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CENTER FOR SEXUAL HEALTH AND EDUCATION

PALM BEACH COUNTY, FLORIDA

DISCLOSURES

- Speakers Bureau for Astellas

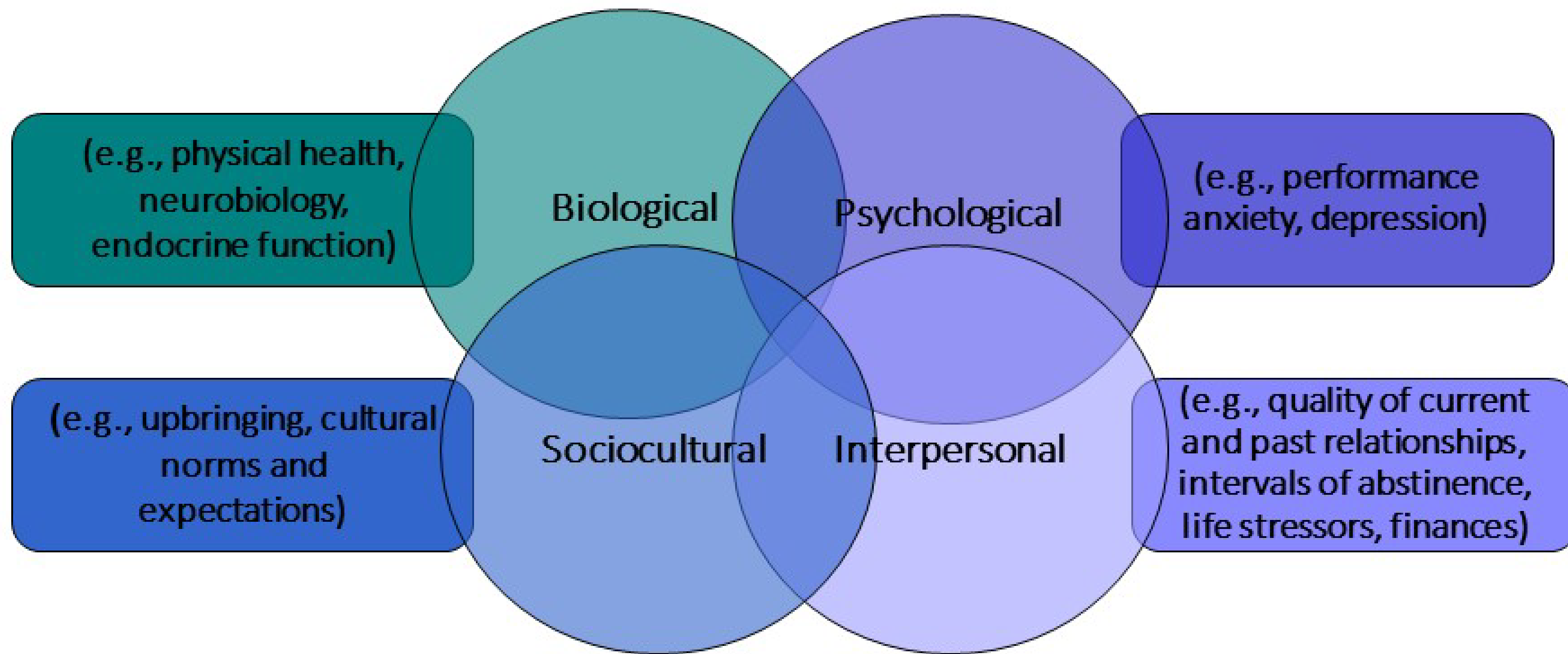
OBJECTIVES

Recognize	Recognize sexual pain as the cause for sexual dysfunction
Perform	Perform a brief assessment to determine common causes
Identify	Identify more common vulvar skin conditions and management
Differentiate	Differentiate risks and benefits of traditional hormone therapy and pellet therapy

"I WANT MY HORMONES CHECKED BECAUSE OF…."

- HAIR LOSS
- FATIGUE
- DRY CREPEY SKIN
- SLEEP PROBLEMS
- WEIGHT GAIN

Biopsychosocial Model of Female Sexual Response



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Addressing Medical Issues Affecting Sexual Function

- Oral contraceptives
- Depression and antidepressant medication
- Other medications
- GSM
- Partner sexual problems

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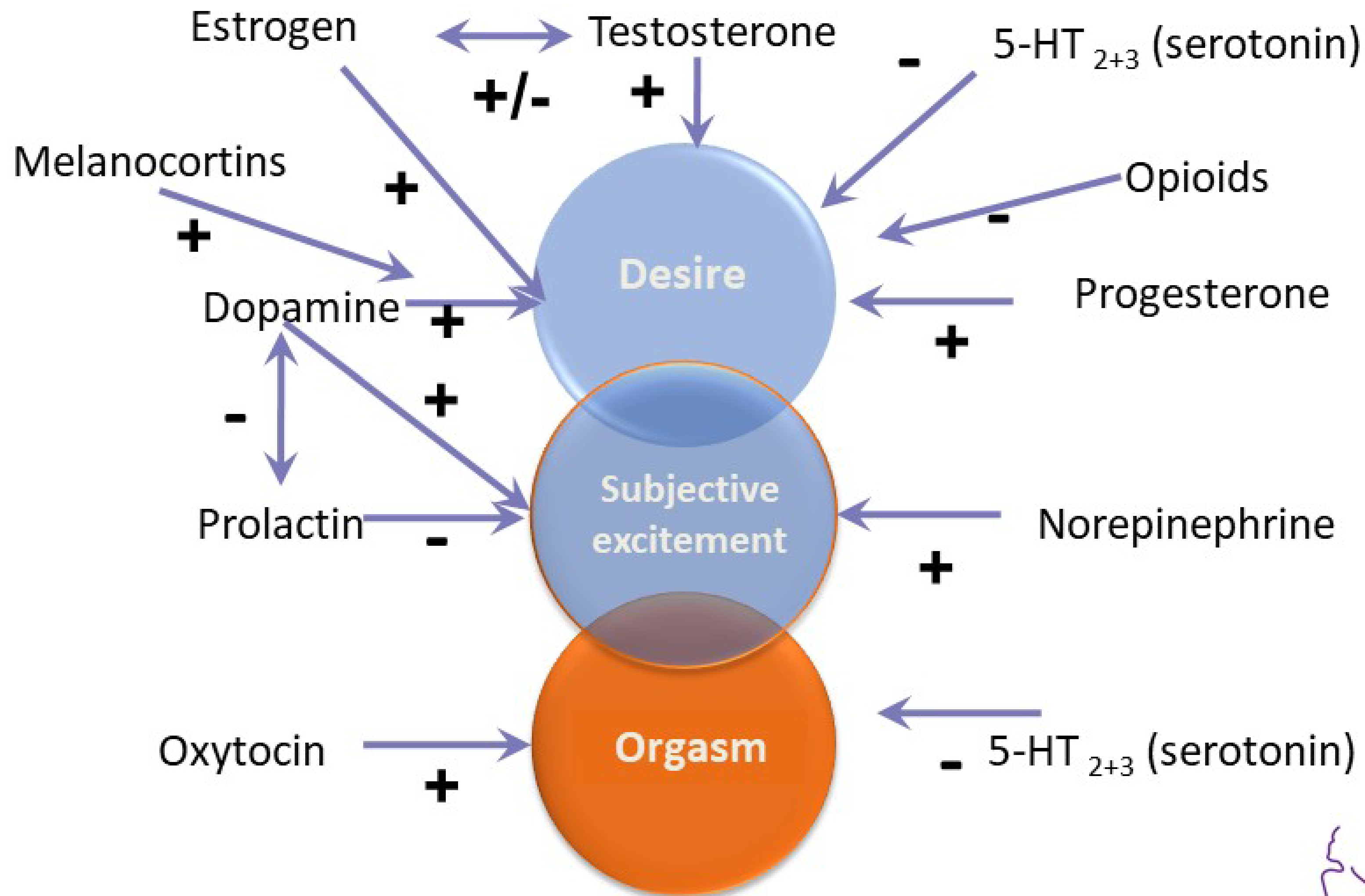
Central Effects of Neurotransmitters and Hormones on Sexual Functioning



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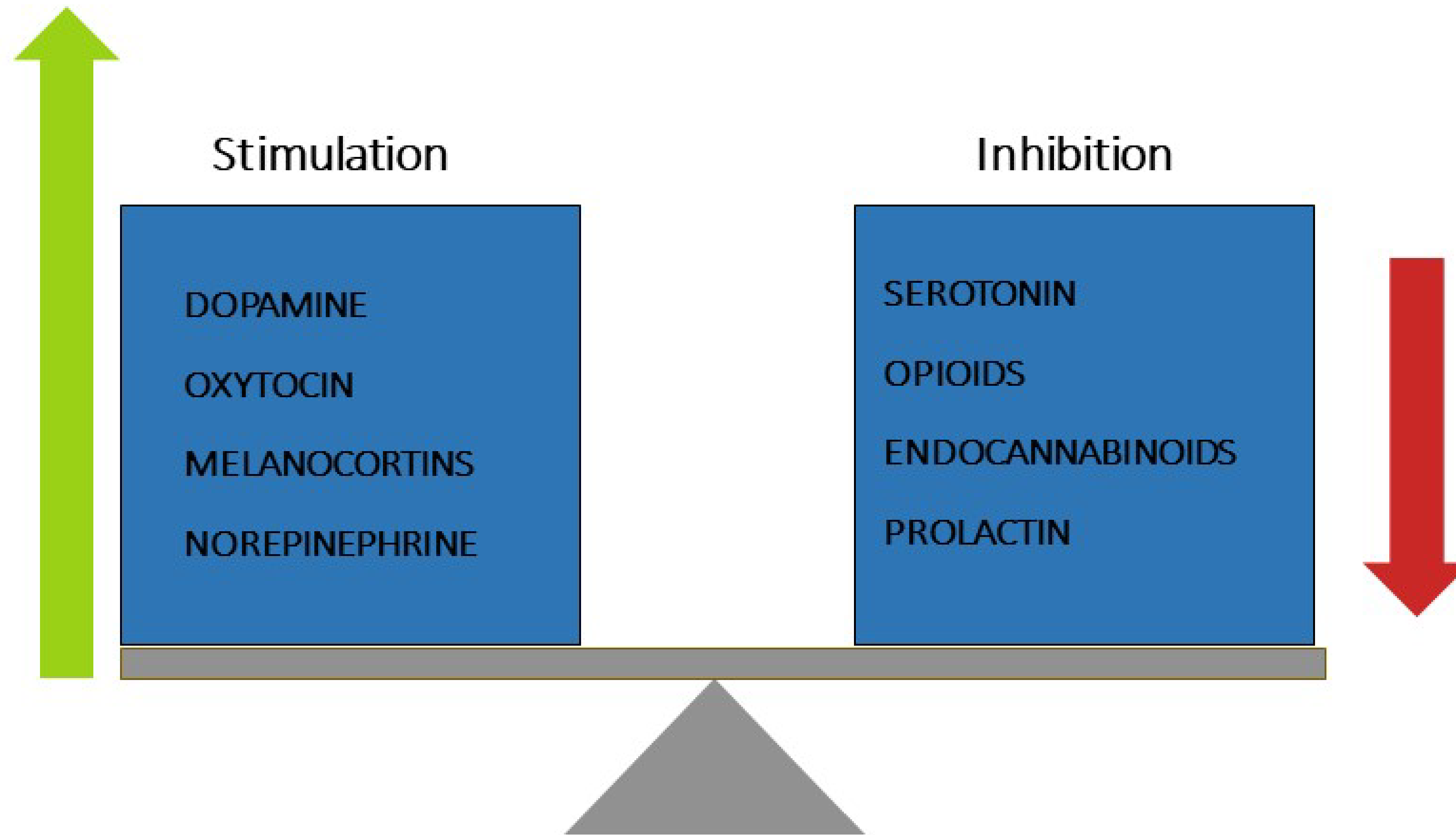
High Excitation/Low Inhibition: Treatment Considerations for PGAD



