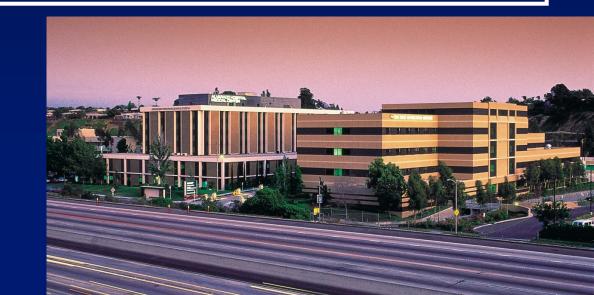
Persistent Genital Arousal Disorder (PGAD) in Women: Mental or Body

Irwin Goldstein MD
Director, Sexual Medicine, Alvarado
Hospital, San Diego, California
Clinical Professor of Surgery,
University of California, San Diego
Editor-in-Chief, The Journal of Sexual
Medicine
Editor-in-Chief, Sexual Medicine
Reviews



Disclosures

Consultant/Advisory Board: Apricus, Emotional Brain, Exploramed, Sprout, Strategic Science & Technologies

Speaker: Ascend, Shionogi

Research: Apricus, Neogyn

Learning objectives:

Characterize the underlying pathophysiologies leading to PGAD and thus direct therapeutic strategies more appropriately

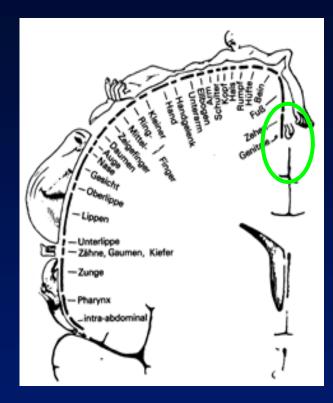
Persistent Genital Arousal Disorder (PGAD)

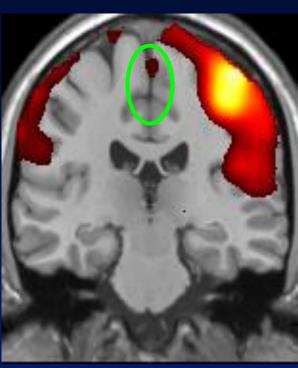
Persistent genital arousal disorder (PGAD) (formerly PSAS) is a rare, unwanted and intrusive sexual dysfunction associated with excessive and unremitting genital arousal and engorgement in the absence of sexual interest

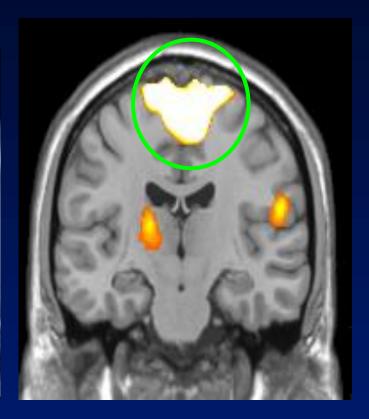
PGAD is extremely frustrating and can lead to suicidal ideation and attempts

The persistent genital arousal usually does not resolve with orgasm

Persistent Genital Arousal Disorder: during PGAD episode







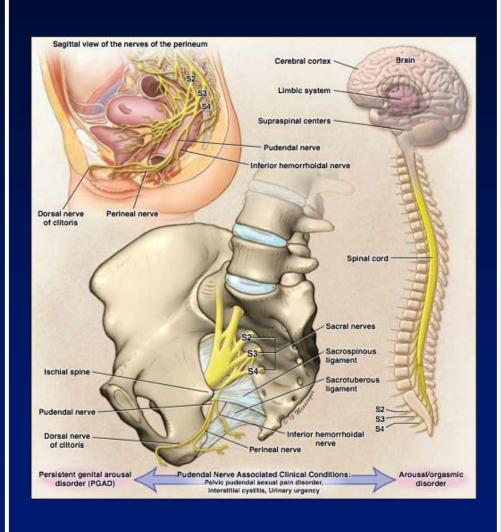
Homuncular genital representation

Normal clitoris projection

PGAD attack

Persistent Genital Arousal Disorder (PGAD)

It is probable that PGAD exists because of excess sensory information passing from a number of peripheral genital pathologies or local central nervous system pathologies, (S2, **S3**, **S4**)



