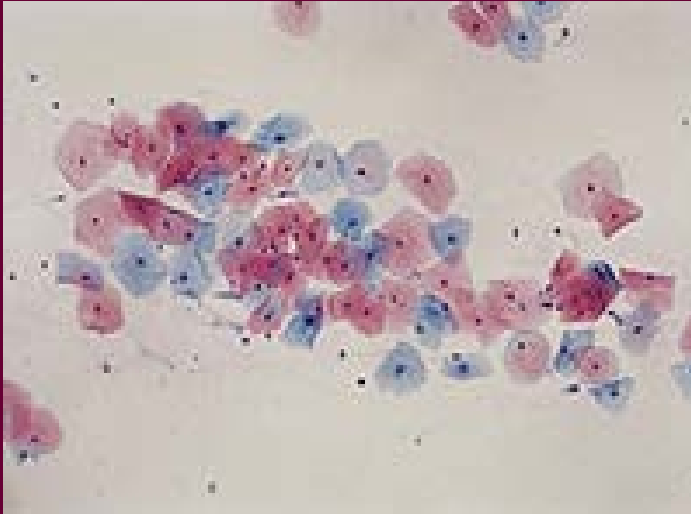
- **Facultative lactobacilli**
- **Gardenerella vaginalis**
- **Coryneforms**
- **Yeasts**
- **Prevotella bivia**
- **Staphylococci**
- **Mycoplasma hominis**
- **Ureaplasma urealyticum**

## **BUT MORE:**

- **Coliforms**
- **Streptococi viridans.**

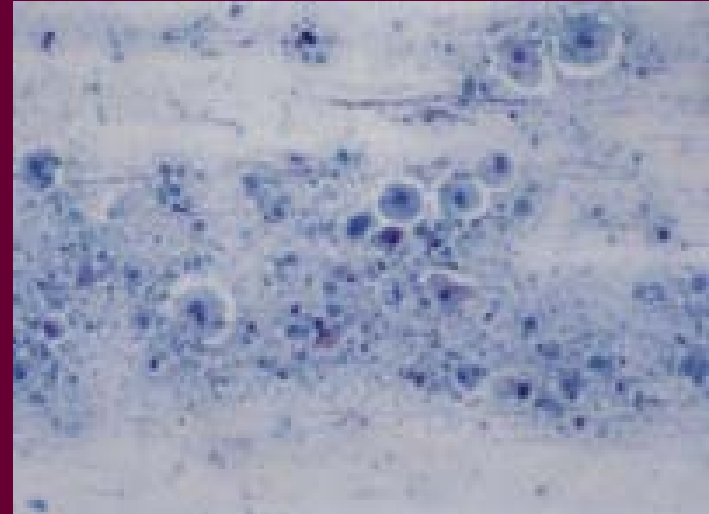


# Atrophic vaginitis under the microscope



## Normal:

- Squamous cells
- Cells with enough cytoplasm and a low nucleus/cytoplasm ratio
- Pyknosis present



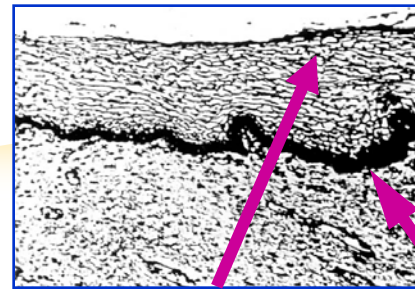
## Atrophic vaginitis:

- Presence of parabasal cells
- Squamous cells with enlarged nuclei
- Inflammation exudate
- "Blue Blobs" – characteristic, round basophilic structures

# Vaginal Atrophy

- Symptoms
  - Vaginal dryness
  - Decreased lubrication
  - Discomfort, burning, soreness
- Predisposition to:
  - Urinary tract infections
  - Vaginal infections
- Advanced signs
  - Contraction of vagina
  - Loss of distensibility

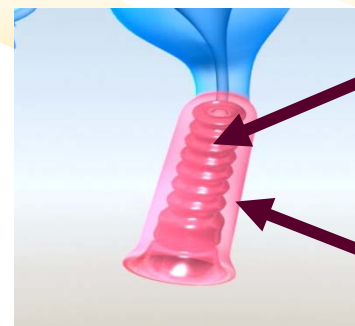
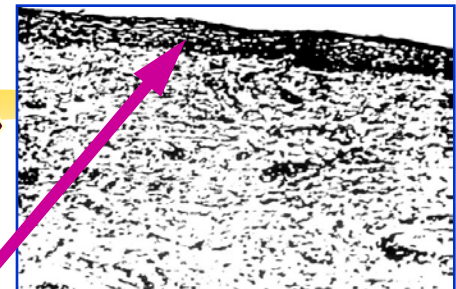
Postmenopausal woman treated with estrogen



Superficial cells

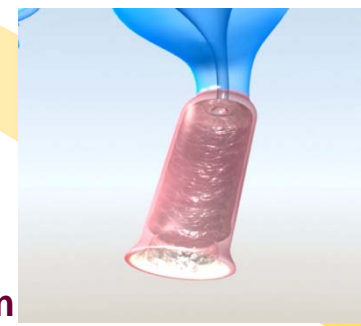
Parabasal cells

Postmenopausal woman without estrogen



Rugae

Vaginal epithelium



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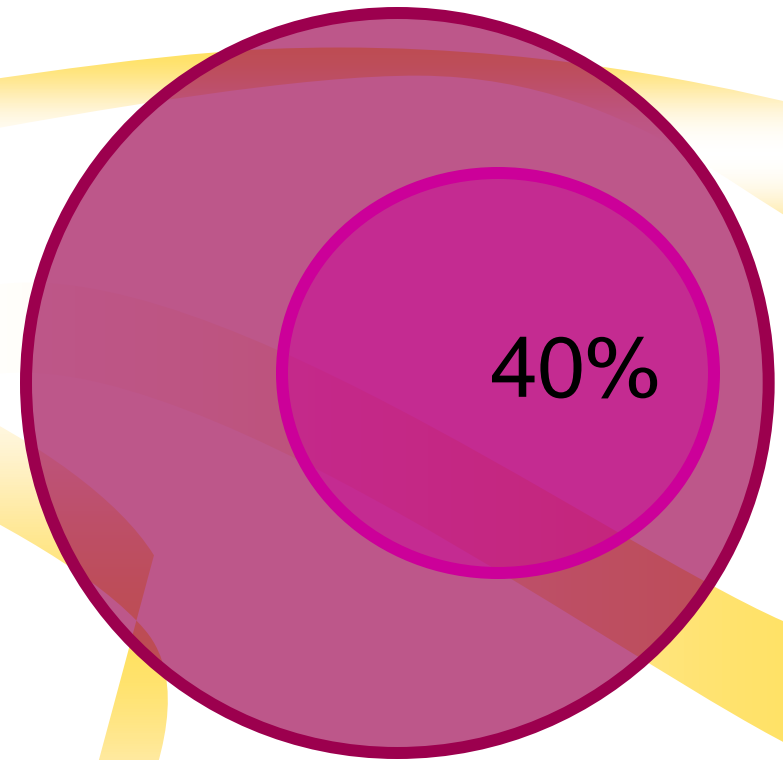
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# Prevalencia de la atrofia vaginal