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Female Sexual Dysfunction: Sexual Pain Disorders

Female Genital-Pelvic Pain Dysfunction

Persistent or recurrent difficulties with at least one of the following:

- Vaginal penetration during intercourse
- Marked vulvovaginal or pelvic pain during genital contact
- Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of genital contact
- Marked hypertonicity or overactivity of pelvic floor muscles with or without genital contact
- Some research and clinical studies have separated sexual pain due to vaginismus from dyspareunia, which may be related to organic pathology
  - Further research is needed to determine validity of this distinction

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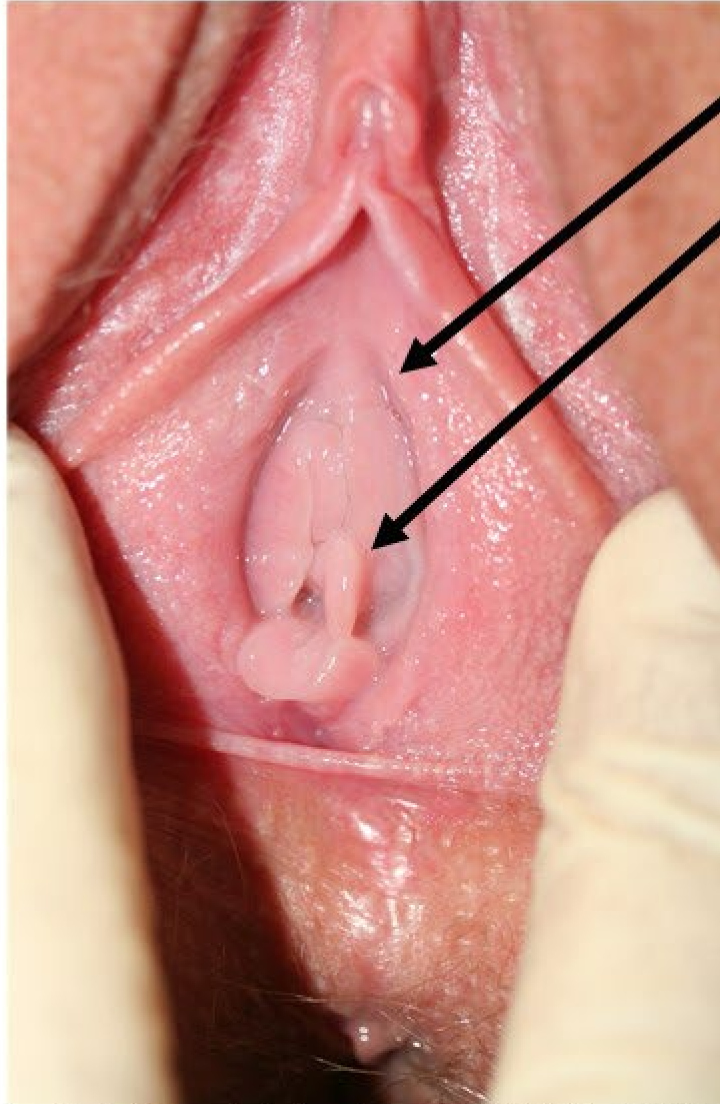
The Vestibule



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- Lateral border is Hart's line
- Medial border is the hymen and urethra
- Ostia of the Bartholin's, Skene's, and minor vestibular glands
- Derived from the primitive urogenital sinus
- Different blood supply from the vagina
- Rich in AR (> ER)

AR= androgen receptor; ER= estrogen receptor

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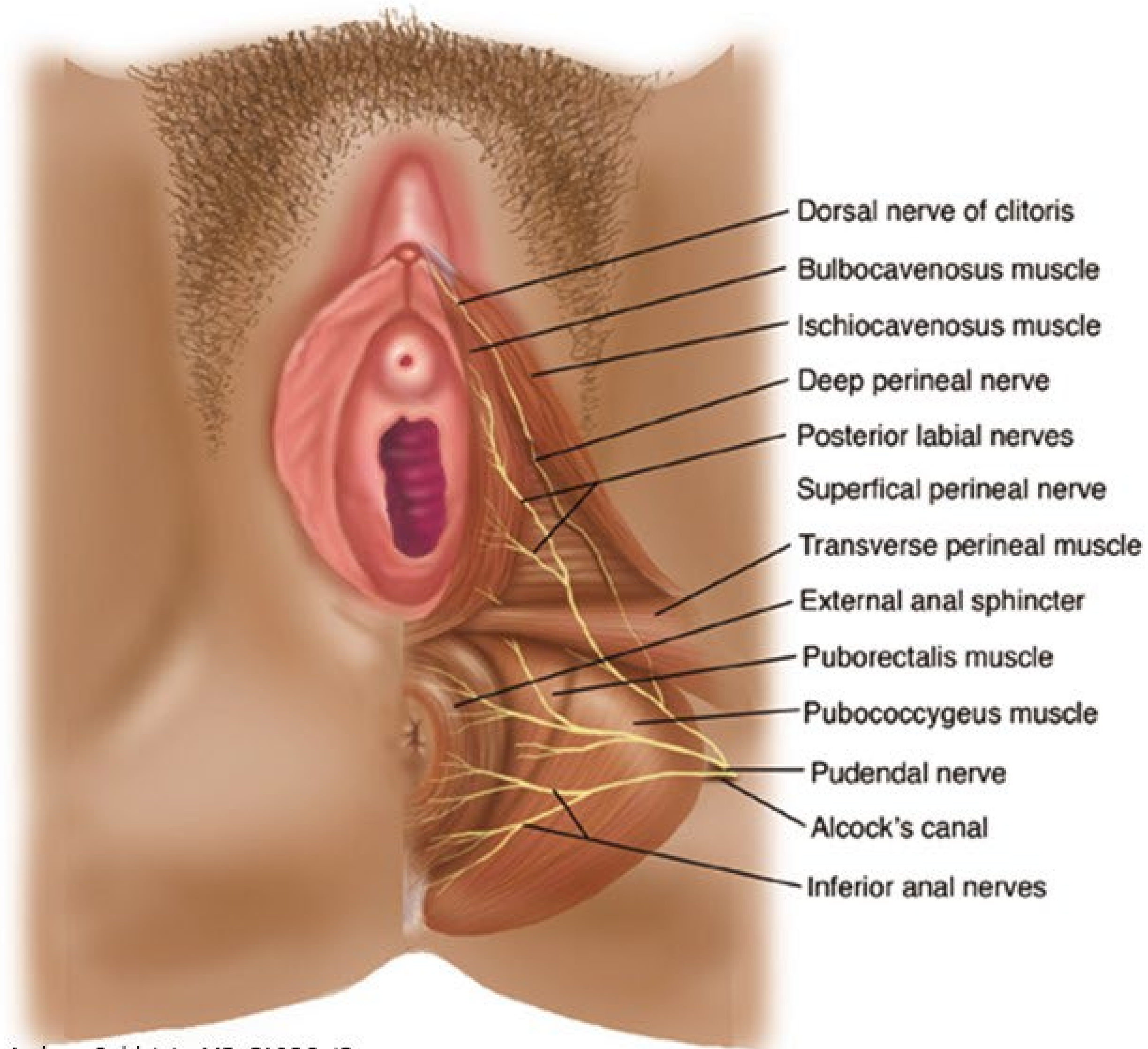
Pudendal Nerve



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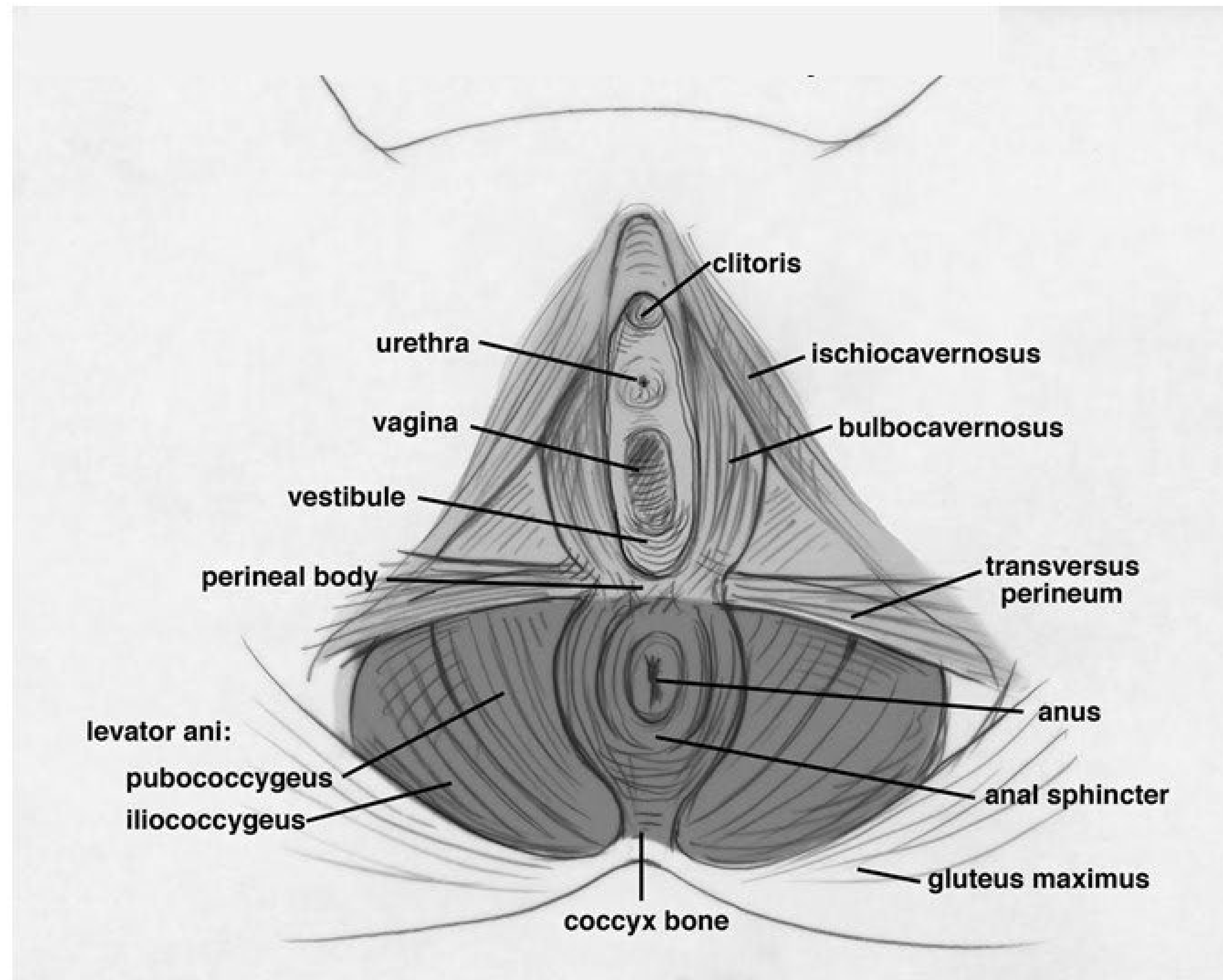
Pelvic Floor Muscles