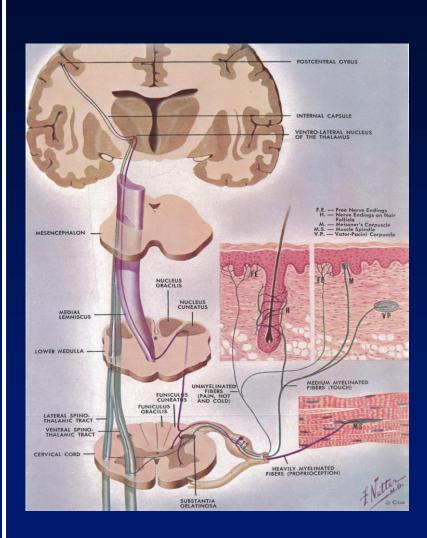
It is probable that PGAD exists because of decreased inhibition of the excess information along the lateral spinothalamic tract, thalamus, and hypothalamus

The lateral spinothalamic tract is a sensory pathway originating in the spinal cord

The lateral spinothalamic tract transmits afferent information to the first order relay area - the thalamus - about pain, temperature, itch and crude touch

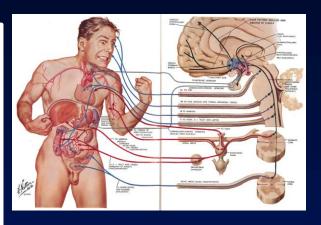
The types of sensory information transmitted via the lateral spinothalamic tract are described as "affective sensation" - the sensation is accompanied by a compulsion to act

For instance, an itch is accompanied by a need to scratch, and a painful stimulus makes one want to withdraw from the pain



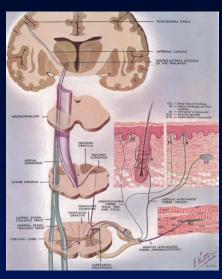
Facial grimaces of pain and the facial grimaces of orgasm are common

Vocal sounds of pain and vocal sounds of orgasm are common





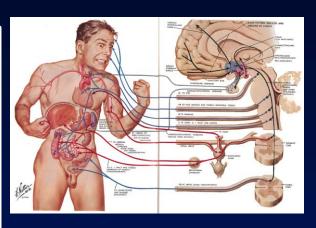






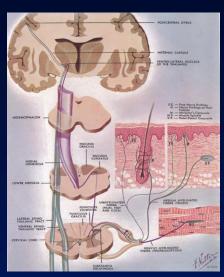


It likely that pain and sexual arousal/orgasm are **BOTH** "affective sensations" that **BOTH** pass to the first order relay area - the thalamus via the lateral spinothalamic tract.







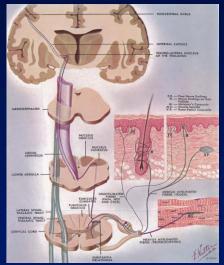




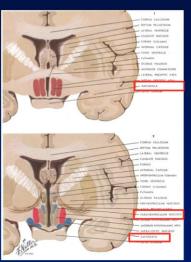


Sexual arousal/orgasm information then passes from the first order relay area, thalamus, to second order relay area, hypothalamus specifically to nucleus accumbens, amygdala, hippocampus, the paraventricular nucleus of the hypothalamus and ventral tegmentum









Second Order Relay Area Hypothalmus:

Nucleus accumbens

Amygdala

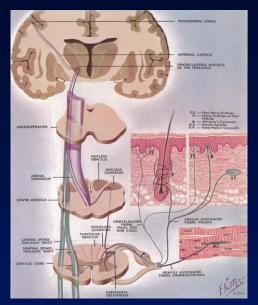
Hippocampus

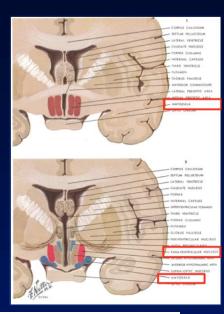
Paraventricular nucleus of the hypothalamus Ventral tegmentum

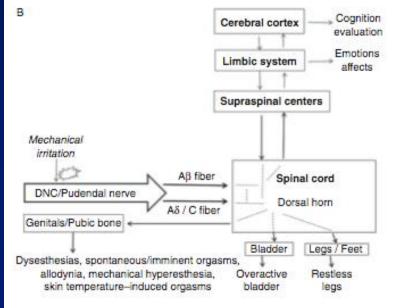
It is probable that PGAD exists because of excess sensory information passing from a number of peripheral genital pathologies or local central nervous system pathologies, (S2, S3, S4)