- **467 millones de mujeres menopausicas en el mundo(1990)**
- **Más del 40% con síntomas de atrofia vaginal—187 millones de mujeres en el mundo**
- **Menos del 25% reciben atención medica**

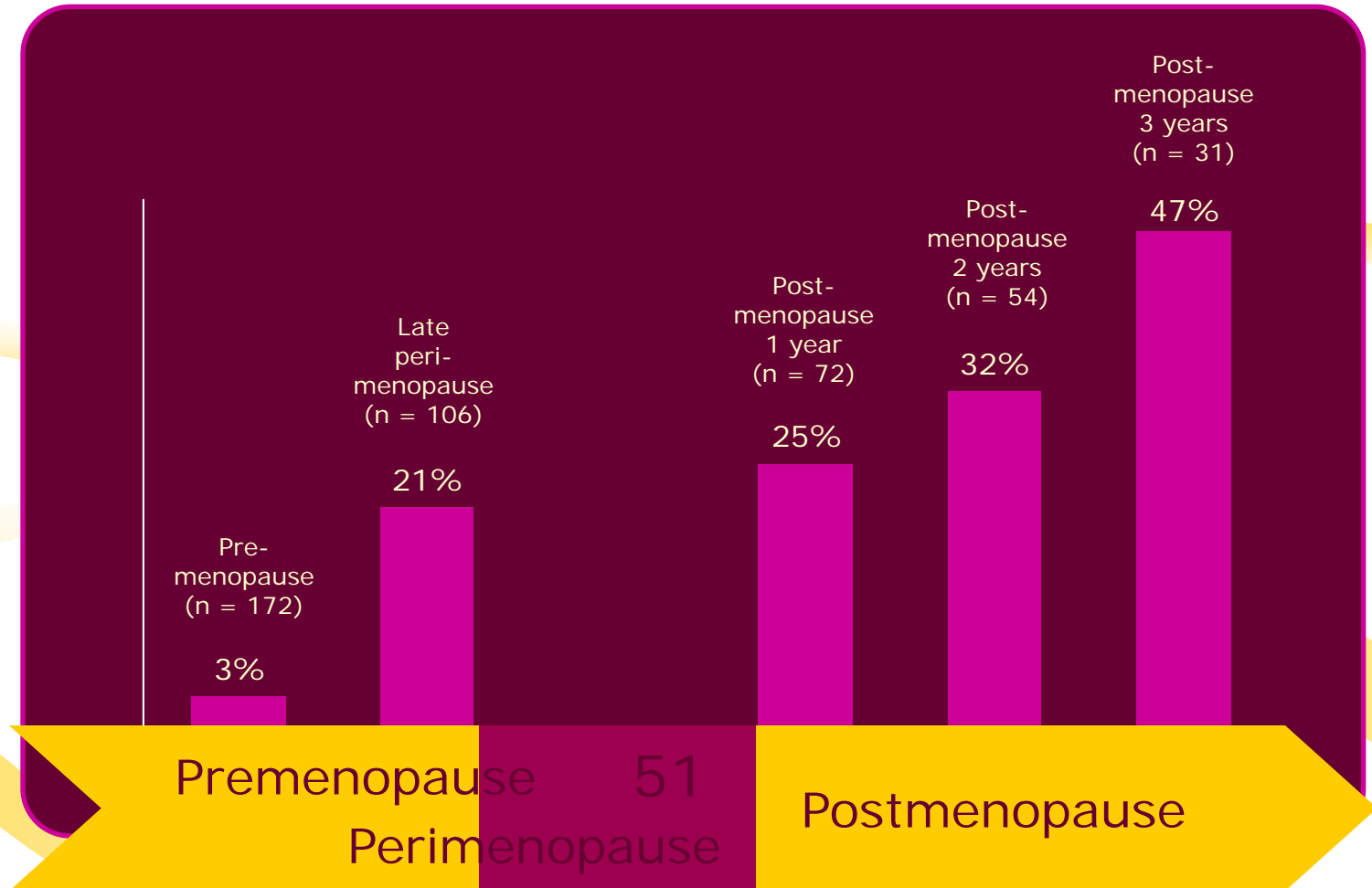


Cardoza, et al. *Obstet Gynecol.* 1998;92:722-7.  
Hill. *Maturitas.* 1996;23:114-27.





