

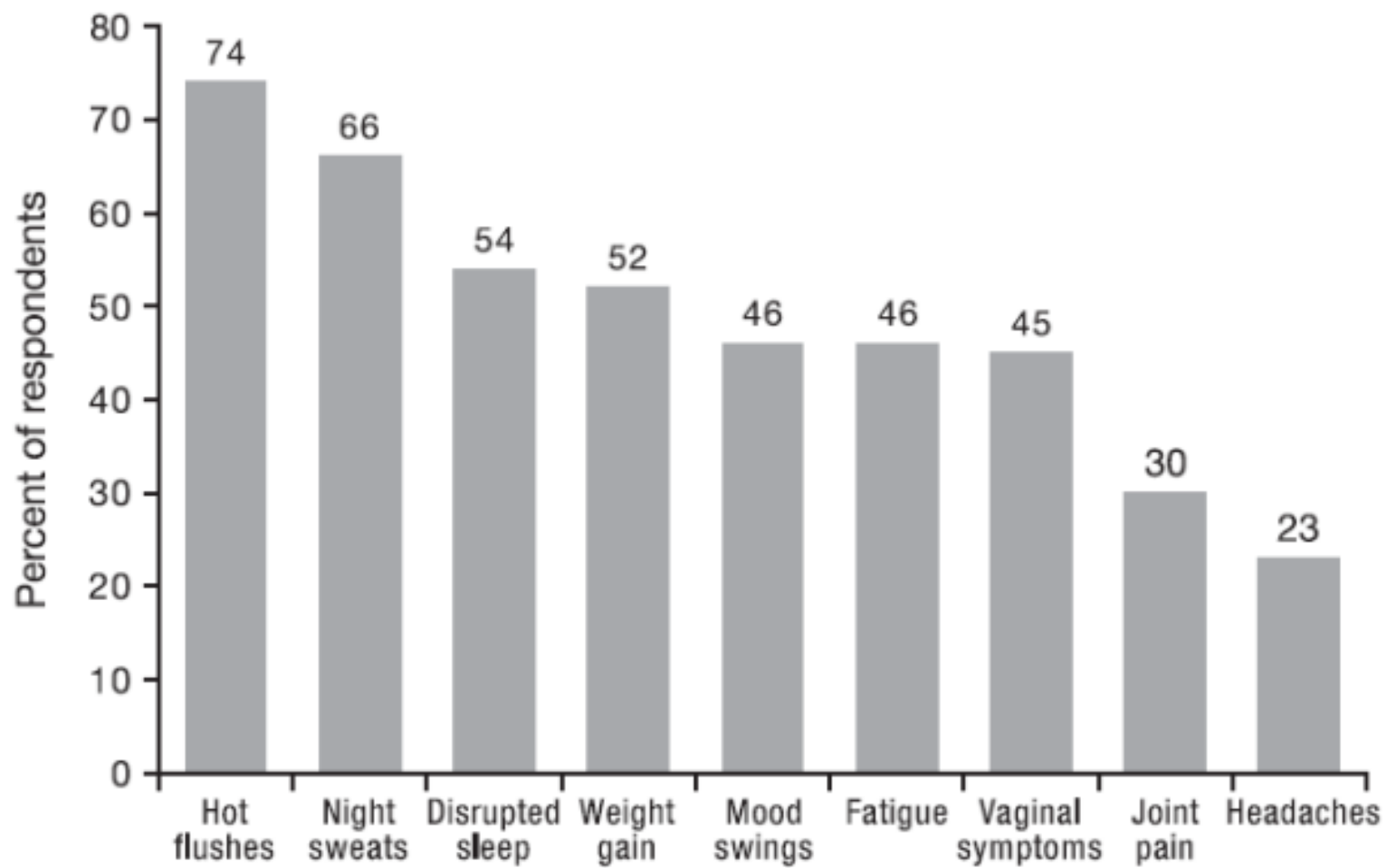
Atrofia vaginale e sindrome genito-urinaria in menopausa

Bologna, 29-30 settembre 2017

Clinical Scenario



- Age....(30-40 years after menopause)
- From menopausal transition to postmenopausal state
- Multiple health issues
- Prophylactic or Therapeutic Options
- Difference between **life expectancy** and **healthy life expectancy** is 11.5 (Global Burden Of Diseases 2010 Study)



ACTIVITY	PERCENT OF WOMEN REPORTING INTERFERENCE
Enjoyment of sexual intercourse	63%
Sense of sexual spontaneity	55%
Ability to be intimate	54%
Relationship with your significant other	45%
Sleeping	29%
Enjoyment of life in general	27%
Temperament (personality traits)	26%
Seeking a new intimate relationship	13%
Traveling	13%
Athletic activities (eg, playing tennis, running, riding a bicycle)	12%
Everyday activities (eg, grocery shopping, cleaning up the house)	11%
Participating in social activities	10%
Ability to work (eg, at a job, volunteering)	7%