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Vulvar Pain Caused by a Specific Disorder

- Infectious (e.g., recurrent candidiasis, herpes)
- Inflammatory (e.g., lichen sclerosus, lichen planus, immunobullous disorders)
- Neoplastic (e.g., Paget disease, squamous cell carcinoma)
- Neurologic (e.g., post-herpetic neuralgia, nerve compression or injury, neuroma)
- Trauma (e.g., female genital cutting, obstetrical)
- Iatrogenic (e.g., post-operative, chemotherapy, radiation)
- Hormonal deficiencies (e.g., genitourinary syndrome of menopause, lactational amenorrhea)

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Overactive Pelvic Floor Muscle Dysfunction

- Increased tone results in:
  - Decrease in blood flow and oxygen to the muscles of the pelvic floor and build up of lactic acid
- Symptoms:
  - Generalized vulvar pain or burning
  - Superficial (mucosal) tenderness where muscles insert (4,6,8 o'clock on the vestibule), resulting in:
    - Introital dyspareunia
    - Urinary symptoms (frequency, hesitancy, incomplete emptying)
    - Constipation, hemorrhoids, and rectal fissures
- Physical exam:
  - Erythema where the muscles insert at the vestibule
  - Multiple trigger points, muscle weakness

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Persistent Vulvar Pain: Physical Examination

- Visual inspection of the vulva
- Vulvoscopy with biopsy, if indicated
- Cotton swab (Q-tip) test
- Vaginal exam with pediatric speculum- insert without touching the vestibule
- Examination of pelvic floor muscles
- Palpation of the urethra and bladder

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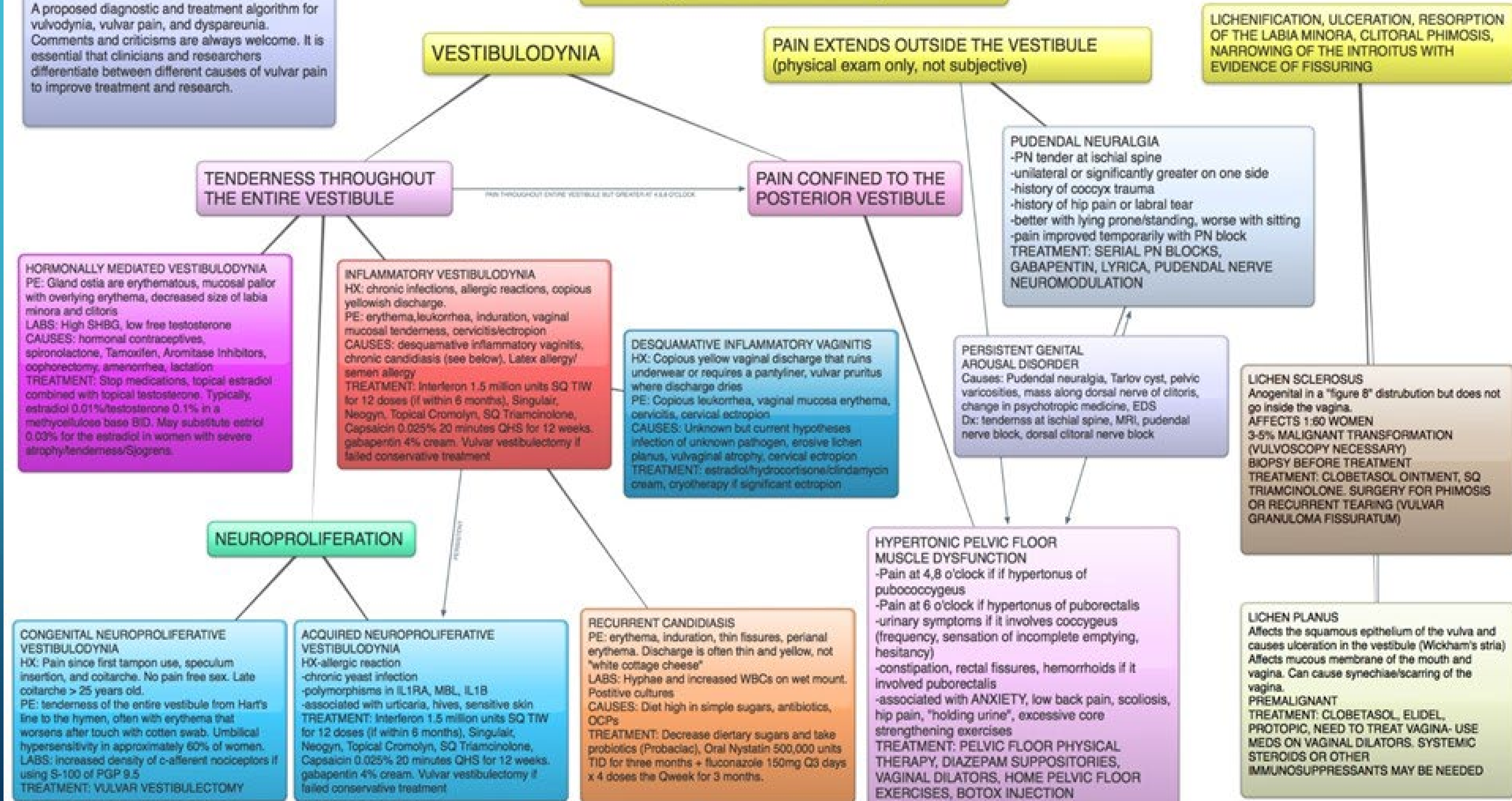
Persistent Vulvar Pain: Diagnostic and Treatment Algorithm



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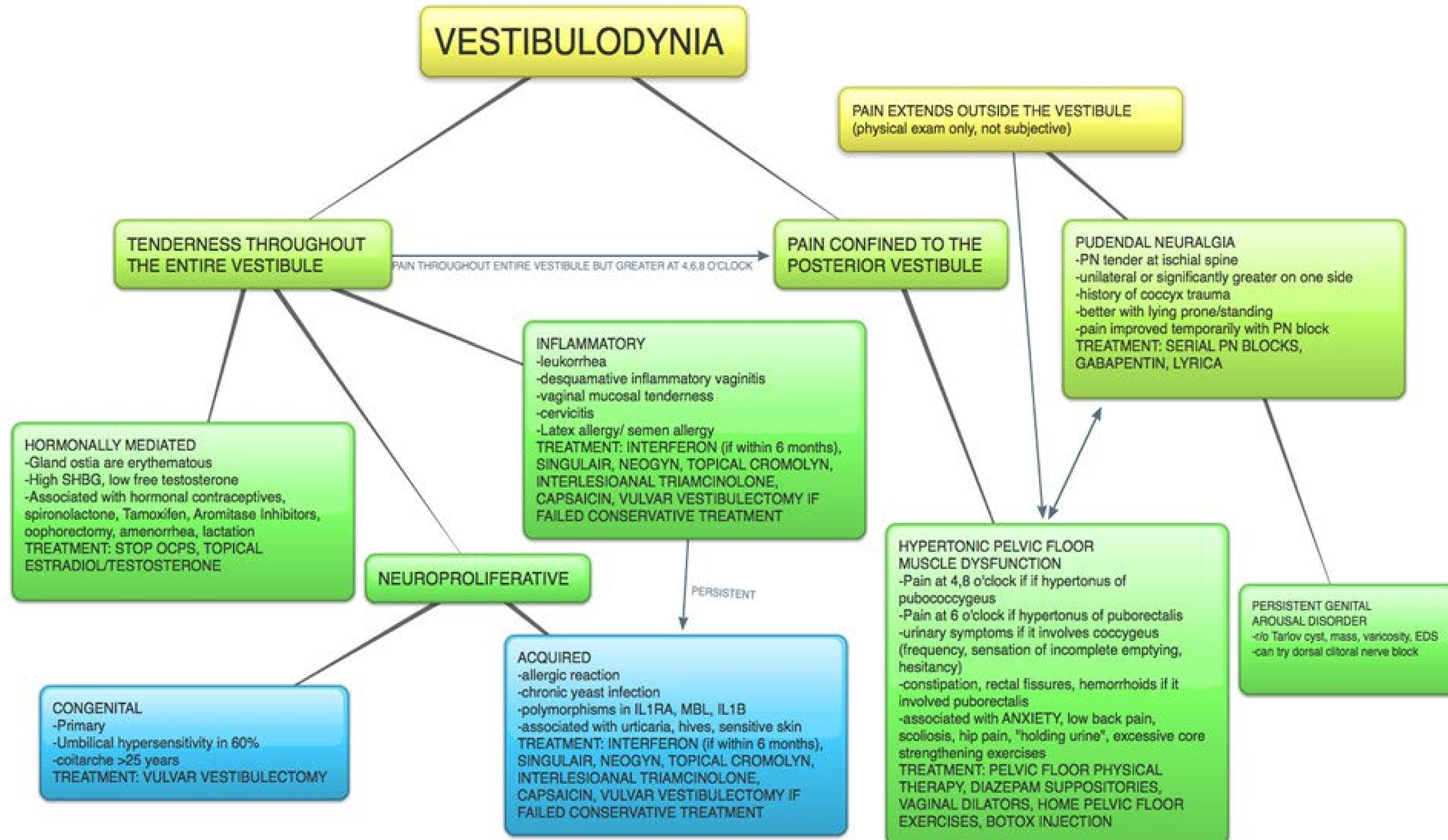
Vestibulodynia: Common Etiological Pathways



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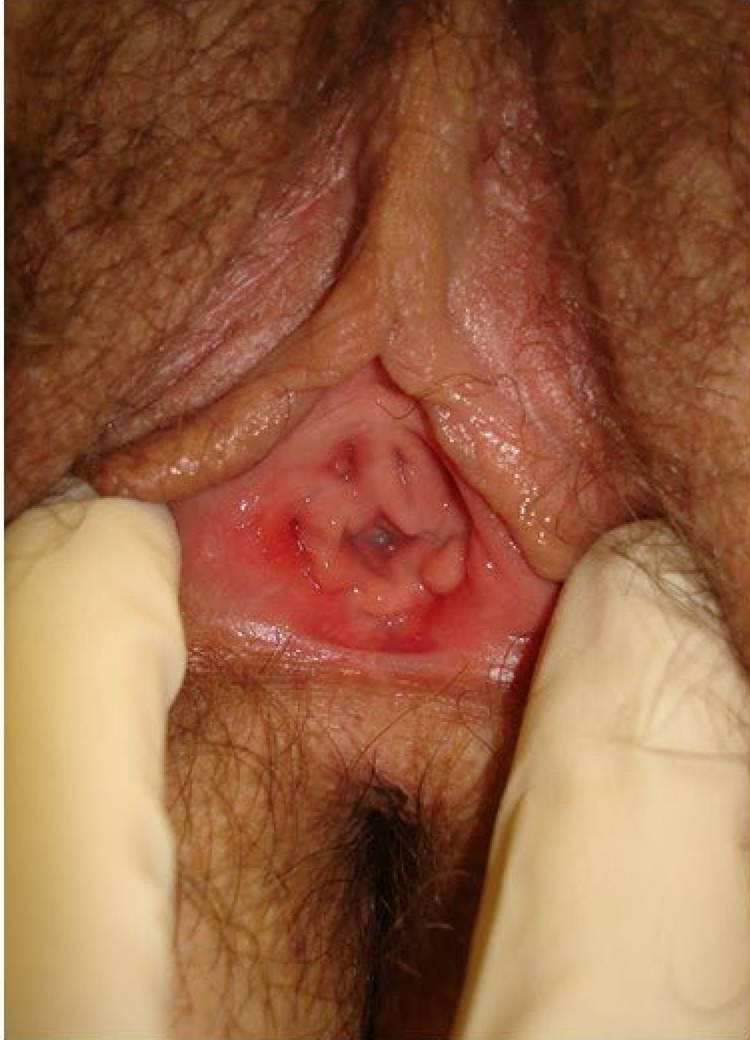
Hormonally-Associated Persistent Vulvar Pain