# Increase in vaginal dryness with age



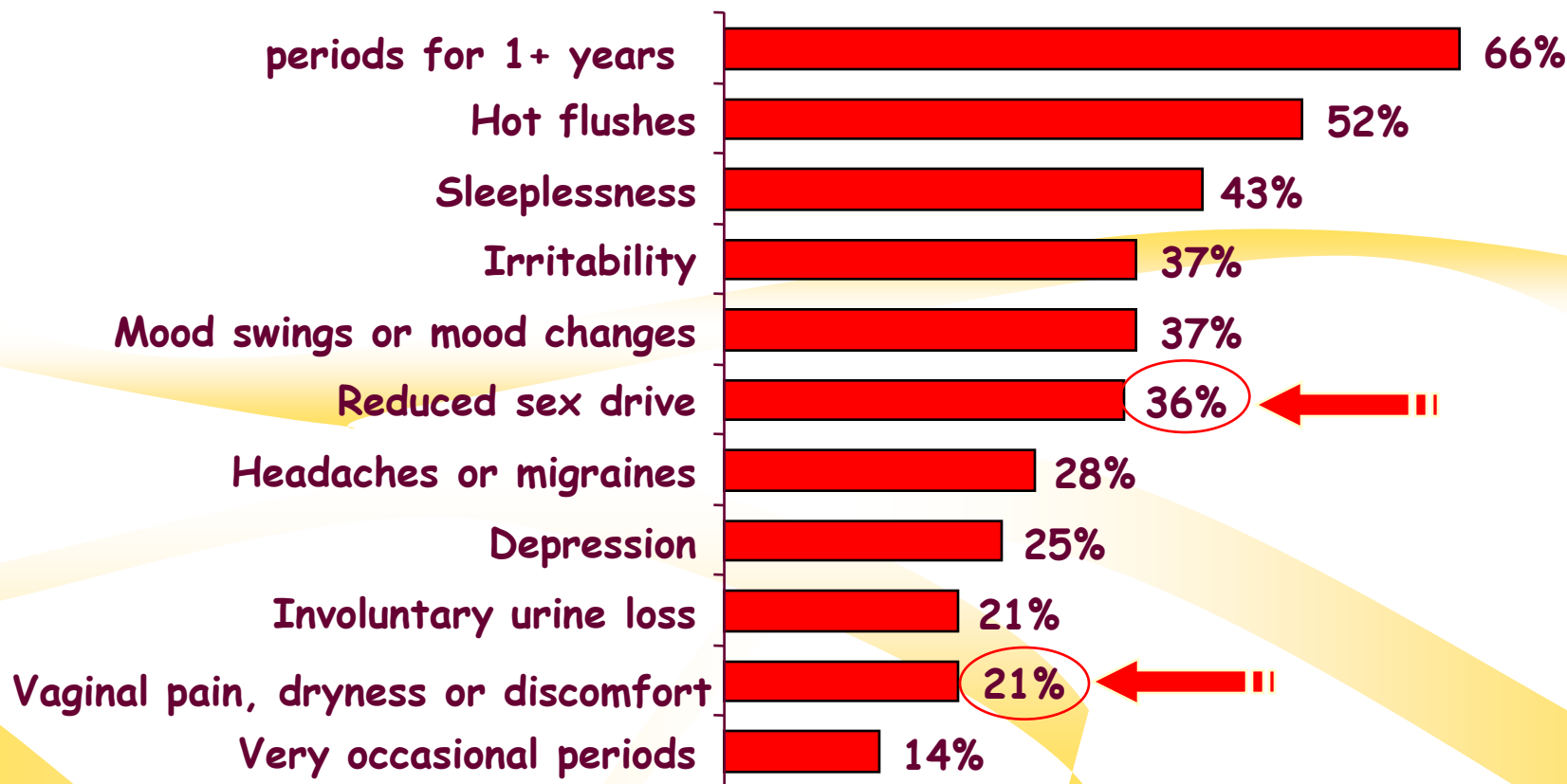
Dryness increased significantly in late perimenopause and postmenopause ( $p < 0.001$ )

Dennerstein L et al., *Obstet Gynecol.* 2000; 96: 351–8





# RELEVANCE OF SEXUAL ISSUES AT MENOPAUSE

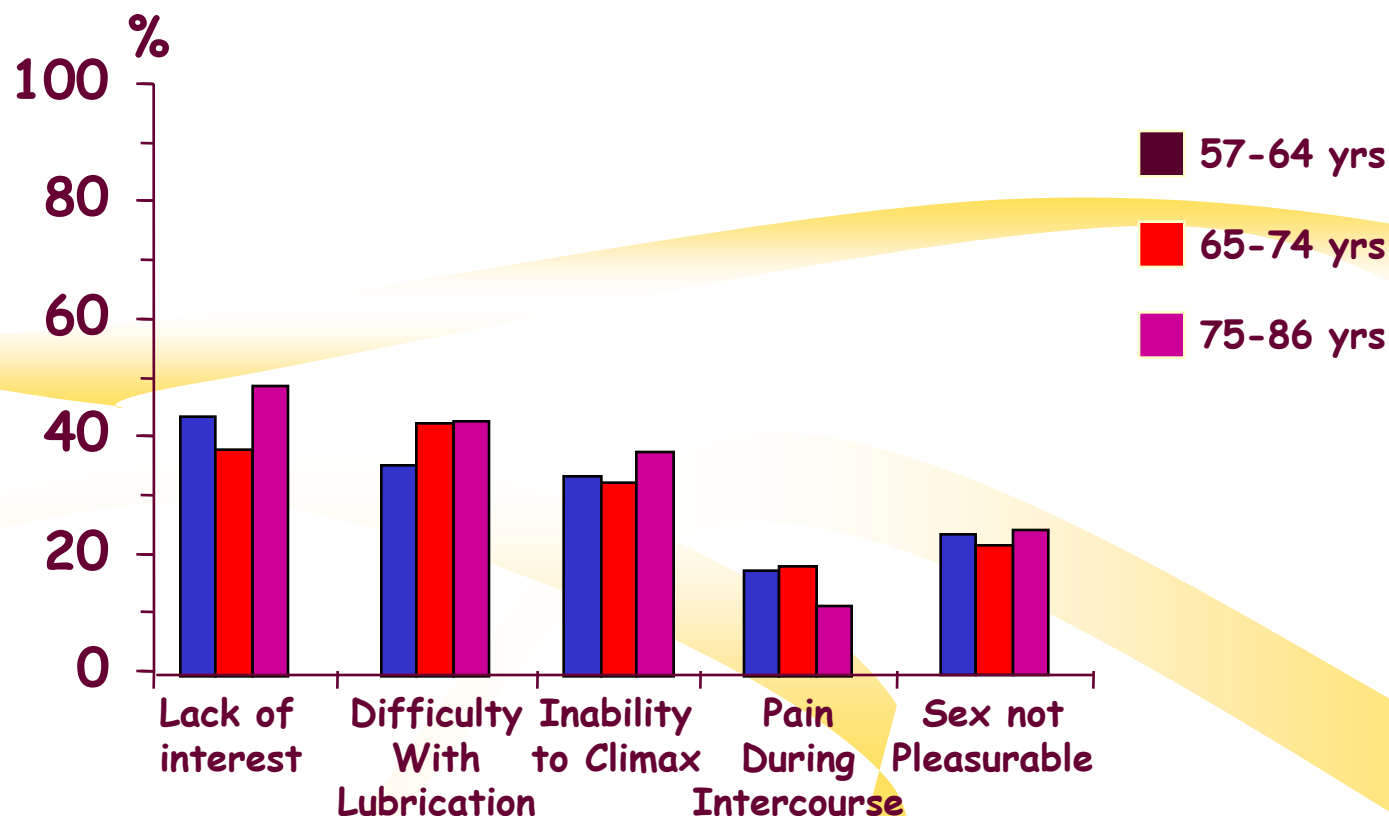


Are you currently experiencing or have you experienced any of the following in the past year?  
Base: Total Sample (n=1805) of European (from Italy, Switzerland, UK, Germany, France, The Netherlands) menopausal women (age: 50-60 yrs) interviewed by phone