Menopause

- Menopause as Inflammation Process (Inflammaging)
- Menopause and therapies
- Atrophic vaginitis ??
- **Genitourinary Syndrome of Menopause (GSM)**

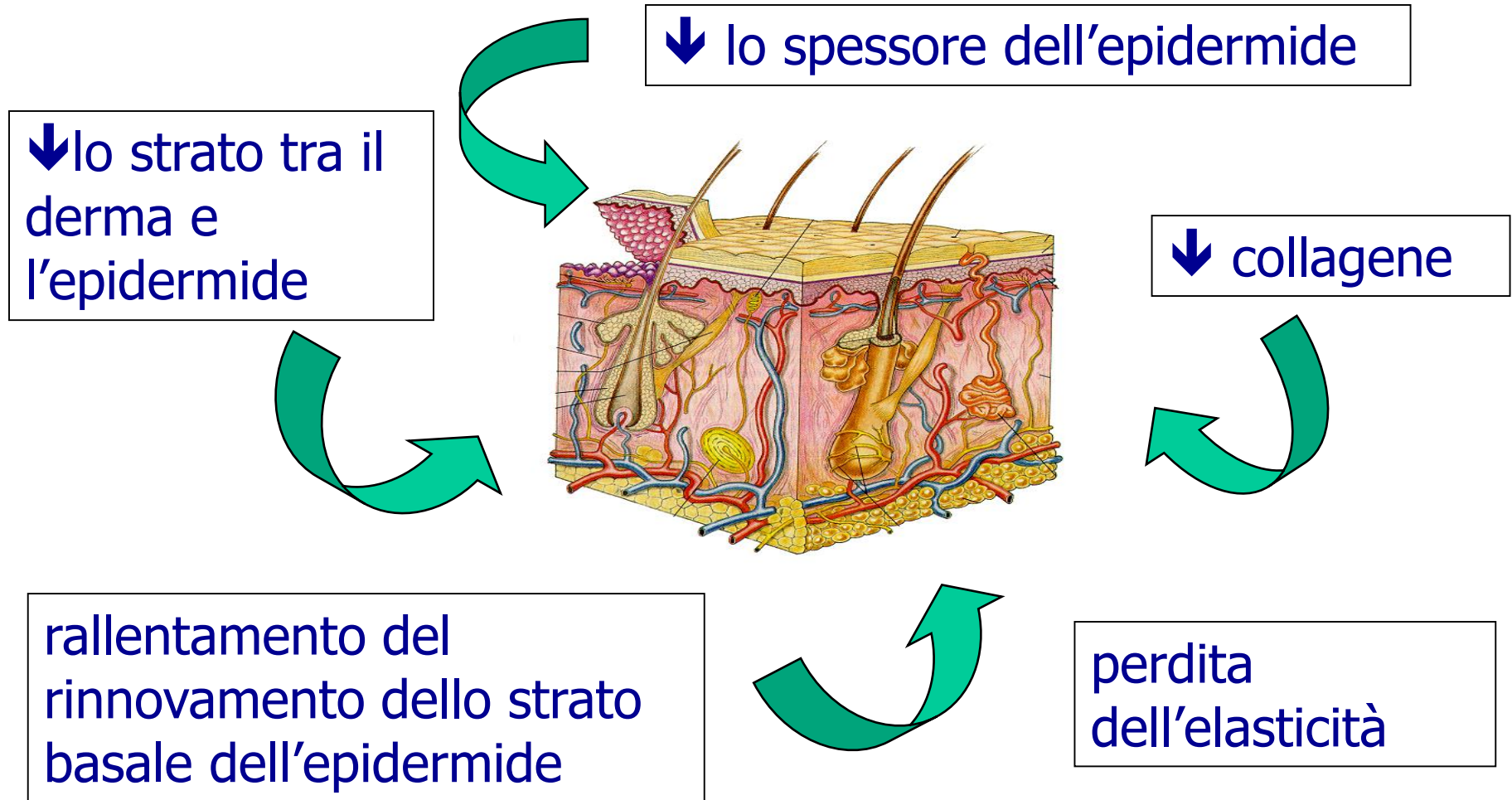


Urogenital Health

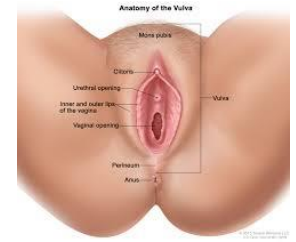
vagina, lower urinary tract, and pelvic floor

- Same embryologic origin
- Estrogen receptors
- Urogenital **Aging @ Modifications** of urogenital tissue