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- Commonly caused by hormonal contraceptives
- Other causes include:
  - Menopause
  - Oophorectomy
  - Hormonal control of endometriosis or hirsutism
  - Breast-feeding
  - Infertility treatments
  - Treatment of breast cancer

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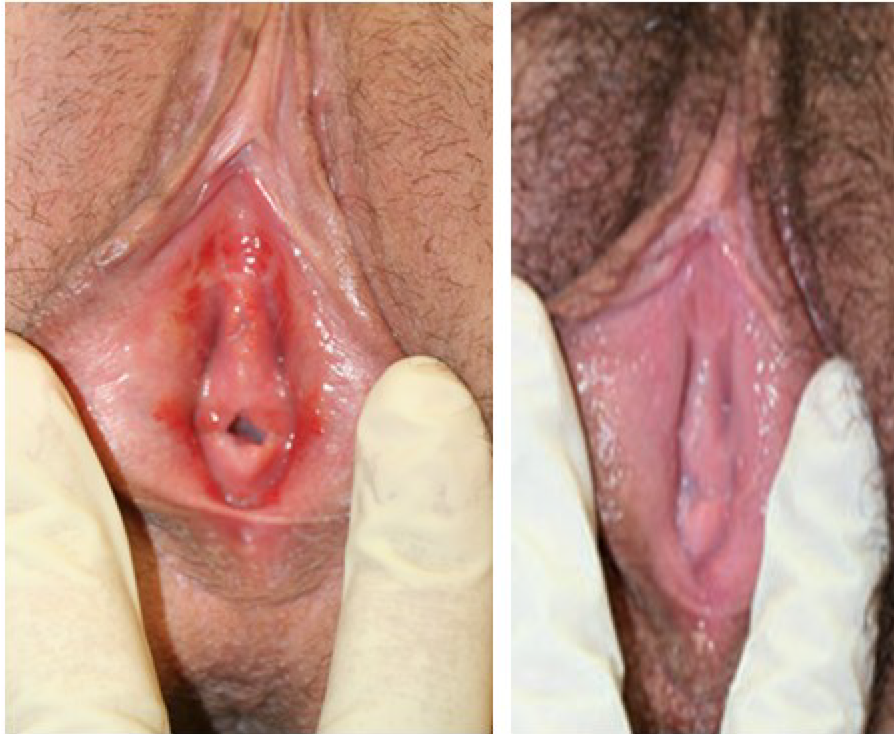
Hormonally-Medicated Vestibulodynia



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- Stop hormonal contraceptives
- Consider topical estradiol 0.03%/testosterone 0.1% in base (e.g., versabase) twice daily to vestibule
- Improvement- none expected at 6 weeks, 50% at 12 weeks
- Consider topical estradiol 0.03%/testosterone 0.01% in base (e.g. methylcellulose) twice daily to vestibule
- Clinical experience suggests estradiol 0.01%/testosterone 0.1% may also be effective

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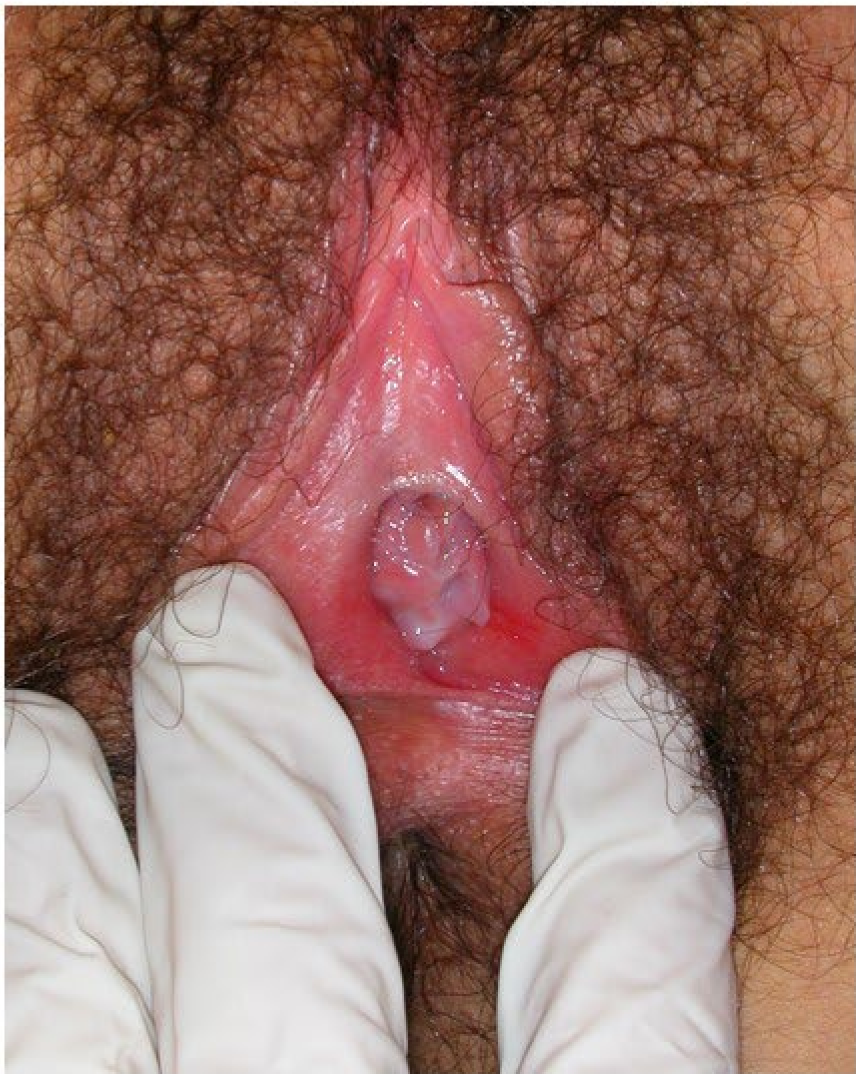
Acquired Neuroproliferative Vulvodynia



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- Women report onset of symptoms after severe or recurrent candidiasis or allergic reaction
- Polymorphism in genes coding for IL-1ra, IL-1b
- Decreased INF-a
- Elevated TNF, IL-1b, IL-6, IL-8, Heparinase
- Increased mast cells in mucosa
- Persistent inflammation can lead to a proliferation of C-afferent nociceptors

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Vulvar Vestibulectomy: Key Points

- High long-term patient satisfaction (93-99%)
- Low complication rates
  - Review true rate of complications
- Proper surgical technique limits complications and improves success
- Vestibulectomy should be offered to patients and not just as a "last resort"

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Vulvar Granuloma Fissuratum: Treatment Strategy

- Conservative treatment
  - First treat the cause of the recurrent tear:
    - Topical clobetasol for lichen sclerosus
    - Topical estradiol/testosterone for atrophy
  - Try vaginal dilators
- If conservative therapy fails, two surgical options exist
  - Fenton's procedure
    - Excise the fissure horizontally and close with vertical interrupted stitches
    - Office procedure with 50%-60% success rate
  - Superficial perineoplasty with vaginal advancement
    - Excise the fissure horizontally and close with vertical interrupted stitches
    - Office procedure with 50%-60% success rate

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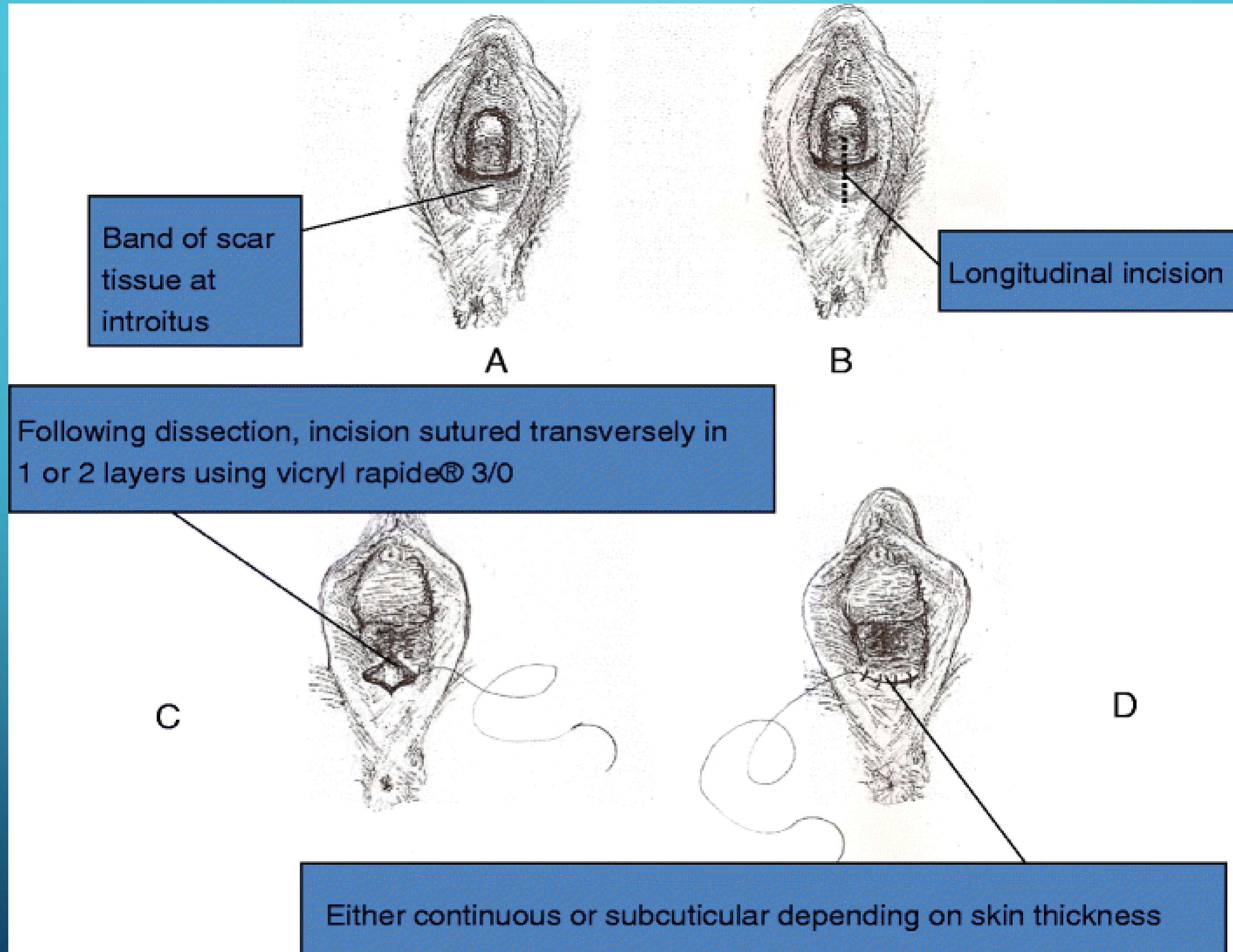
Fenton's Procedure



Persistent Vulvar Pain: Recurrent Vulvovaginal Candidiasis

- Culture for speciation and sensitivity CRITICAL
  - Dominant infections species and virulence vary geographically
  - Send patients home with culturette tubes
  - Treat orally as topical medications contain potential allergens
- *C. Albicans*
  - Fluconazole 150mg weekly for 6 months + Nystatin 500,000 units orally three times daily for 3-6 months + probiotics + dietary changes
- *T. Glabrata*
  - Boric acid 600mg daily for 3 weeks or flucytosine 17% cream for three weeks

Note: Bacterial vaginosis does not cause chronic dyspareunia!