The excess sensory information passes along the lateral spinothalamic tract to the first order relay area, thalamus, and then inadvertently to the second order relay area, hypothalamus

The brain misinterprets the excess information as sexual arousal/orgasm







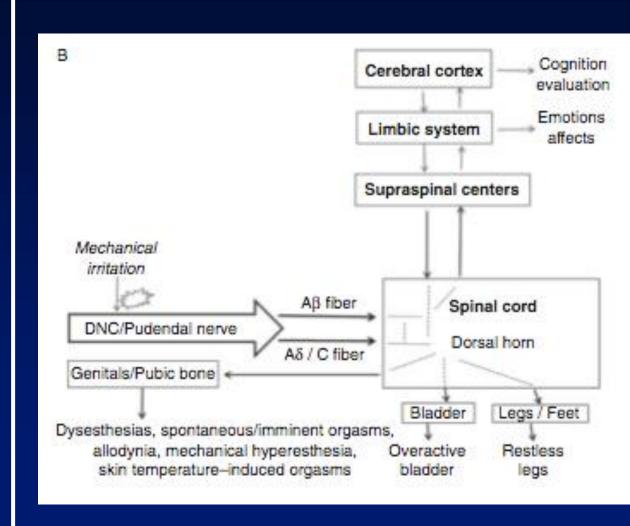
Persistent Genital Arousal Disorder (PGAD)

In PGAD there are often concomitant secondary symptoms (may be related in part to associated high tone pelvic floor dysfunction):

Bladder (urinary frequency, urinary urgency) problems

Bowel (irritable bowel) problems

Restless leg problems



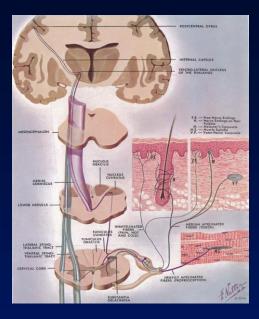
Excess sensory information passing from a number of peripheral genital pathologies or local central nervous system pathologies, (S2, S3, S4)

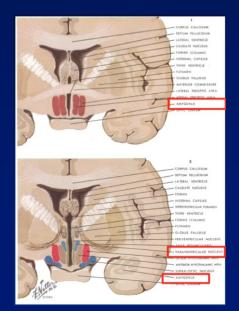
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- b) altered menopausal hormone integrity vulvovaginal atrophy/genitourinary syndrome of menopause
- c) increased nerve fiber density genetic susceptibility leading to elevated levels of nerve growth factor substances
- d) an injury to, or irritation of, the pudendal nerves that transmit pain and other sensations
- e) abnormal response of tissues to Candida infection, or recognized allergies or non-specific allergies
- f) dermatologic conditions: lichen sclerosus or lichen planus
- g) vulvar granuloma fissuratum
- h) peri-urethral glans pathology
- i) clitorodynia
- j) pelvic congestion syndrome
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The keys to treatment of PGAD:

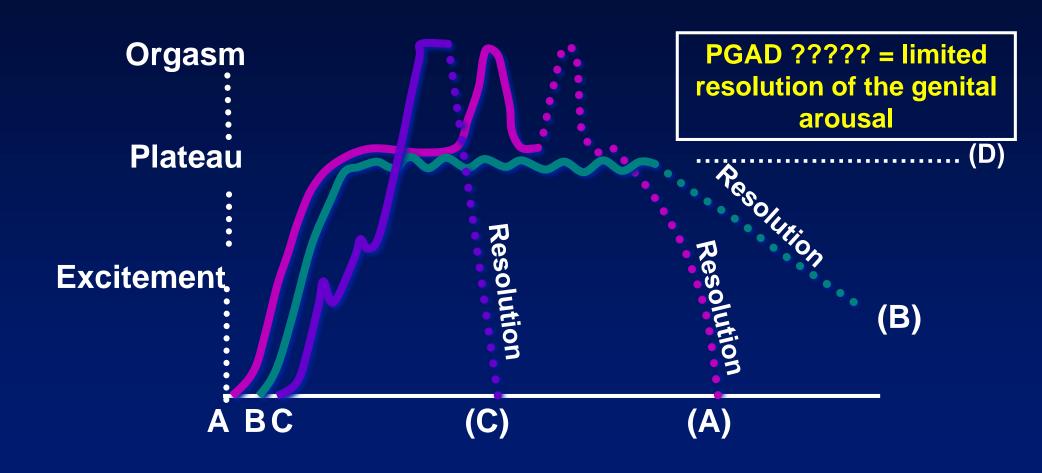
- 1. REDUCE the excess peripheral sensory input from peripheral genital pathologies or local central nervous system pathologies, (S2, S3, S4)
- 2. INCREASE inhibition of the excess information along the lateral spinothalamic tract