## PREVALENCE OF WOMEN'S SEXUAL DYSFUNCTION among older adults in the US

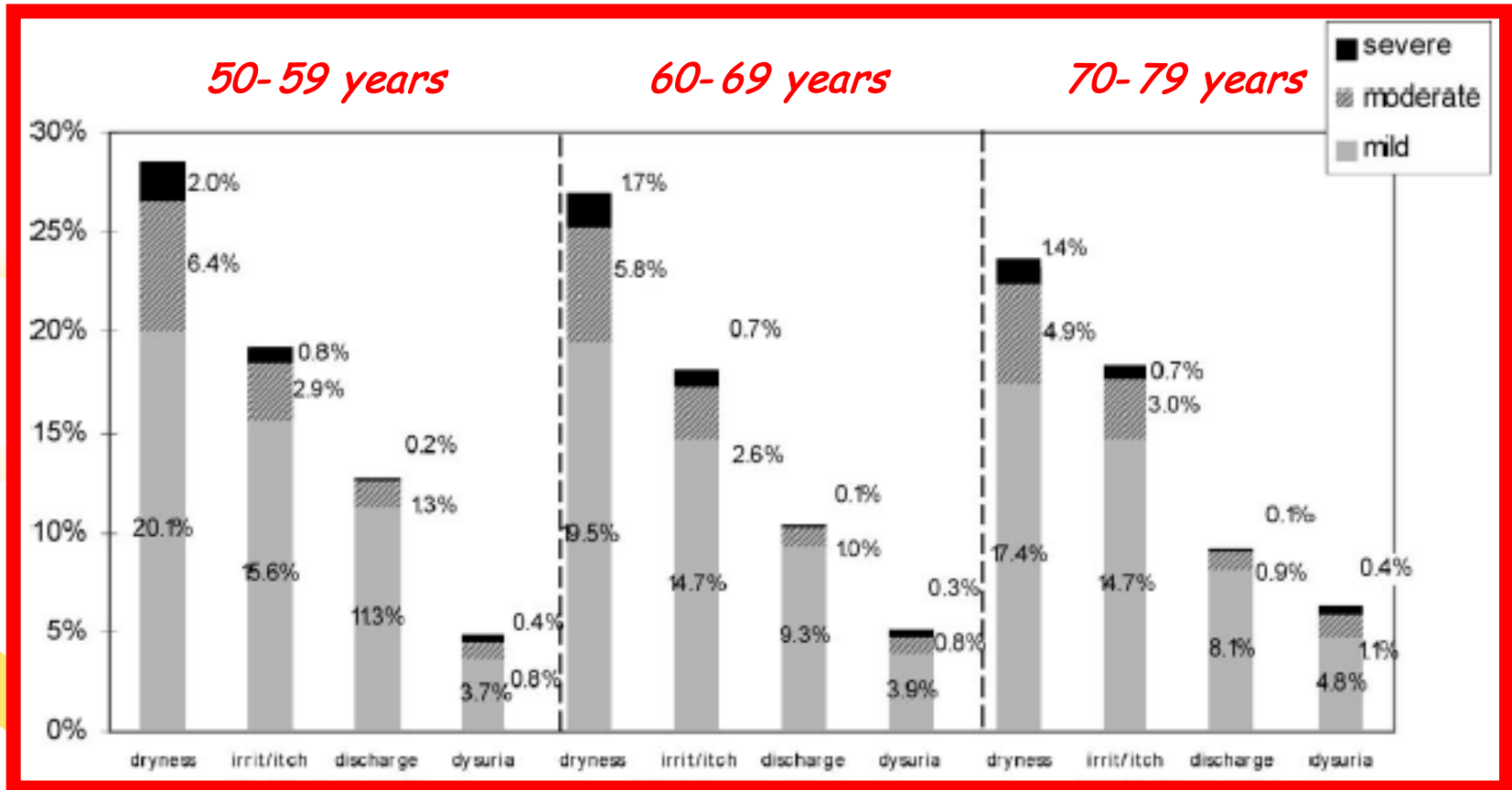


- The most prevalent sexual problems among women were low desire (43%), difficulty with vaginal lubrication (39%), and inability to climax (34%). A total of **22% of women** reported having discussed sex with a physician since the age of 50 years. Lindau et al, 2007

# URO-GENITAL SYMPTOMS MENOPAUSE & AGING



*Cross-sectional Analysis on n= 98705 Women enrolled in the US-based Women's Health Initiative (WHI) observational study and clinical trials*



Prevalence rates:

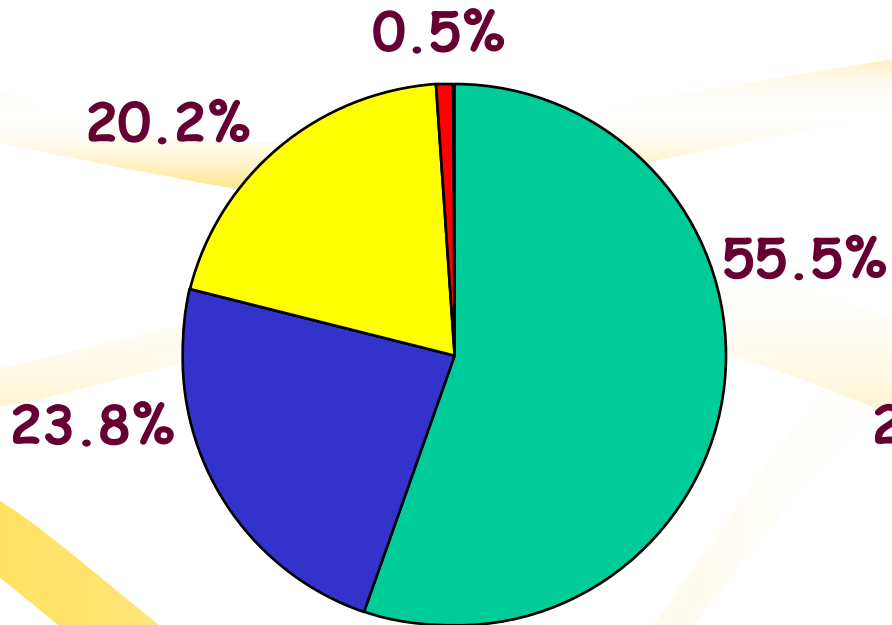
**dryness 27.0%; irritation or itching 18.6%; discharge 11.1%; dysuria 5.2%**