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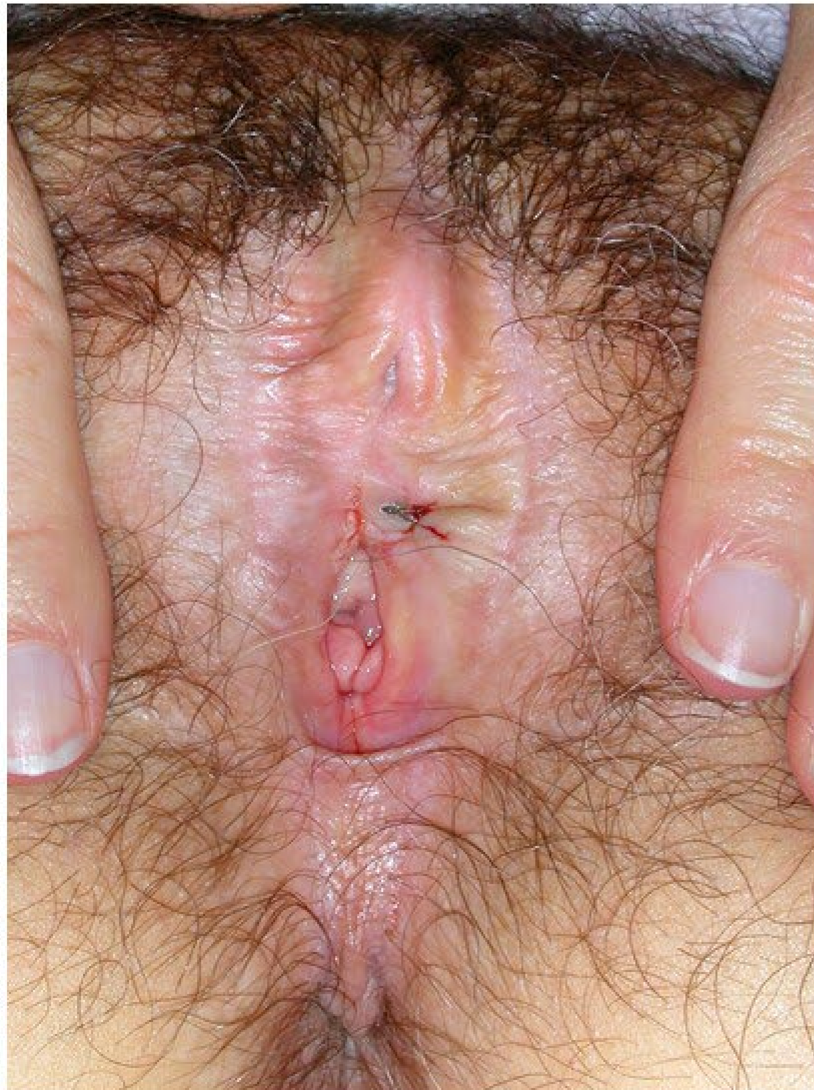
Sexual Pain Disorders: Vulvar Skin Disorders

Lichen Sclerosus



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Lichen Sclerosus: General Information

- Probably autoimmune
  - Association with auto-immune disorders (thyroid disease, alopecia areata, vitiligo, pernicious anemia, lichen planus)
  - Proliferation of monoclonal T lymphocytes
  - High levels of circulating auto immune antibodies
- Prevalence 1 in 70 women
- Females, any age
  - Young children, toddlers and infants
  - Most common is postmenopausal women (median age 51) **But this may be a detection bias as women without estrogen have more symptoms.*

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Lichen Sclerosus: General Information

- Childhood LS usually does not resolve at puberty though symptoms may decrease because of estrogen
- Often misdiagnosed (yeast infections, herpes, vitiligo)
- 3-6% risk of developing vulvar squamous cell carcinoma
- Women with LS are less likely to be sexually active (vaginal intercourse, oral intercourse, masturbation)

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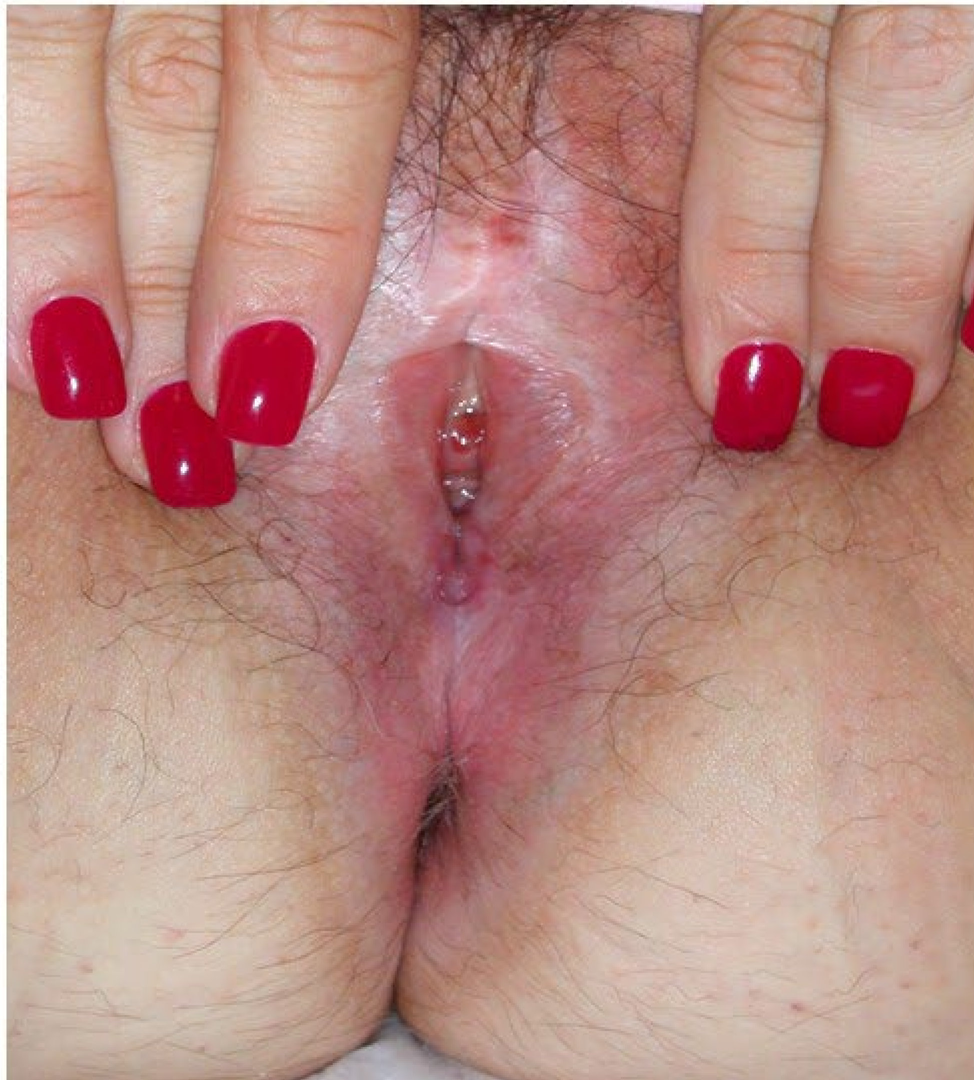
Lichen Sclerosus



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Lichen Sclerosus: Treatment

- Clobetasol 0.05% ointment once daily after soaking
  - Reduce frequency to 1-2x/week and/or potency when all active LS has resolved, not when asymptomatic (do not stop after two weeks!)
- Testosterone does not work better than petrolatum ointment alone
- Current research focused on using topical macrolide immunosuppressants.

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Lichen Sclerosus: Treatment

- Surgery if needed for narrowing of introitus and continued tearing at posterior fourchette
  - Only after all active disease has resolved and tissue has been treated with topical estradiol
  - 85-90% success rate
- Surgical correction of clitoral phimosis

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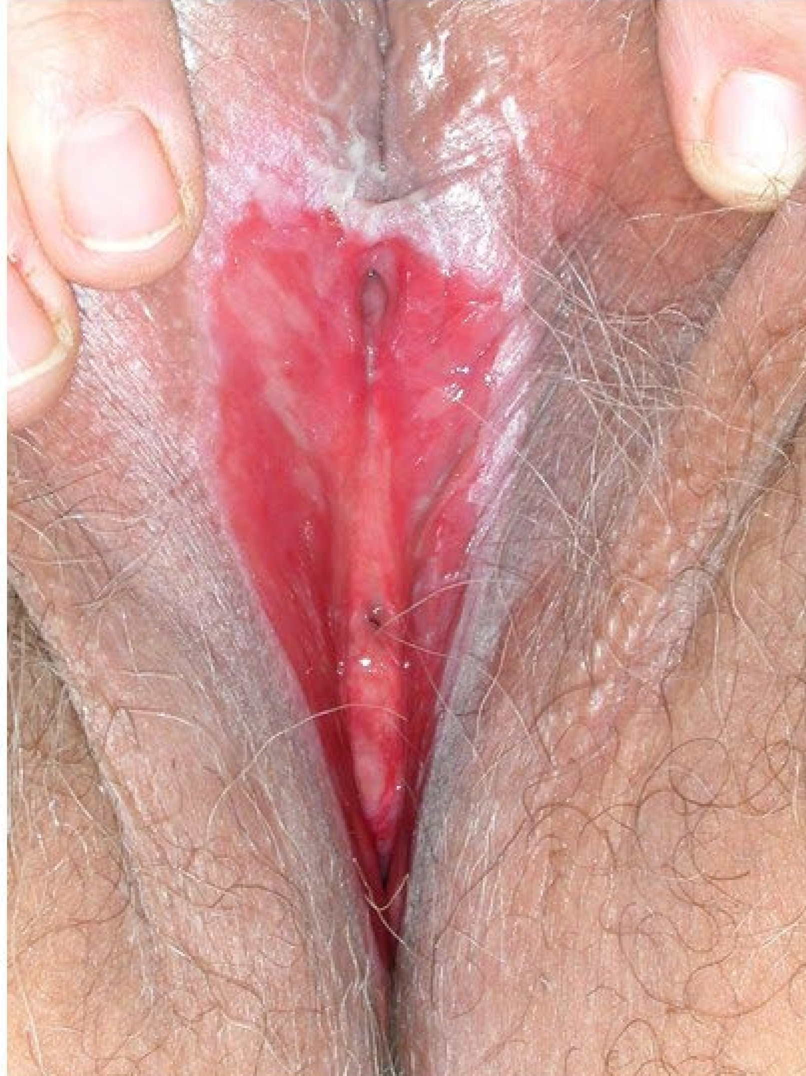
Erosive Lichen Planus



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Lichen Planus: Diagnosis

- Symptoms
  - Burning pain, severe dyspareunia, vaginal stenosis, sticky yellow discharge
- Physical exam
  - Red plaques on mucous membranes (vulva, vagina, mouth) with white "lacey" edges or violaceous borders
- Considerations
  - May resemble lichen sclerosus
    - Particularly when late agglutination and architectural distortion occurs
    - LS is never above the hymen
    - Can co-exist with LS
- Biopsy to confirm diagnosis
  - Direct immunofluorescence useful to rule out bullous diseases