Successful PGAD management utilizes BOTH strategies - to keep the PGAD condition manageable





Female Sexual Response Cycle



Persistent Genital Arousal Disorder—Update on the Monster
Sexual Dysfunction

J Sex Med 2013;10:2357–2358

- 1. PGAD is not so rare—I personally have spoken with and/or cared for well over 100 women and men with PGAD. I have asked healthcare providers at numerous sexual meetings to raise their hands if they have cared for individuals with PGAD and under most situations, approaching 1 in 4 or 5 providers have managed such patients.
- 2. PGAD can be cured—We have several patients diagnosed with PGAD who are no longer suicidal or bothered/distressed after treatment(s).

Persistent Genital Arousal Disorder (PGAD)

It takes a lot of courage to tell the world I have PGAD. It is something we don't talk about. It's a secret. If someone were to find out, we could be ridiculed and sexually harassed for the rest of our lives. Some of us don't even tell our spouses due to the fact that we're afraid that they will leave us.

PGAD can last for hours or days with no relief; it is unrelenting and unwanted. It causes a lot of suffering and is often associated with social withdrawal and suicidal thoughts and plans-at one time I had plans. I am very lucky to be standing here today. I was bed ridden. I could not ride in a car; the thought of even getting in a car was unthinkable, as the vibration from driving would stimulate the PGAD. I couldn't wear tight clothing or even underwear. I wore only dresses so nothing would touch me and aggravate my PGAD. I couldn't carry out my regular household duties, cooking, cleaning, washing clothes. Just walking would trigger my PGAD. It is embarrassing and humiliating. I had to be near a bathroom at all times. It caused me to not want to live.

Persistent Genital Arousal Disorder (PGAD)

There are no recognized safe and effective evidence-based treatments

Most physicians are uninformed and unaware of PGAD

No animal models of PGAD yet exist

Primary versus acquired

Biopsychosocial pathophysiologies –

Psychologic – especially STRESS

Musculoskeletal

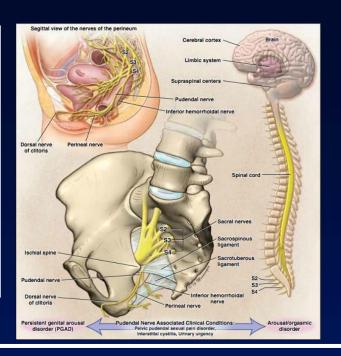
Hormonal

Vascular

Neurological

Pharmacologic Causes

It is probable that PGAD exists because of excess sensory information passing from a number of peripheral genital pathologies or local central nervous system pathologies, (S2, S3, S4)



It is probable that PGAD exists because of decreased inhibition of the excess information centrally along the lateral spinothalamic tract, thalamus and hypothalamus

The keys to treatment of PGAD:

- 1. REDUCE the excess peripheral sensory input from peripheral genital pathologies or local central nervous system pathologies, (S2, S3, S4)
- 2. INCREASE inhibition of the excess information along the lateral spinothalamic tract

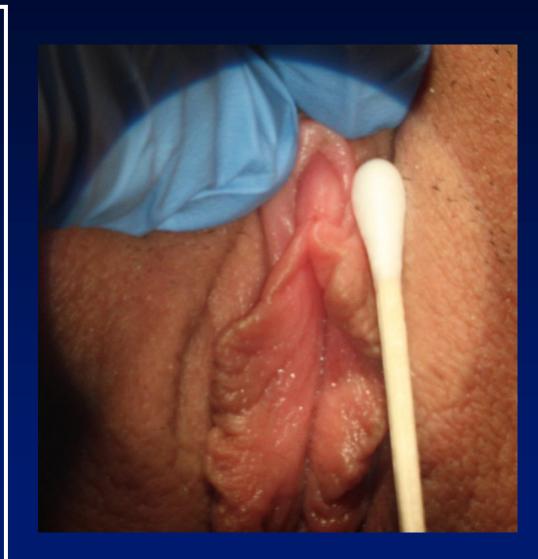
Successful PGAD management utilizes BOTH strategies - to keep the PGAD condition manageable