MODIFICAZIONE DELLA CUTE VULVARE

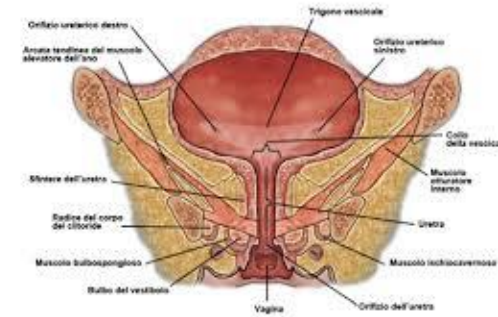


GSM and vagina



- The labia minora thin and regress, the introitus retracts, and the hymenal carunculae involute and lose elasticity
- Physiologic changes result in **reduced vaginal blood flow, diminished lubrication, decreased flexibility and elasticity** of the vaginal vault, and increased vaginal **pH**

GSM and Urinary tract



- Reduced collagen content and **hyalinization**
- Decreased **elastin**, thinning of the epithelium
- Altered appearance and function of **smooth muscle cells**, increased density of connective tissue, and **fewer blood vessels**
- The **urethral meatus** appears prominent relative to the introitus and becomes vulnerable to physical irritation and trauma.



”Lactobacillus Acidophilus as key point”

Età

Estrogeni

Epitelio


Glicogeno

pH

Microbiota

Fertile	++++		++	3,5 - 4	LACT. ACIDOPHILUS Gardnerella
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Menopausa	+		—	7	Aerobi Anaerobi fecali
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Menopausa HRT	+		-	3,5 - 4	LACT. ACIDOPHILUS Gardnerella
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Symptoms	Signs
Genital dryness	Decreased moisture
Decreased lubrication with sexual activity	Decreased elasticity
Discomfort or pain with sexual activity	Labia minora resorption
Post-coital bleeding	Pallor/Erythema
Decreased arousal, orgasm, desire	Loss of vaginal rugae
Irritation/Burning/Itching of vulva or vagina	Tissue fragility/fissures/ petechiae
Dysuria	Urethral eversion or prolapse
Urinary frequency/urgency	Loss of hymenal remnants
	Prominence of urethral meatus
	Introital retraction
	Recurrent urinary tract infections

Supportive findings: pH >5, increased parabasal cells on maturation index, and decreased superficial cells on wet mount or maturation index.

Managing Menopause



Recommendations

1. Conjugated estrogen cream, an intravaginal sustained-release estradiol ring, and low-dose estradiol vaginal tablets are recommended as effective treatment for vaginal atrophy. (I-A)
2. Routine progestin co-therapy is not required for endometrial protection in women receiving vaginal estrogen therapy in an appropriate dose. (III-C)
3. Vaginal lubricants may be recommended for subjective symptom improvement of dyspareunia. (II-2B)
4. Because systemic absorption of vaginal estrogen is minimal, its use is not contraindicated in women with contraindications to systemic estrogen therapy, including recent stroke and thromboembolic disease. (III-C) However, there are currently insufficient data to recommend its use in women with breast cancer who are receiving aromatase inhibitors (where the goal of adjuvant therapy is a complete absence of estrogen at the tissue level). Its use in this circumstance needs to be dictated by quality-of-life concerns after discussion of possible risks. (III-C)

Managing Menopause



5. Systemic estrogen therapy should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence given the lack of evidence of therapeutic benefit. (I-A)
Vaginal estrogen may, however, be recommended, particularly for the management of urinary urge incontinence. (II-1A)
6. As part of the management of stress incontinence, women should be encouraged to try non-surgical options, including weight loss (in obese women). (I-A)
Pelvic floor physiotherapy, with or without biofeedback, (II-1B) weighted vaginal cones, (II-2B) functional electrical stimulation, (I-B) and/or intravaginal pessaries (II-2B) can also be recommended.
7. Behavioural modification, (II-2B) functional electrical stimulation, (II-1B) and antimuscarinic therapy (I-A) are recommended for the treatment of urge urinary incontinence.
8. Vaginal estrogen therapy can be recommended for the prevention of recurrent urinary tract infections in postmenopausal women. (I-B)

The 2012 Hormone Therapy Position Statement of The North American Menopause Society

Vaginal symptoms

ET is the most effective treatment of moderate to severe symptoms of vulvar and vaginal atrophy (eg, vaginal dryness, dyspareunia, and atrophic vaginitis).⁵ Many systemic HT products and all local vaginal ET products have government approval for treating symptomatic vaginal atrophy. Some low-dose systemic regimens may be inadequate for the relief of vaginal symptoms and may require the addition of low-dose local ET to achieve the desired results. When ET is considered solely for treatment of vaginal atrophy, local vaginal ET is advised. Lower doses of vaginal ET than previously used, with less frequent administration, often yield satisfactory results.⁶

A progestogen is generally not indicated when ET at the recommended low doses is administered locally for vaginal atrophy, although clinical trial data supporting endometrial safety beyond 1 year are lacking.⁷ Because endometrial hyperplasia increases with increasing dose and duration of estrogen exposure, thorough evaluation of any uterine bleeding in women using low-dose local ET is advised.