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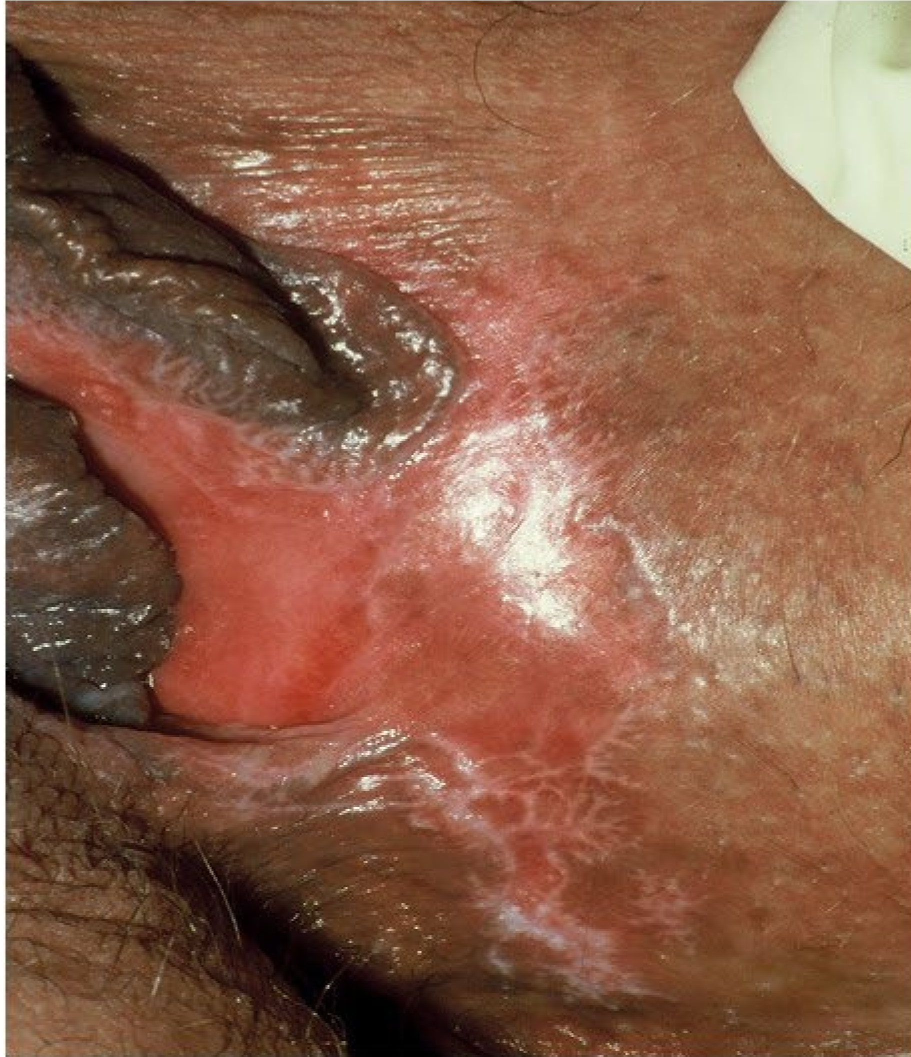
Lichen Planus: Classic Presentation



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- LP with painful vulvar erosion and irregular white lacy border (Wickham Striae)

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Lichen Planus: Treatment

- Options
  - Ultrapotent corticosteroids (clobetasol)
  - Tacrolimus or pimecrolimus (be careful – absorbed form vagina)
  - Systemic steroids, retinoids. MPM, cyclosporine, methotrexate
  - Vaginal dilators essential to prevent vaginal stenosis from synechiae

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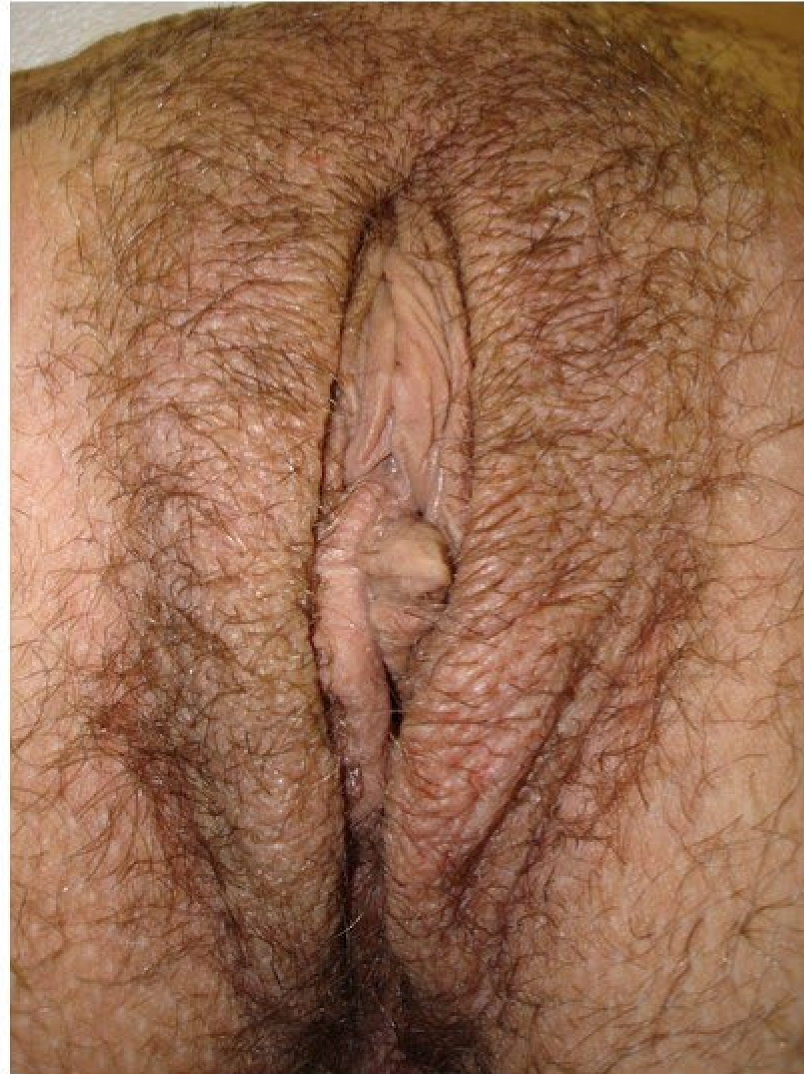
Lichen Simplex Chronicus



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Lichen Simplex Chronicus: General Information

- Also known as: vulvar eczema, vulvar dermatitis, atopic dermatitis, neurodermatitis
- Initiated by
  - Irritants
  - Allergens
  - Infections
  - Vulvar intraepithelial neoplasia (VIN)
  - Mast cell/histamine mediated

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Lichen Simplex Chronicus: Clinical Presentation

- End stage of itch-scratch cycle
- Symptoms and exam findings
  - Intense pruritus, temporary relief with scratching
  - Thick, lichenified skin, erythema – mainly of labia majora
  - May exhibit erosions, fissuring, broken hairs, alopecia, exaggerated skin marking
- May be superinfected with yeast or bacteria
- Pathology
  - Hyperkeratosis, spongiosis, acanthosis, and chronic dermal inflammatory infiltrate

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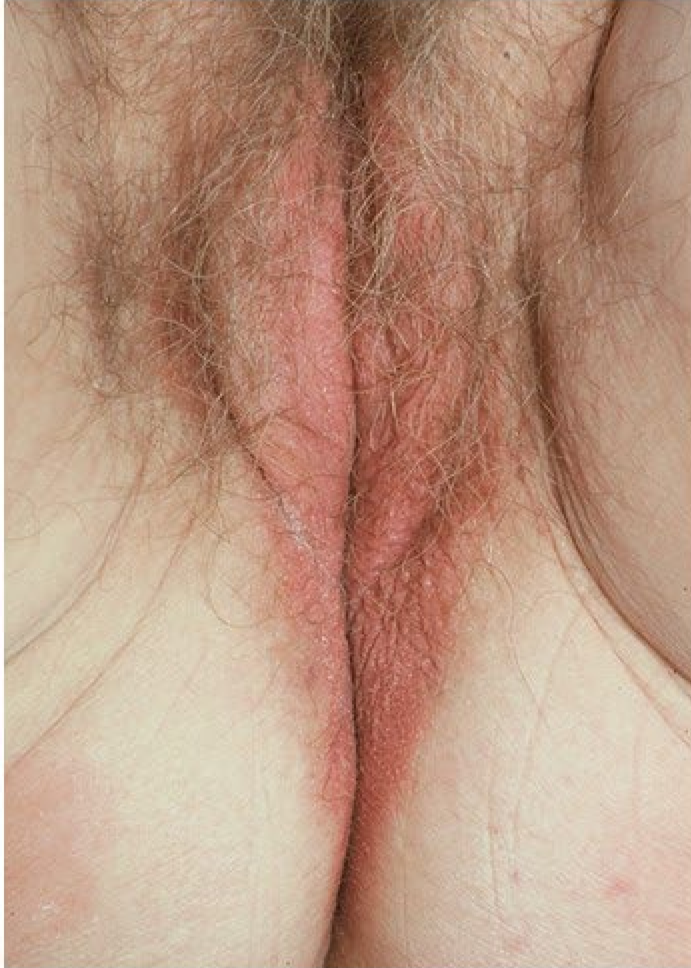
Lichen Simplex Chronicus



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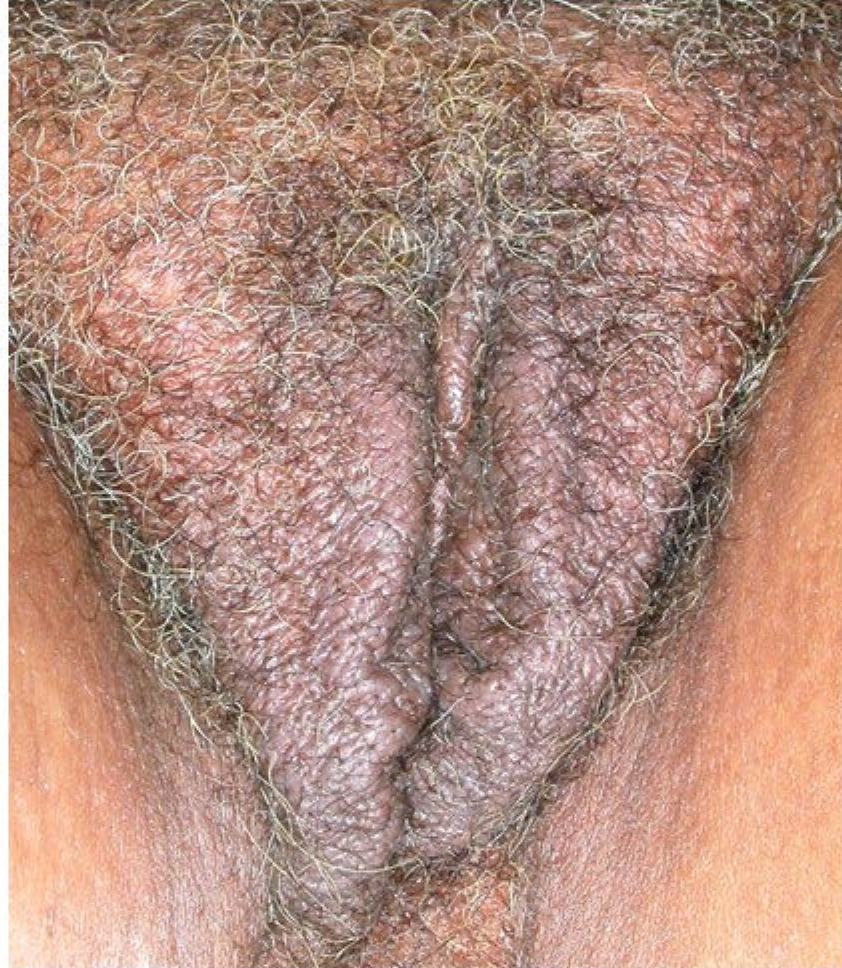

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Lichen Simplex Chronicus: Treatment

- Remove all irritants
  - Soaps, detergents, douches, etc.
- Sitz baths
  - Warm water 1x/day for 10-15 minutes
- High potency topical corticosteroid ointment
  - Rub in for 90-120 seconds
- Nigh time routine
  - Amitriptyline 10-50mg at bedtime
  - Ice (frozen peas) at bedtime to stop scratching during sleep
- Treat underlying infection
  - Amoxicillin/clavulanic acid + fluconazole
- Current research: pimecrolimus versus corticosteroid.