Persistent Genital Arousal Disorder (PGAD)

PGAD symptoms include:

Persistent perception that the clitoris, labia, vagina are engorged and throbbing and are fully sexually aroused - even though there is no sexual stimulation

Physical examination locally does not usually show local clitoral, labial or vaginal engorgement – despite thepresence of PGAD



Persistent Genital Arousal Disorder (PGAD):

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Hormonally Mediated Provoked Vestibulodynia

Most commonly caused by hormonal contraceptives (may not resolve just by stopping OCPs.) Other causes include: menopause, oophorectomy, hormonal control of endometriosis or hirsutism, breast-feeding, infertility treatments, treatment of breast cancer



Hormonally Mediated Provoked Vestibulodynia

Diffuse vestibular tenderness of the entire vestibule

Ostia of glands are frequently erythematous

The vestibule may have a diffuse pallor with superimposed erythema

Low estradiol, low free testosterone, very high SHBG



Hormonally Mediated Provoked Vestibulodynia

Treatment:

Stop hormonal contraceptives

Systemic testosterone

- ideal calculated
free testosterone 0.8
ng/dl

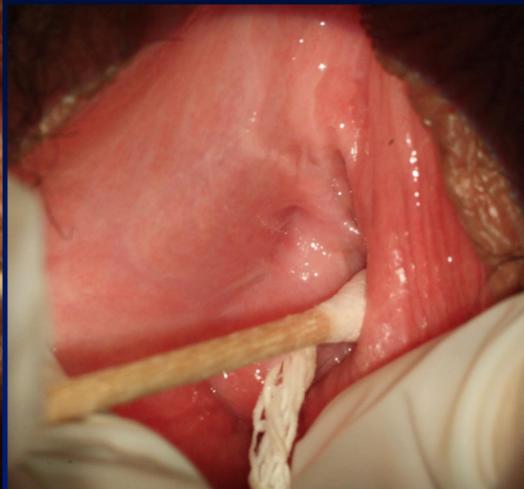
Local to vestibule estradiol 0.02%/testosterone 0.1% in methylcellulose BID

Expect no improvement for 6 weeks, 30-40% by 12 weeks

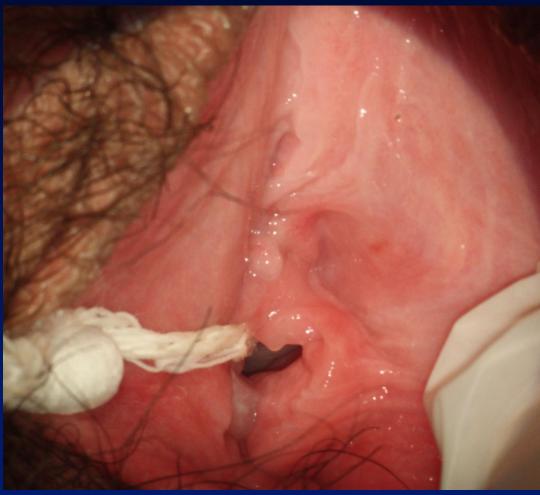








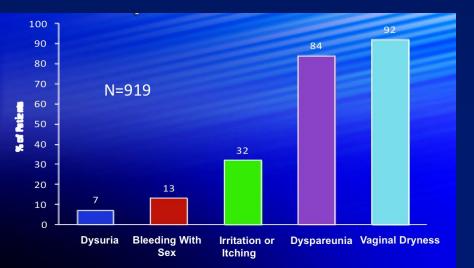




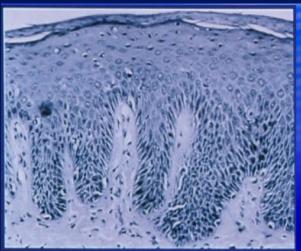
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Dryness and insufficient moistness **Diminished blood flow Dyspareunia** Itching **Burning sensation** Soreness Loss of elasticity Thinning of the vaginal tissue and alteration of keratinization