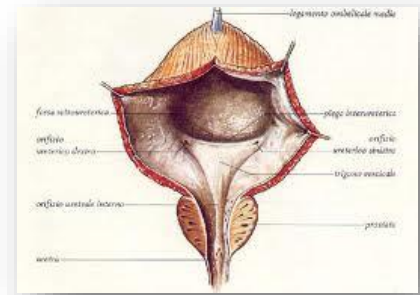
Urinary tract health

Local ET may benefit some women with overactive bladder.¹¹ One RCT found that an estradiol ring had a clinical benefit equivalent to that of oxybutynin among women with overactive bladder.¹² Systemic HT may worsen or provoke stress incontinence.¹³⁻¹⁵ Ultralow-dose transdermal estradiol therapy neither increased nor decreased incontinence.¹⁶ A large RCT reported an increased risk of kidney stones with HT.¹⁷

Two studies reported a decreased risk of recurrent urinary tract infection through the use of intravaginal estrogen.^{18,19} Only ET administered by the vaginal route has been shown to be effective for this purpose. No HT product has government approval for any urinary health indication.

ET is the most effective treatment of symptoms of vulvar and vaginal atrophy; low-dose, local vaginal ET is advised when only vaginal symptoms are present.

Management of lower urinary tract symptoms



- The reduction in quantity and strength of collagen may weaken bladder neck support and hence increase the risk of developing **urinary stress incontinence**
- **Exogenous estrogen** therapy has an effect on collagen remodeling (reduction in total collagen concentration, decrease in collagen cross linking and increase in the levels of collagen turnover markers)
- Women with stress urinary incontinence have been shown to have a reduction in total collagen and an increase in the level of collagen degradation products after taking oral estrogen therapy for six months

Management of lower urinary tract symptoms

- Evidence from a systematic review and meta-analysis would suggest a benefit from estrogen (**vaginal route** more than oral)
 - in the management of **recurrent lower urinary tract infection**
 - in reducing **vaginal dryness, pruritis and dyspareunia**
 - in the management of **OAB** and for symptoms of **urgency and frequency**



POSITION STATEMENT

Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society

*...Vaginal ET is inappropriate for postmenopausal women with undiagnosed vaginal/uterine bleeding and **controversial** in women with **estrogen dependent neoplasia** (eg, breast, endometrial). **Comanagement with the woman's oncologist** may be considered in the case of estrogen-dependent neoplasia.*



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ospemifene

- Ospemifene is a selective oestrogen receptor modulator (SERM)
- Stimulates the receptor for oestrogen in some tissues in the body such as the vagina
- Not stimulate oestrogen receptors in other tissues such as the breast and womb

TSEC

The combination of BZA a SERM for the prevention and treatment of postmenopausal osteoporosis, and CE is a tissue-selective estrogen complex (TSEC) which is intended to provide clinical benefits of each of the two components.

BZA/CE has been designed to relieve vasomotor and vulvovaginal symptoms and to prevent bone loss while being safe for the endometrium and breast. Studies revealed that BZA (20 mg) / CE (0.45 or 0.625 mg) significantly improved vulvovaginal symptoms and dyspareunia, although BZA alone did not have positive vaginal effects.