# SEXUAL SYMPTOMS & SURGICAL MENOPAUSE



## VAGINAL DRYNESS

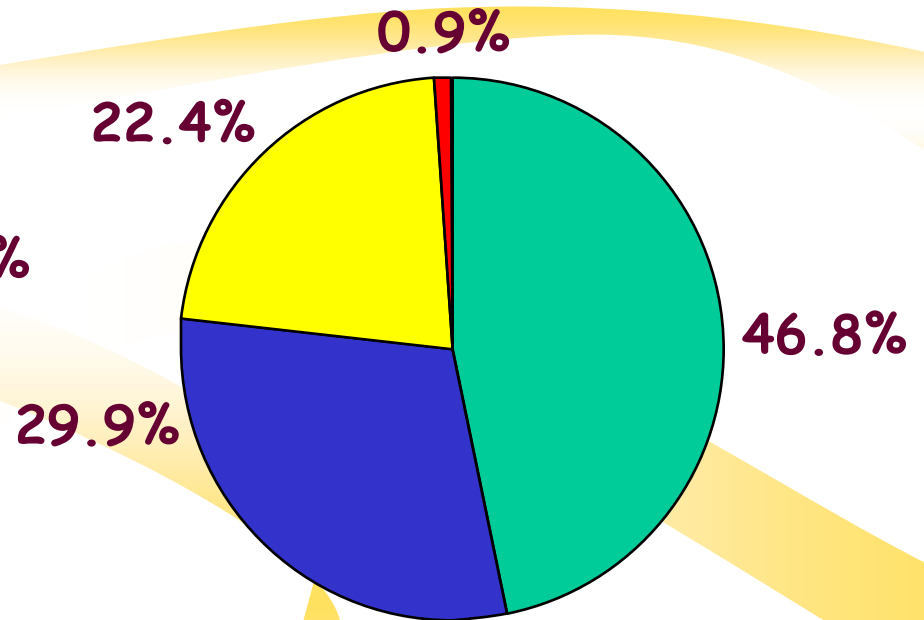
Q: After surgical menopause did you noticed the appearance/worsening of...



Sample: 568 women with surgical menopause

## SEXUAL DESIRE

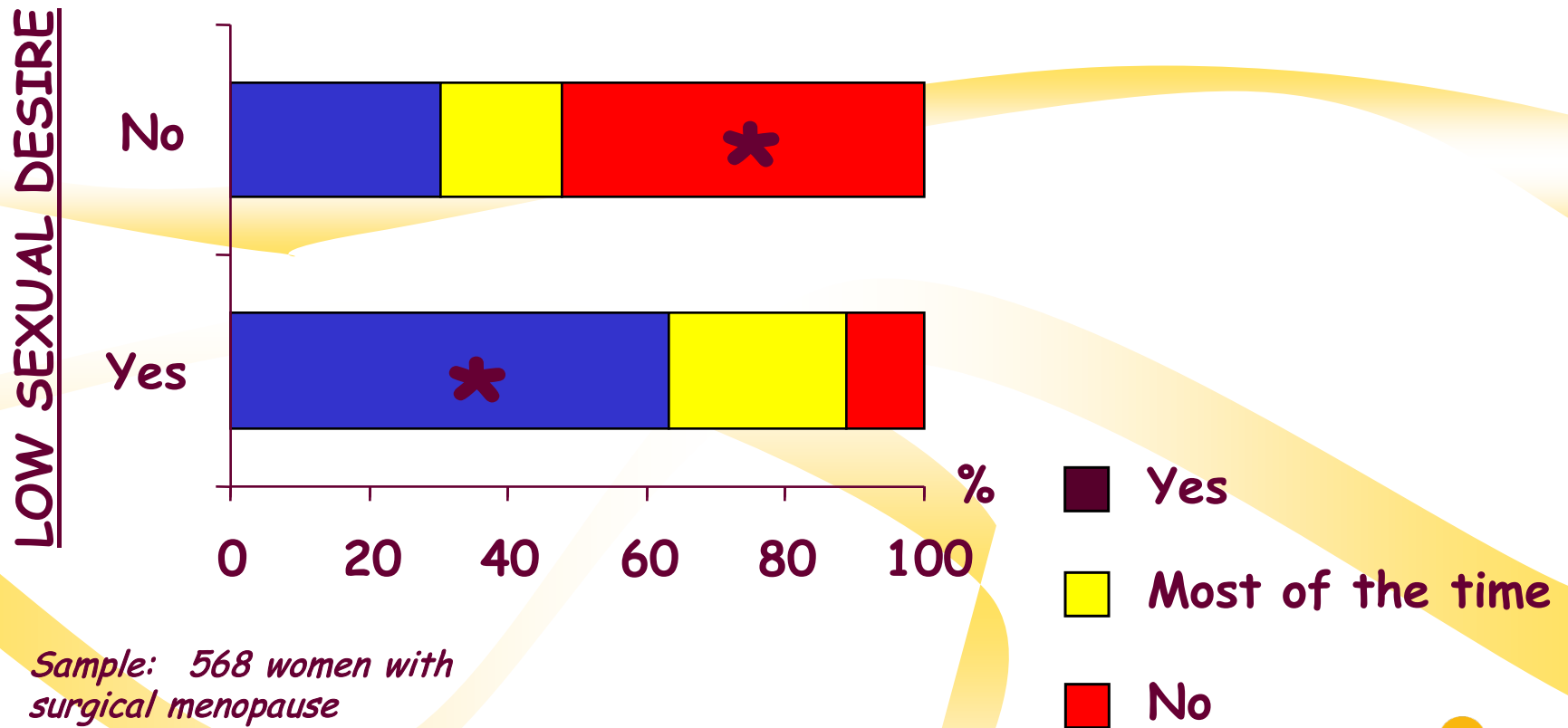
Q: After surgical menopause did you noticed a reduction of...