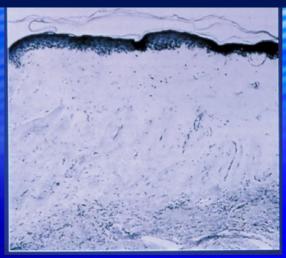


Mucosal defects including petechiae, microfissures, ulceration and inflammation
Shortening, fibrosis, obliteration of vaginal vault and/or
Narrowing of vaginal entrance
Smoothing of fornix, flattening of vaginal rugae



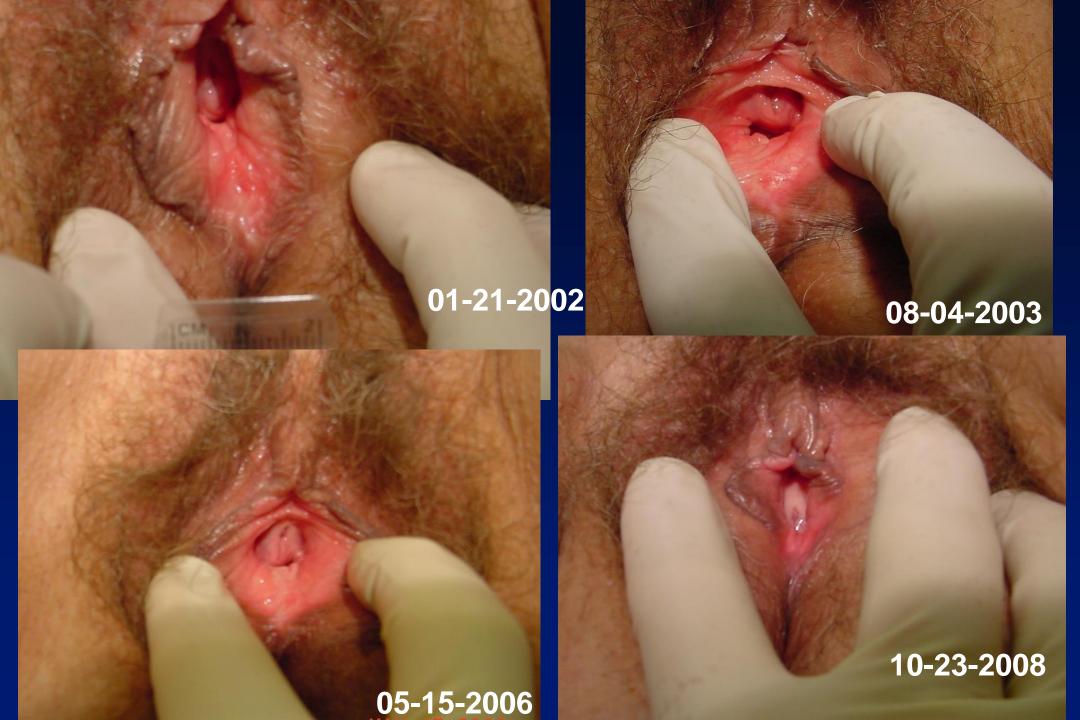
Premenopause

Epithelium well-estrogenized, multilayered with good blood supply, superficial cells rich in glycogen



Postmenopause

Estrogen-deficiency atrophy with marked thinning of epithelium, blood supply reduced and loss of glycogen





Vulvoscopy 10/5/12 Vulvoscopy 1/18/13

MENOPAUSE MANAGEMENT – FIVE TREATMENTS

Testosterone Therapy

Use FDA-approved testosterone at 10% of male dose

- 1. Daily transdermal gel 1/10th tube daily to calf/thigh Daily transdermal solution (0.3 ml daily underarm
- Weekly IM injections 0.1 ml 50 mg/ml testosterone enanthate/cypionate - into vastus lateralis muscle – anterolateral mid-thigh; 27 gauge needle; 1 ml syringe
- 3. 4-6 month subcutaneous testosterone pellet

Estradiol Therapy

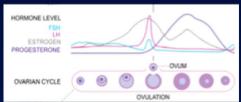
Consider FDA-approved biologically identical estradiol

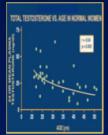
- 1. Daily oral (↑ SHBG, ↑ VTE, ↑ lipids)
- 2. Daily transdermal gel, emulsion, spray
- 3. Twice weekly, weekly transdermal patch
- 4. Three month vaginal ring
- 5. Weekly IM injections 0.1 ml estradiol valerate 10 mg/ml; 5 ml bottle; vastus lateralis muscle anterolateral mid-thigh 27 gauge needle; 1 ml syringe