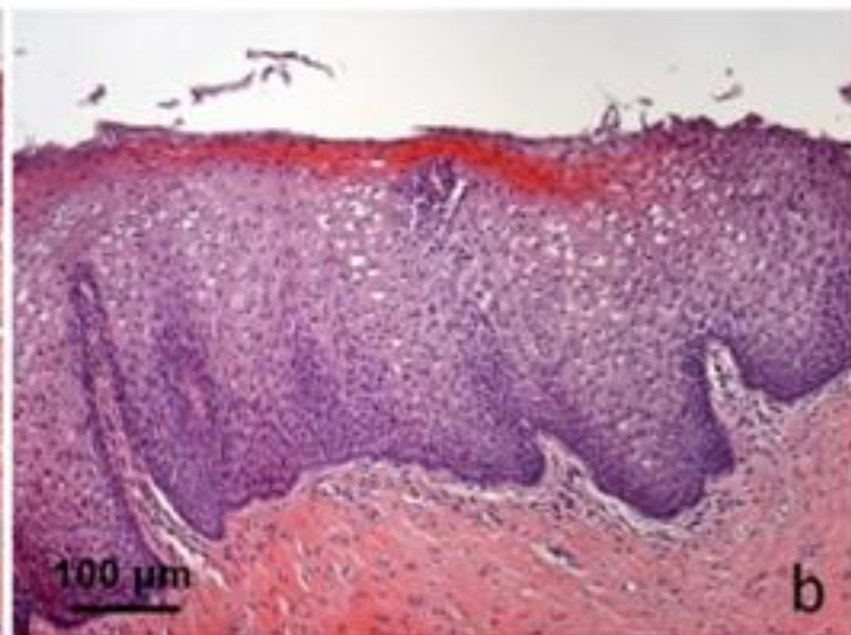
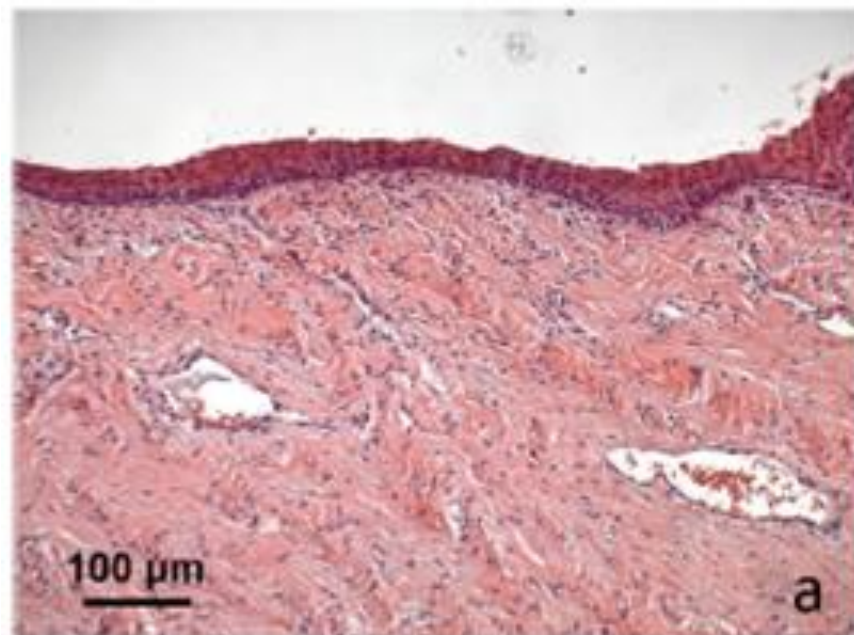
Laser and VVA ?

Vulvo-vaginal atrophy: A new treatment modality using thermo-ablative fractional CO₂ laser

Antonino Perino^a, Alberto Calligaro^b, Francesco Forlani^{a,*}, Corrado Tiberio^a, Gaspare Cucinella^a, Alessandro Svelato^a, Salvatore Saitta^c, Gloria Calagna^a

- Anti-aging medicine to the vagina mucosa
- Topical remodeling of connective tissue and the production of collagen and elastic fibers
- This collagen remodeling in the skin was present 3 months after the last laser session





Treatment of Vaginal Relaxation Syndrome with an Erbium:YAG Laser Using 90° and 360° Scanning Scopes: A Pilot Study & Short-term Results

- “Loose vagina”
- Ability to limit damage depth with Er:YAG (2940 nm) vs CO₂ (10600 nm) called laser-assisted vaginoplasty



Fig. 1: The 360° scanning scope (left) and the 90° scanning scope (right).

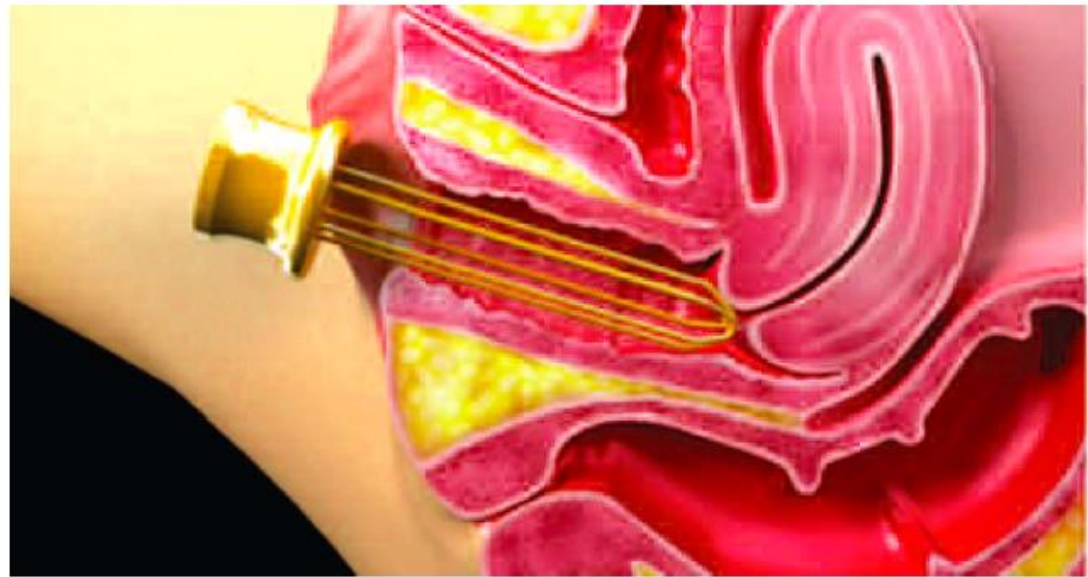


Fig. 2: Illustration showing the special support for the scanning scopes inserted in the vagina.