# SEXUAL COMORBIDITY IN SURGICAL MENOPAUSE



## VAGINAL DRYNESS



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# MANAGEMENT OPTIONS

- a) Lifestyle modifications
- a) Non-hormonal treatment (lubricants, moisturizers)
- a) Hormonal therapy, systemic or local
- a) Others: herbal, soy, vitamins





# LIFE STYLE MODIFICATIONS

## 1 .Cessation of smoking

Kalogeraki. In Vivo. 1996

## 2. Sexual activity.

**Both regular coital activity and masturbation provide protection**

***“USE IT OR LOSE IT”***

Leiblum et al. JAMA. 1983

## 3. Cranberry - lingonberry juice concentrate reduces risk of UTI in postmenopausal women.

Kontiokari. BMJ. 2001



# NON HORMONAL THERAPY

## *LUBRICANTS*

Temporary measures to relieve vaginal dryness during intercourse,

- ❖ Combination of protectants and thickening agents in water soluble base.
- ❖ Short duration of action, needs frequent application and reapplication before sex.

- Astroglide
- K-Y jelly
- Lubrin
- H-R jelly
- Surgilube
- Touch

Wilhite et al. Pharmacology. 2001



# MOISTURIZERS

- ❖ **Bioadhesive polycarbophil-based polymer which adheres to mucin and epithelial cells on vaginal wall**
- ❖ **Carry up to 60x its weight in water and holds water in place against vaginal epithelium until cells sloughs off, about 24 hours.**
- ❖ **2-3 applications per week.**
- ❖ **No need for reapplication prior to sex**
- ❖ **Symptomatic relief, acidic PH**
- ❖ **Some effect on vaginal elasticity**

*Replens  
Moist Again*



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## Randomized Control Trial Results Summary: Individual\* and Summary P Values

Study	Patient symptoms	Dyspareunia	Physician assessment	pH vaginal	Cytologic findings
Bellatoni et al <sup>10</sup>	.007				<.001
Campbell et al <sup>11</sup>	.010				
Campbell et al <sup>11</sup>	.001				
Erikson and Rasmussen <sup>12</sup>	.021	.003	.002		
Felding et al <sup>13</sup>			.328		.118
Foidart et al <sup>14</sup>	.001				
Laufer et al <sup>15</sup>					.001
Molander et al <sup>16</sup>	.015	.244		<.001	<.001
Raz and Stamm <sup>17</sup>				.112	
Van der Linden et al <sup>18</sup>					<.001
Summary	<.001	.015	.016	.001	<.001

\* Individual P values are for one-sided comparisons between active drug and placebo.

***Meta analysis of placebo controlled trials revealed estrogen to be more effective than placebo for all variables measured***

Cardozo et al. Obstet Gynecol. 1998



## Effect of Route of Administration on Outcomes

Outcome measure	Oral		Vaginal		Parenteral	
	<i>n</i>	Effect	<i>n</i>	Effect	<i>n</i>	Effect
Patient report*	6	0.59	15	1.38	3	0.52
Dyspareunia <sup>†</sup>	1	1.20	8	1.05		
Physician assessment <sup>‡</sup>	2	0.50	20	1.47	2	1.02
pH <sup>§</sup>	3	1.36	6	1.68		
Cytology <sup>  </sup>	17	0.50	28	0.69	6	0.65
Estradiol level <sup>¶</sup>	12	0.32	14	0.68	3	3.56
Estrone level <sup>**</sup>	13	0.50	16	0.36	5	1.77

The higher the number, the greater the effect size.

*The vaginal route of administration correlated with better reports of symptomatic relief, greater improvement in cytologic findings*

Cardozo et al. Obstet Gynecol. 1998



## Effect of Type of Dosing on Outcomes

Outcome measure	Systemic estrogen		Low-dose oral estriol		Low-dose vaginal estriol		Low-dose vaginal estradiol	
	<i>n</i>	Effect	<i>n</i>	Effect	<i>n</i>	Effect	<i>n</i>	Effect
Patient report*	8	0.55	2	1.44	5	0.88	9	1.66
Dyspareunia <sup>†</sup>	1	0.49	1	1.20	2	1.43	5	0.94
Physician assessment <sup>‡</sup>	8	0.80	1	0.69	6	1.31	9	1.52
pH <sup>§</sup>	2	0.67	2	4.0	3	1.67	2	1.67
Cytology <sup>  </sup>	27	0.58	6	0.76	8	0.39	10	0.69
Estradiol level <sup>¶</sup>	17	1.02	4	-0.00	2	-0.06	6	0.71
Estrone level <sup>**</sup>	21	1.22	4	0.02	4	-0.07	5	0.36

The higher the number, the greater the effect size.

***Low dose vaginal estradiol was the most efficacious***

Cardozo et al. Obstet Gynecol. 1998



## Effect of Treatment Duration on Outcomes

Outcome measure	<1 mo		1-3 mo		>3 mo	
	<i>n</i>	Effect	<i>n</i>	Effect	<i>n</i>	Effect
Patient report*	2	0.80	13	1.32	9	0.94
Dyspareunia <sup>†</sup>	2	0.63	5	1.09	2	1.05
Physician assessment <sup>‡</sup>	7	1.45	8	1.59	9	1.02
pH <sup>§</sup>			5	2.49	4	1.46
Cytology <sup>  </sup>	28	0.58	19	0.90	4	0.34
Estradiol level <sup>¶</sup>	10	1.13	6	0.29	13	0.43
Estrone level <sup>**</sup>	12	0.89	9	0.53	13	0.32

The higher the number, the greater the effect size.