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Behcet's Disease

- A rare chronic inflammatory disorder most common in young women of Asian or Mediterranean descent
- Recurrent oral ulcers at lease three times in one year PLUS any two of the following:
  - Recurrent vulvar ulcers
  - Eye lesions (uveitis, vasculitis)
  - Skin lesions (erythema nodosum, acneiform nodules)
  - Positive pathergy test

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Evidence for Laser Therapy

- Aims: Assess the safety and efficacy of the fractional CO_2 laser for the treatment of genitourinary syndrome of menopause
- Pilot of 30 women, mean age 58.6 +/-8.8 years; participants received 3 treatments at 6 week intervals. Women were evaluated at baseline and 3 months after final treatment
- Primary outcome measure: Visual Analog Scale change in 6 categories
  - vaginal pain, burning, itching, dryness, dyspareunia, and dysuria

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Evidence for Laser Therapy

- Results:
  - 26 of 27 women (96%) were reportedly satisfied or extremely satisfied at follow-up
  - 25/30 participants (83%) showed increase in comfortable dilator size at 3-month follow up
  - Treatment for dryness and dyspareunia showed the most profound improvement
    - Vaginal Health Index
    - Female Sexual Function Index

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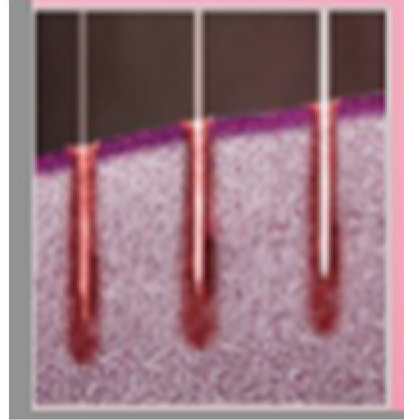
Mechanism of Action



- Fractionated beams of light penetrate small areas of tissue
- Small ablated wounds are created in mucosa epithelium and lamina propria
- Sufficient lateral energy so "spared tissue" also treated

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Female Sexual Dysfunction in Special Circumstances: Testosterone Use in Women

Testosterone Levels and Sexual Function

- Androgenic effects vary from person to person based on enzymatic activity and receptor response
- Testosterone levels do not always correlate with degree of sexual dysfunction
  - However, randomized, placebo-controlled trials consistently show benefits of transdermal testosterone vs. placebo for sexual desire and arousal, orgasm, pleasure, satisfaction, and pain
- Use of testosterone therapy is based on clinical evidence that exogenous testosterone improves libido, arousal, pleasure and overall satisfaction

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Efficacy of Testosterone in Postmenopausal Women: RCTS

	Doses (mcg/d)	Subjects (n)	Estrogen
Shifren et al, 2000	150/300	SM (75)	+
Braunstein et al, 2005	150/300/450	SM (447)	+
Buster et al, 2005	300	SM (533)	+
Simon et al, 2005	300	SM (562)	+
Davis et al, 2006	300	SM (61)	+ (patch)
Davis et al, 2006	300	SM (76)	+ (aromatase inhibitors)
Shifren et al, 2006	300	NM (486)	+
Davis et al, 2008	150/300	NM/SM (814)	-
Panay et al, 2010	300	NM (272)	+/- groups

NM= naturally menopausal
SM= surgically menopausal

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Summary of Efficacy and Safety

- RCTs have established efficacy of transdermal patch for relieving symptoms of HSDD
  - Naturally and surgically menopausal women
  - With and without concomitant ET or EPT
- Main side effects: increased hair growth and acne
- Reassuring safety data, although inconclusive, with respect to cardiovascular, breast, endometrial outcomes
  - Long term safety data demonstrate no significant impact on intermediate metabolic endpoints and a low rate of cardiovascular events and breast cancer in post-menopausal women at increased cardiovascular risk.

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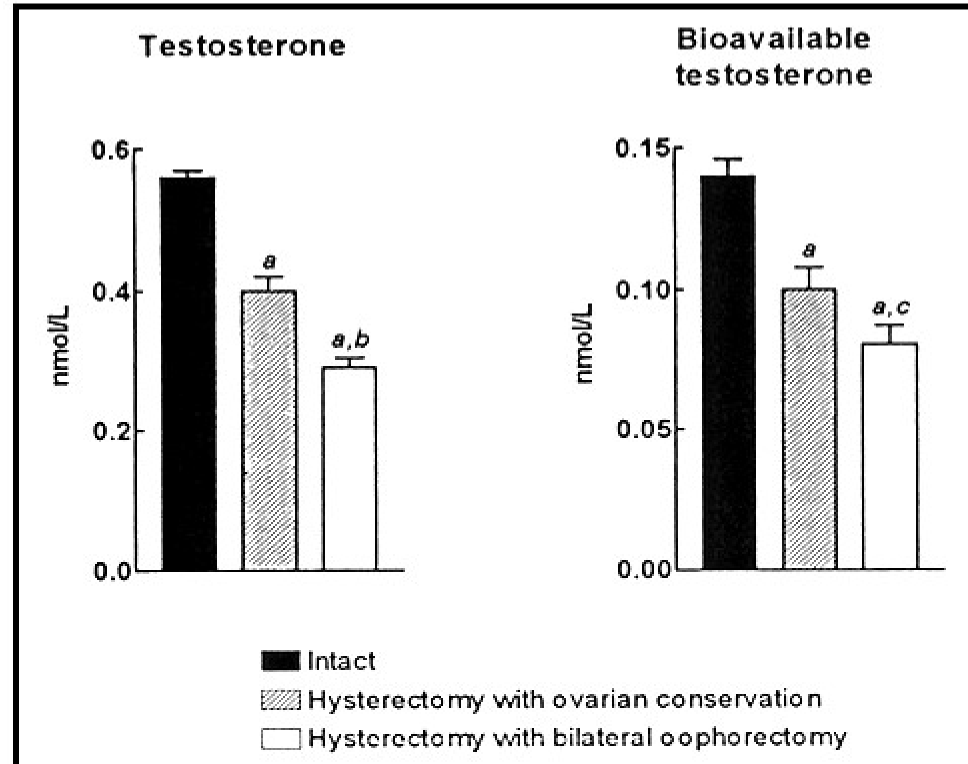
Testosterone After Hysterectomy

Hysterectomy With and Without Bilateral Salpingo-oophorectomy



The uterus, cervix and ovaries share the same blood supply. After hysterectomy, ovarian function may be affected even if the ovaries are intact.

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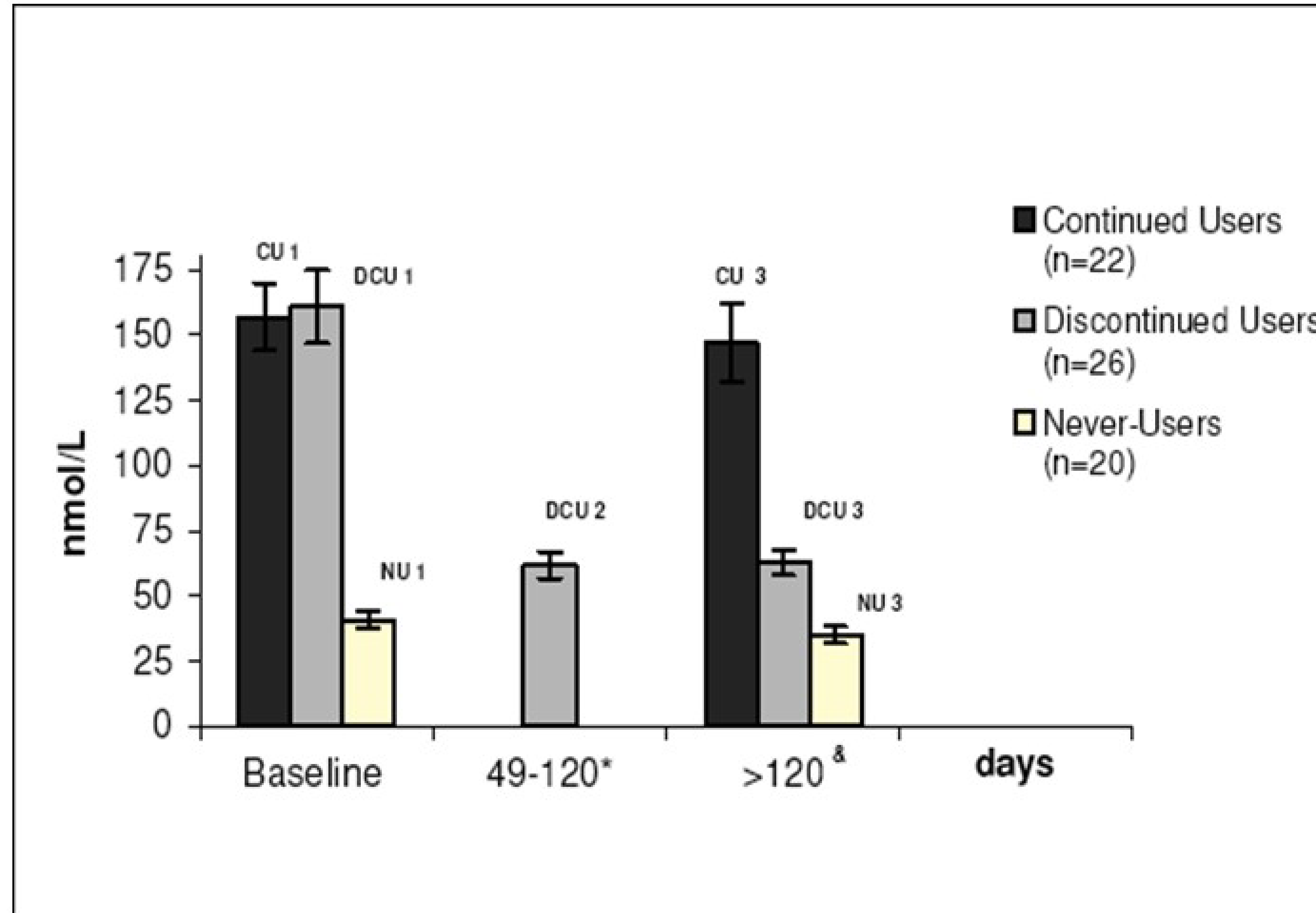
Impact of Oral Contraceptives on Sex Hormone-Binding Globulin and Androgen Levels