”Atrophy : why, who, when ?”

Età

Estrogeni

Epitelio

Glicogeno

pH

Microbiota

Menopausa

+



-

7

Aerobi

Anaerobi

fecali

Probiotics

Menopausa
HRT

+



-

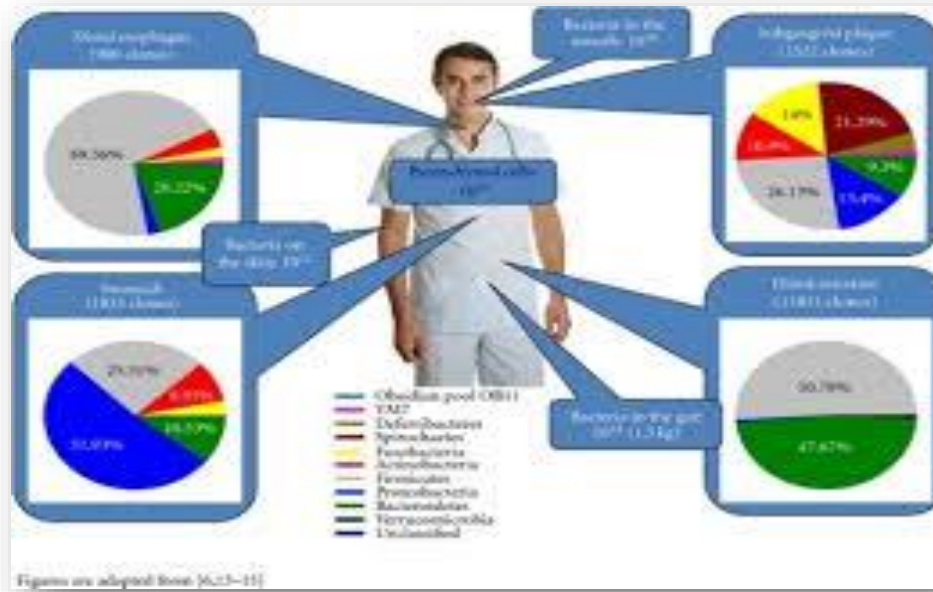
3,5 - 4

LACT.
ACIDOPHILUS
Gardnerella

?

GSM as a imbalance of microbiota ??