*Major effect on patient report occurs between 1 and 3 months after the start of treatment and is maintained thereafter*





# Types of local oestrogen treatment of atrophic vaginitis

Type of oestrogen	Mode of administration	
Estriol E3 <i>(Metabolite of Estradiol)</i>	Cream	(Ovestin <sup>®</sup> )
	Vagitories	(Ortho Gynest <sup>®</sup> )
Estradiol E2 <i>(Human estrogen)</i>	Tablets	(Vagifem <sup>®</sup> )
	Ring	(Estring <sup>®</sup> )
Conjugated <i>(Equine estrogens)</i>	Cream	(Premarin <sup>®</sup> )



# Vaginal application forms



## Creams

**Premarin®**  
vaginal cream  
(PVC) conjugated equine  
estrogens (CEE)

**Estrace®**  
estradiol cream  
in an applicator-  
free tube



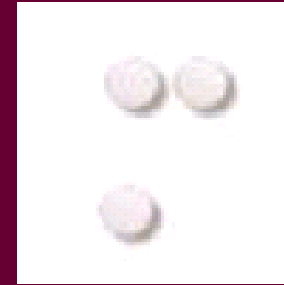
## Vaginal Ring

**Estring®**  
contains  
estradiol,  
releases  
estradiol in  
a consistent  
manner over  
90 days



## Vagitories

**Ortho Gynest®**  
vaginal estriol  
suppositories



## Vaginal tablets

**Vagifem®**  
first and only  
vaginal  
oestrogen tablet



# Other Treatments - SERMs

- SERMs elicit different effects in differential tissues
  - Agonist (bone)
  - Antagonist (breast)
- Previous SERMs have different actions:
  - Tamoxifen and raloxifene both act as antagonist in the breast and agonist in the bone
  - Only tamoxifen acts as agonist in the uterus
  - Neither tamoxifen nor raloxifene have an effect on the vagina
- New SERM – Lasofoxifene
  - Agonist behavior in bone, the vagina, and the cardiovascular system
  - Antagonist behavior in breast and uterine tissue



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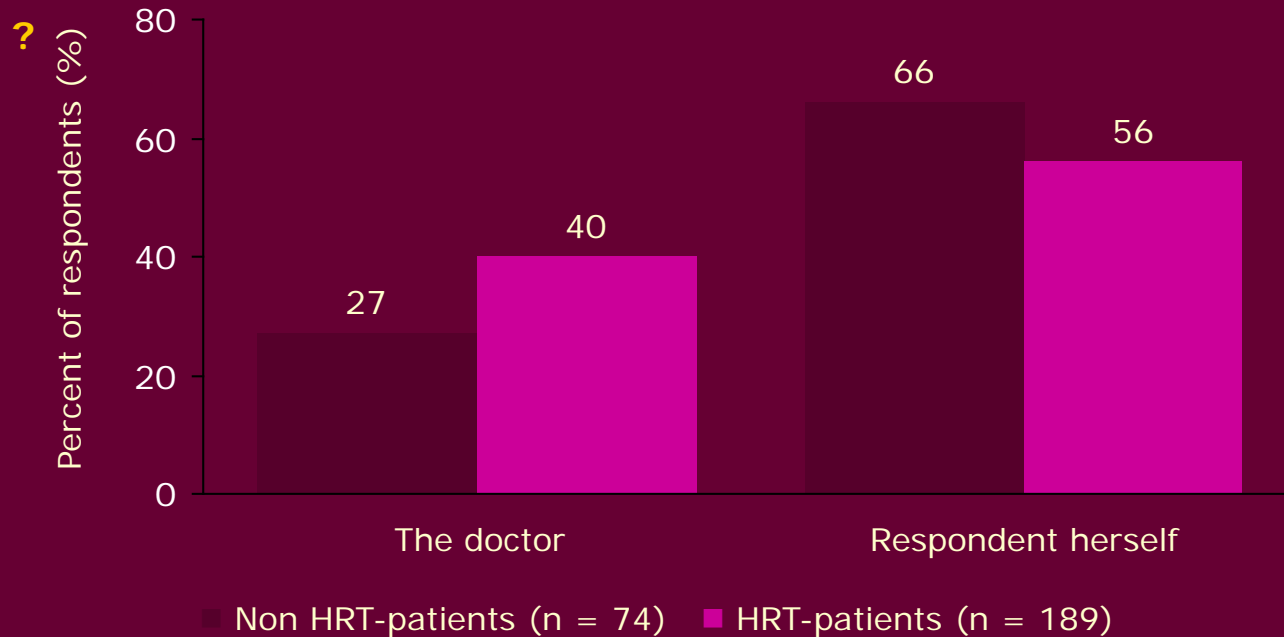


# Initiation of dialogue about vaginal dryness

## Women

### Selection:

respondents having discussed “vaginal dryness” with physician



# Potential Barriers to Discussing Sexual Health with your Patients

## Patient barriers

- Emotional factors (shame, anxiety, embarrassment)
- Age (life stage)
- Perception that sexual functioning is not an important medical problem
- Lack of awareness about treatment possibilities
- Physician characteristics (gender, age, speciality)