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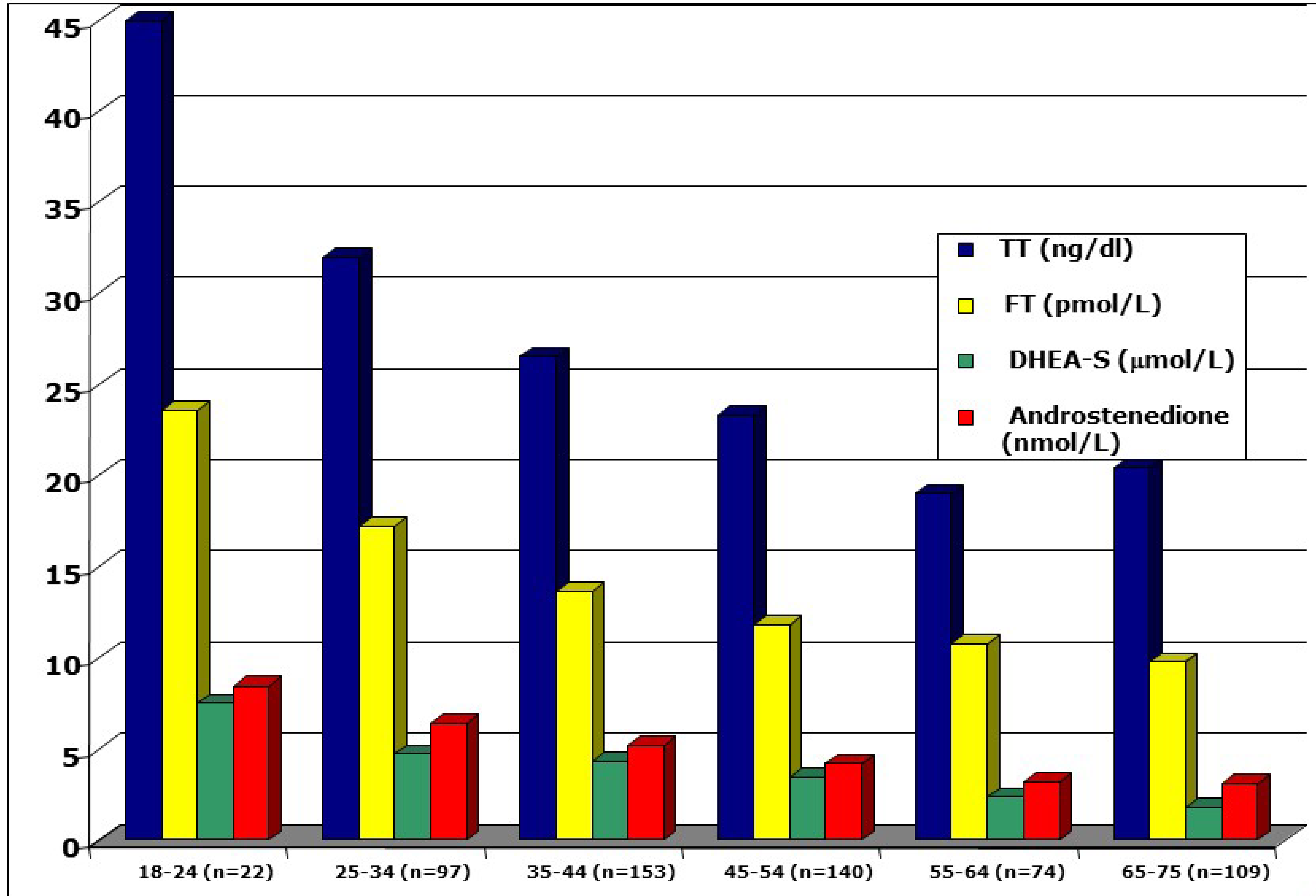
Relationship Between Age and Androgens in Women



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Off-label Testosterone

- Two million prescriptions written for ♀ 2006-7
- 21% of prescriptions for branded male testosterone products written for ♀
- Figures do not include substantial number of prescriptions for compounded testosterone
- Compounded products contain variable concentration of testosterone
- 10 compounding pharmacies in one metro area
- 30-50% within 20% of prescribed dose
- 2 FDA approved male gels consistent
- Compounded products have no systematic trials to support safety concerns and no black box warnings.

Slide courtesy of Dr. Sharon Parish

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Summary of Testosterone for Women

- Transdermal testosterone treatment has been shown to improve sexual function in postmenopausal women
- May be a role for testosterone in select patients
- Long term safety and efficacy RCT data are lacking
- Not FDA-approved for women
  - Intrinsa Patch- Never received FDA approval, approved in Europe, taken off the market
  - Libigel- Never received FDA approval
- Aim for normal physiologic range in premenopausal women

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Female Sexual Dysfunction in Special Circumstances: Aging, Menopause, GSM

Estrogen Loss Increases Urogenital Symptoms

- Estrogen loss increases urinary frequency, urgency, dysuria, and UTI's
- Estrogen – replete vagina:
  - Acidic – pH 4.5 – 5.5
  - Favors lactobacillus, discourages pathogens
- Estrogen – deprived vagina:
  - Alkaline – pH 6.5-7.0
  - Permits colonization by pathogens that can migrate to the urinary tract
  - Many patients have recurrent UTIs
- Local estrogen application can restore vaginal pH to ~5.5

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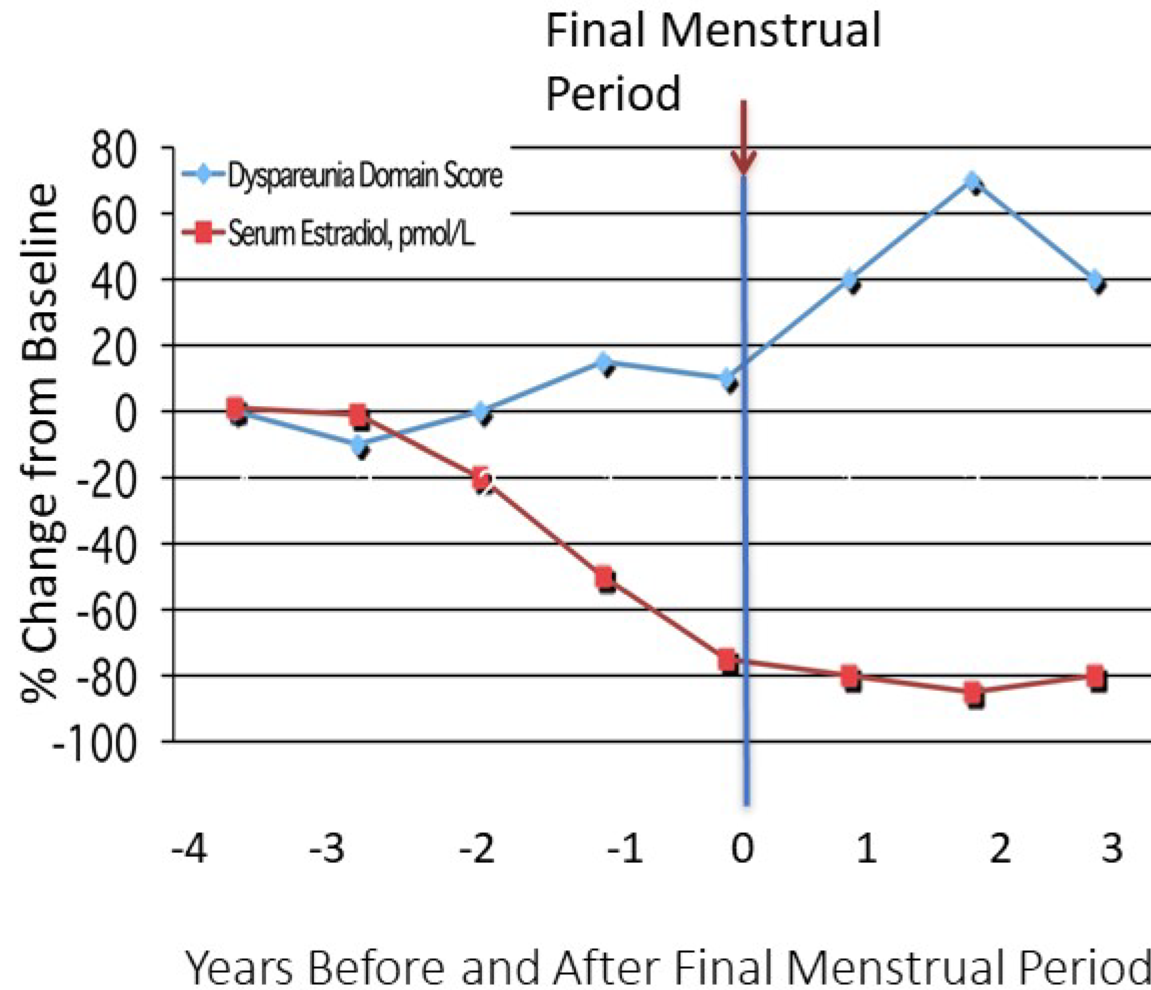
Estrogen Decline and Dyspareunia



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Non-Hormonal Treatment of GSM

- Behavioral
  - Smoking cessation
  - Regular painless sexual activity
- Non-Hormonal vaginal therapy
  - Moisturizers
  - Lubricants
  - Dilators
  - Fractional CO_2 Laser

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Lubricants

Base	Ingredients	Safe with latex?	Staining	Comments
Water	Deionized water, glycerin, propylene glycol	Yes	No	Rarely causes irritation but dries out with extended activity
Petroleum	Mineral oil, petroleum jelly, baby oil	No; do not use with condoms, diaphragms, or cervical caps	Yes	Irritating to vagina
Natural oil	Avocado, olive, peanut, corn	Unclear (not recommended)	Yes	Safe (unless peanut allergy); non-irritating to vagina
Silicone	Silicone polymers	Yes	No	Non-irritating to vagina, long-lasting and waterproof

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Estrogen Treatment of GSM

- Lowers vaginal pH
- Thickens epithelium
- Increases proportion of superficial cells and decreases proportion of parabasal cells
- Increases rugae and elasticity
- Increases vaginal secretions
- Increases vibratory sensation
- Alleviates subjective symptoms of dryness, itching and irritation

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Vaginal Estrogens Available for Postmenopausal Use

Composition	Name	Dosing	Notes
Vaginal Cream Estradiol CEE	 Estrace® Premarin®	Initial: 0.5-1 g/d for 1-2 wk Maintenance: 0.5-1 g/d (0.1 mg active ingredient/g) 0.5-1 g (0.625 mg active ingredient/g) 2-3 X weekly	
Vaginal Ring Estradiol	 Estring®	Device containing 2mg releases 7.5 mcg/d for 90 d	Estring® for localized tx Femring® for systemic use. Need endometrial protection for women with a uterus
Vaginal Tablet Estradiol	Vagifem® Yuvafem®	Initial: 1 tablet/d for 2 wk Maintenance: 1 table 2x/wk (10.3 mcg tablet of estradiol hemihydrate equivalent to 10 mcg of estradiol)	The 10 mcg does is the only available formulation in the US
Vaginal Insert Estradiol	Imvexxy®	Initial: 1 insert/d for 2 wk Maintenance: 1 insert 2x/wk	Available in 4 mcg and 10 mcg dose

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DHEA for VVA/GSM

- DHEA 0.5% 6.5 mg vaginal suppository (Intrarosa) FDA-approved for treatment moderate to severe dyspareunia associated with VVA/GSM
  - Inserted intravaginally once daily at bedtime
  - Phase 3 trials reveal improvements compared to baseline over placebo of 4 coprimary objectives
    - Decreased percentage of parabasal cells
    - Decreased vaginal pH
    - Decreased pain with sexual activity
    - Improvement in moderate to severe vaginal dryness
  - Serum steroid levels remained well within normal postmenopausal range
  - Most common adverse effect: vaginal discharge due to melting vehicle (6%)
  - No change in endometrial atrophy after 12 months

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Questions?