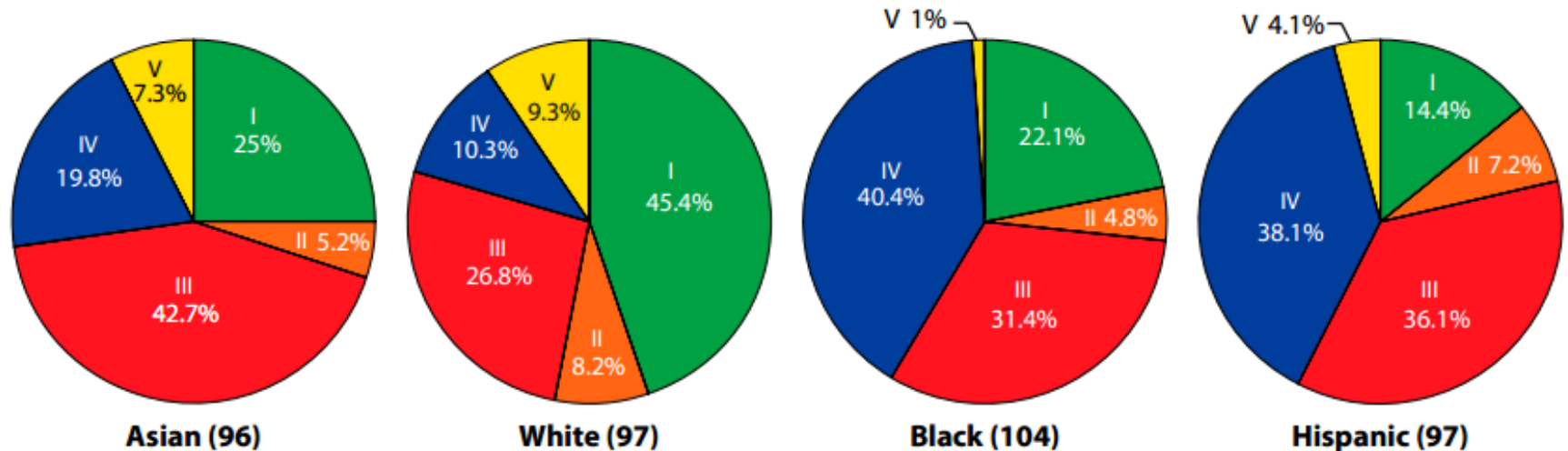




De Seta 2014

Vaginal microbiome of reproductive-age women

Jacques Ravel^{a,1}, Pawel Gajer^a, Zaid Abdo^b, G. Maria Schneider^c, Sara S. K. Koenig^a, Stacey L. McCulle^a, Shara Karlebach^d, Reshma Gorle^e, Jennifer Russell^f, Carol O. Tacket^f, Rebecca M. Brotman^a, Catherine C. Davis^g, Kevin Ault^d, Ligia Peralta^e, and Larry J. Forney^{c,1}



- ***L. crispatus***
- ***L. gasseri***
- ***L. jensenii***
- ***L. iners***

L. Acidophilus
?5-10%

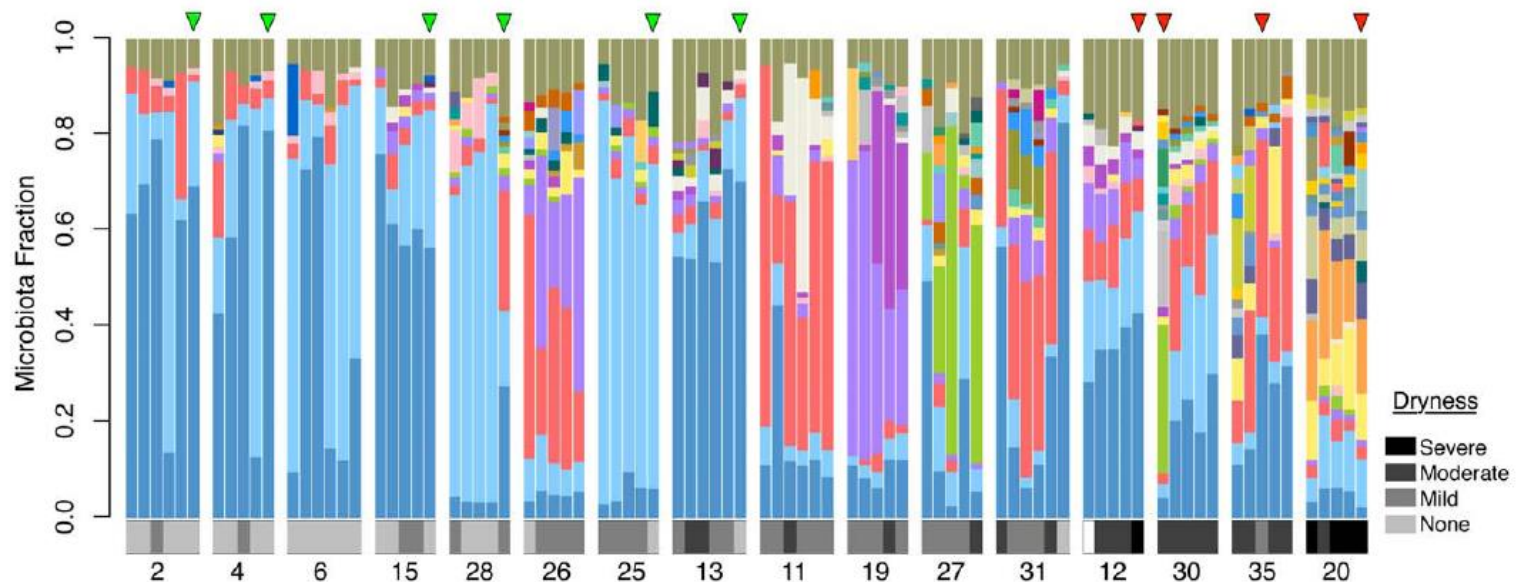
Association between the vaginal microbiota, menopause status, and signs of vulvovaginal atrophy

Rebecca M. Brotman, PhD, MPH,^{1,2} Michelle D. Shardell, PhD,² Pawel Gajer, PhD,¹ Doug Fadrosh, MS,¹ Kathryn Chang, RN,³ Michelle I. Silver, ScM,³ Raphael P. Viscidi, MD,⁴ Anne E. Burke, MD, MPH,⁵ Jacques Ravel, PhD,^{1,6} and Patti E. Gravitt, PhD, MS³