## Contextual barriers

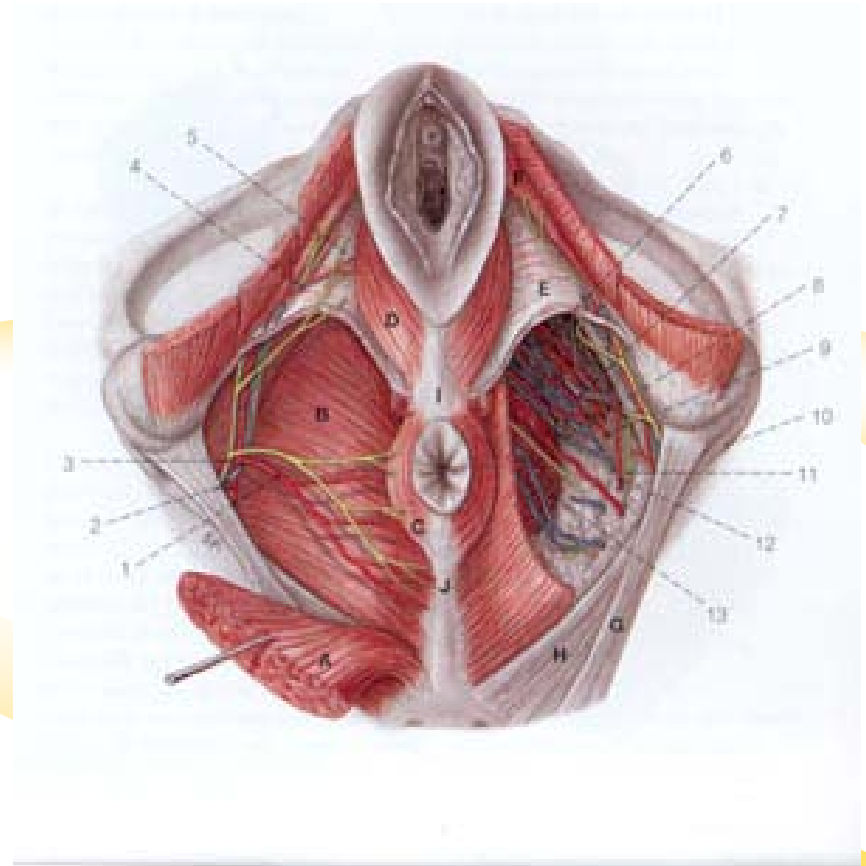
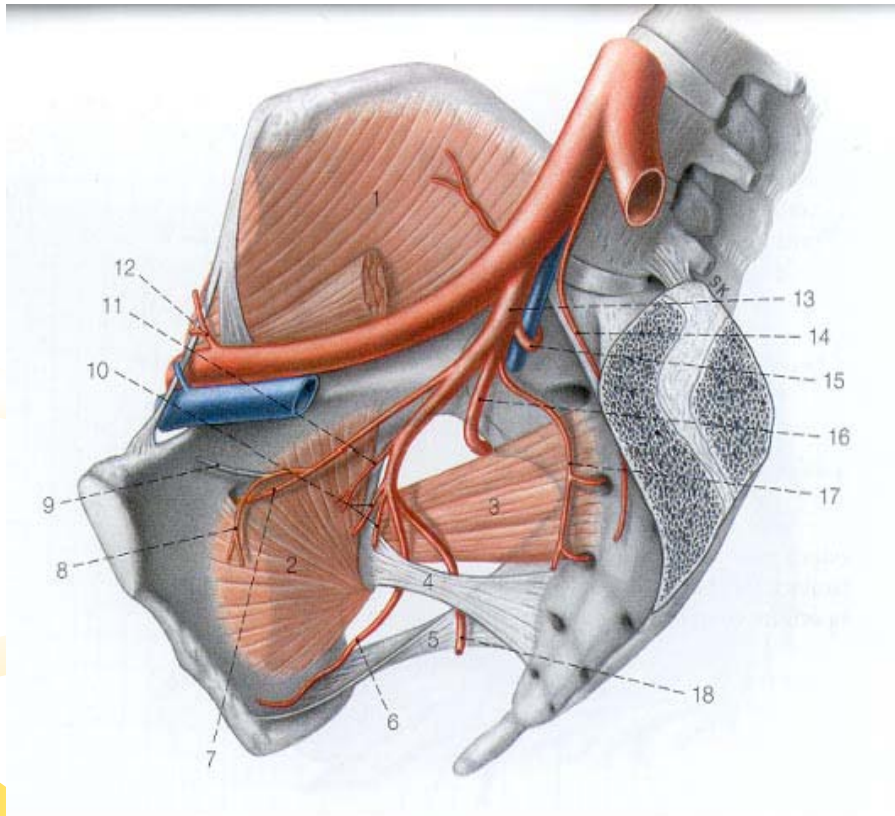
- Lack of confidentiality
- Lack of privacy
- Poor reimbursement<sup>3</sup>

## Doctor barriers

- Embarrassment<sup>1</sup>
- Feeling overwhelmed by more urgent healthcare issues
- Lack of specific training in sexual medicine<sup>2</sup>
- Feeling therapeutically helpless
- Lack of awareness of associated comorbid conditions

1. Korenman S.G (1998) *Am J Med.* **105**: 135-144; 2. Broekman CPM, et al.(1994) *Int J Impot Res.* **6**: 67-72; 3. Baum N, et al.(1998) *Patient Care* Spring (suppl):17-21

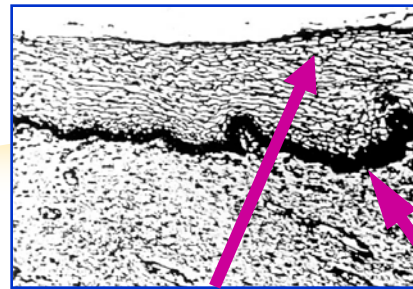




# Hypotesis

- | vaginal temperature
- | blood flow
- | vaginal lubrication
- | vaginal atrophy
- | dyspareunia
- | FSD

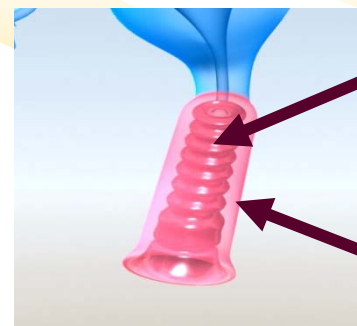
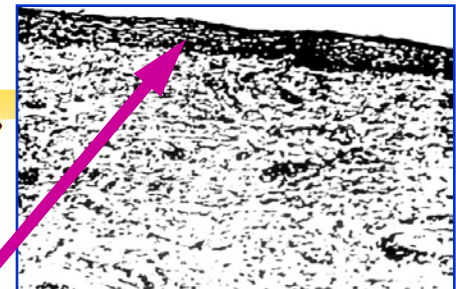
Postmenopausal woman  
treated with estrogen



Superficial  
cells

Parabasal  
cells

Postmenopausal woman  
without estrogen



Rugae

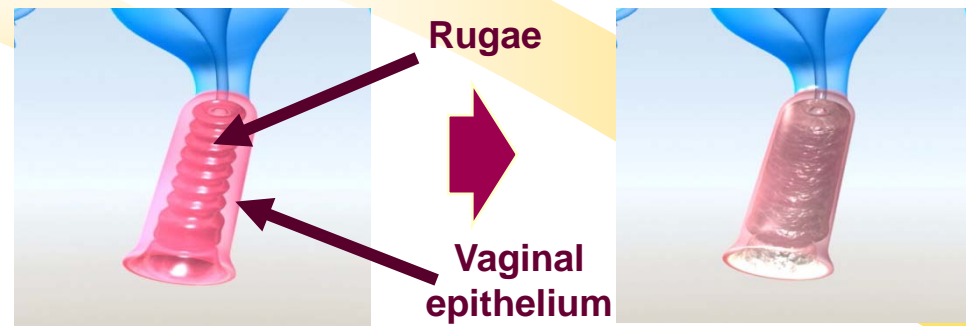
Vaginal  
epithelium





# Emea vaginal atrophy

- . Vaginal tolerance
- . Vaginal pH
- . Vaginal maturation index
- . Severity of most bothersome VA symptoms



# Proposal vaginal atrophy

- . Phase I n° 30-50 vaginal tolerance
- . Phase II n° 200 2 doses vs placebo
- . Phase III n° 400 1 dose vs placebo