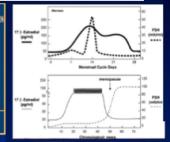
Progesterone Therapy

Consider FDA-approved biologically identical progesterone

- 1. Oral micronized progesterone 100 mg q MWF (intact uterus, q MTh hysterectomy)
- 2. Vaginal progesterone suppository 6 per month
- 3. Compound progesterone cream











Vestibular Hormonal Therapy

Compound estradiol 0.02%/testosterone 0.1% in hypoallergenic base (methylcellulose); apply pea-sized volume x 2 (right and lft sides; directly onto entire vestibule; QD – BID

Intravaginal Hormonal Therapy

- 1. Daily compound estradiol 0.02%/testosterone 0.1% in hypoallergenic base (methylcellulose); apply pea-sized volume directly into vagina
- 2. Daily vaginal estradiol cream pea-sized amount
- 3. Daily 10 mg DHEA tablet/1% DHEA suppository
- 4. Three month vaginal ring

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Acquired Neuro-Proliferative Vestibulodynia

Women reports onset of symptoms after severe or recurrent candidiasis or allergic reaction^{1,2}

Polymorphism in genes coding for IL-1ra, IL-1 $\beta^{2,3}$

Decreased INF- α^3

Elevated TNF, IL-1β, IL-6, IL-8, Heparanse³

Increased mast cells in mucosa4

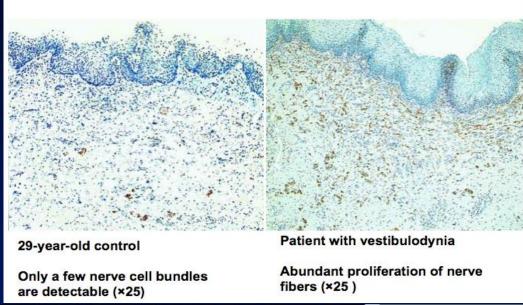
Persistent inflammation can lead to a proliferation of C-afferent nociceptor⁴

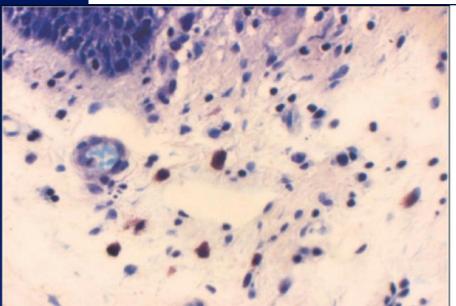


- 1. Harlow BL Ann Epidemiol. 2009 Nov;19(11):771-77
- 2. Witkin SS Am J Obstet Gynecol. 2002 Mar;186(3):361-4.
- 3. Foster Am J Obstet Gynecol. 2007 Apr;196(4):346.e1-8
- 4. Bornstein J Int J Gynecol Pathol. 2008 Jan;27(1):136-41.

Neuroproliferative Vestibulodynia

S-100 Immunostain





Involvement of Heparanase in the Pathogenesis of Localized Vulvodynia.

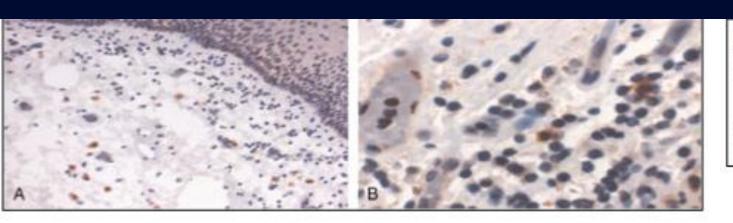
Bornstein, Jacob; Cohen, Yitzhak; Zarfati, Doron; Sela, Shifra; Ophir, Ella

International Journal of Gynecological Pathology. 27(1): 136-141, January 2008.

DOI: 10.1097/pgp.0b013e318140021b

FIG. 1 . A x600 Giernsa stain depicting the mast cells subepithelially in a specimen from localized vulvodynia.

Neuroproliferative Vestibulodynia



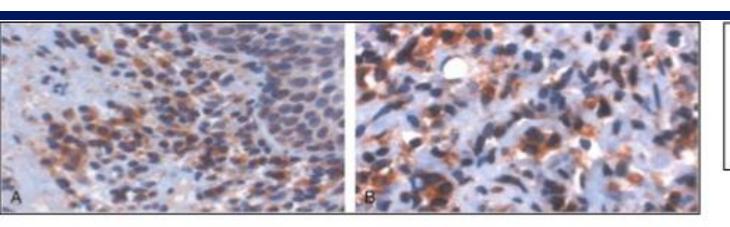
Involvement of Heparanase in the Pathogenesis of Localized Vulvodynia.