		CST I (<i>Lactobacillus crispatus</i>)	CST IV-A (low <i>Lactobacillus</i> , diverse)	Postmenopause	P ^a
CST (d)				7 (25.0)	0.004
CST				1 (3.6)	
CST				5 (17.9)	
CST				8 (28.6)	
CST				5 (17.9)	
CST				2 (7.1)	
Vaginal atrophy					
	None	21 (84.0)	2 (22.2)		
	Mild	3 (12.0)	3 (33.3)		
	Moderate	1 (4.0)	4 (44.4)		
Vaginal dryness					
	None	23 (92.0)	5 (55.6)		0.002
	Mild	1 (4.0)	0 (0.0)		
	Moderate	1 (4.0)	4 (44.4)		
	Severe	0 (0.0)	0 (0.0)		0.011

Vaginal Microbiome and Epithelial Gene Array in Post-Menopausal Women with Moderate to Severe Dryness

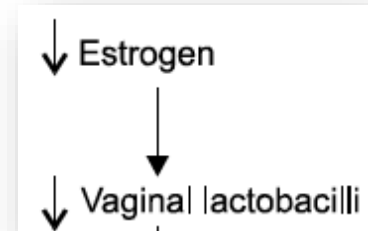
Ruben Hummelen^{1,2§}, Jean M. Macklaim^{1,3§}, Jordan E. Bisanz^{1,4§}, Jo-Anne Hammond^{1,5}, Amy McMillan^{1,4}, Rebecca Vongsa⁶, David Koenig⁶, Gregory B. Gloor^{1,3¶}, Gregor Reid^{1,4*}



reported previously. There was an inverse correlation between *Lactobacillus* ratio and dryness, a condition commonly found after menopause, which shown here to be associated with changes in vaginal epithelial cell integrity and inflammation.

GSM more than a simply depletion of lactobacilli or increase of anaerobes

- Down regulation of complement system and activation expression cytokines
- Mucosal immune activity (**inflammation**)
- Production of acetylcholine with activation of alfa cholinergic nerves (**pain**)
- Conversion plasminogen- plasmin (**tissue sensitivity and bleeding**)

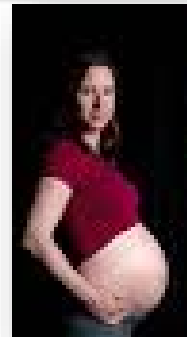


Probiotics as functional food

- Characterize the properties of individual gut microbes with potent **immunomodulatory** potential effect
- The transcriptional and metabolic impact of probiotics are present upon cessation of **probiotic intake**
- **Second generation** probiotic formulations may target specific human disease states



Probiotics in relation to Women Health



Gynec

Fertilization

Pregnancy

Menopause

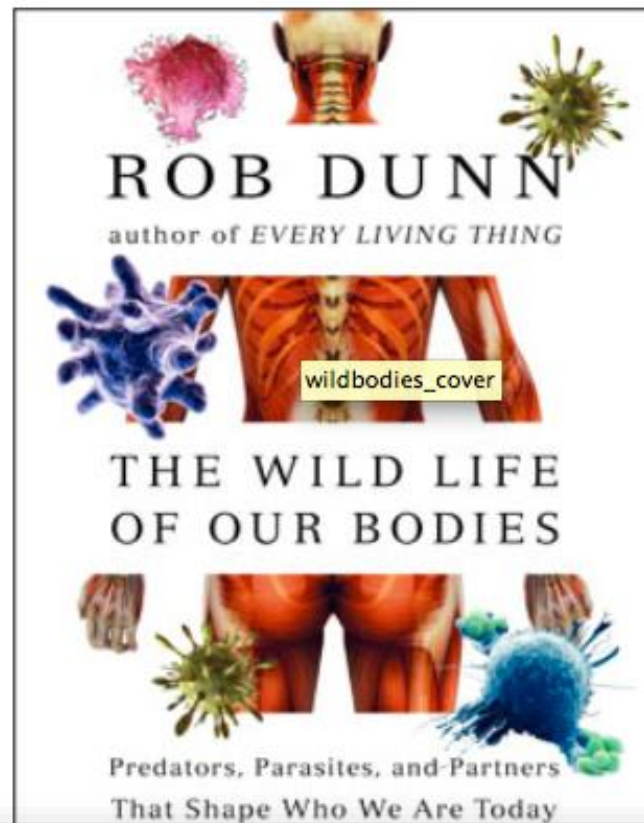
**STD
Vaginitis
Vaginosis**

**Pro-inflammatory cytokines
Sperm motility and viability**

**Preterm delivery
PIH
GDM**

**UTI ?
Atrophy ?**

Thank you for the attention



“There are hundreds of kinds of prebiotics and probiotics in stores,” he said. “As a consumer, it’s almost impossible to figure out what is best. What are the specific species in your intestines, and how will