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FIG. 2 . A x400 (A) and x600 (B) CD117 (C-kit) stain depicting mast cells. They are located subepithelially, among other inflammatory cells, in a specimen from localized vulvodynia.



Involvement of Heparanase in the Pathogenesis of Localized Vulvodynia.

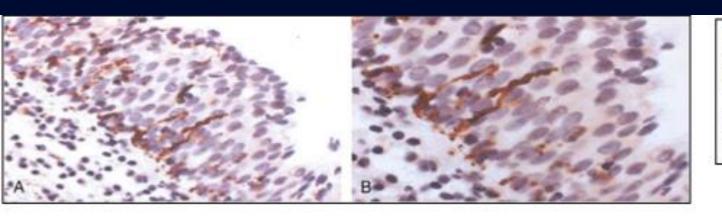
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FIG. 3. Heparanase expression. x400 (A) and x600 (B). Positive cytoplasmatic staining is seen in the subepithelial layer, close to the epithelial basement membrane.

Neuroproliferative Vestibulodynia



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FIG. 4 . x400 (A) and x600 (B) staining for PGP 9.5. The nerve fibers are seen intruding into the epithelium to more than half its depth.

Characteristic	Score (0-3)						
	Localized Vulvodynia			Control			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	2-Sided P*
No. mast cells (Giemsa stain)	2.14 ± 0.378	2.0	2-3	0.14 ± 0.378	0.0	0-1	0.001
Separanase expression	2.71 ± 0.488	3.0	2-3	0.14 ± 0.378	0.0	0-1	0.001
Subepithelial innervation (PGP 9.5)	2.0 ± 0	2.0	2-2	0.71 ± 0.488	1.0	0-1	0.001
Intraepithelial innervation (PGP 9.5)	2.0 ± 0	2.0	2-2	0.14 ± 0.378	0.0	0-1	0.001

Involvement of Heparanase in the Pathogenesis of Localized Vulvodynia.

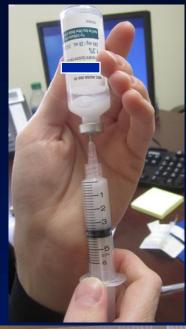
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VESTIBULAR ANESTHESIA TEST









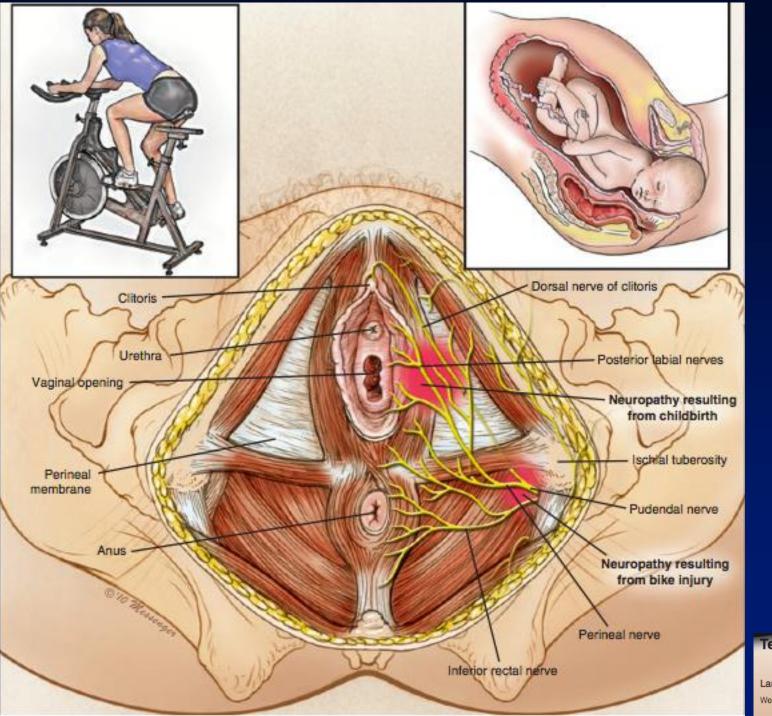




6 weeks post-op



- a) altered pre-menopausal hormone integrity hormonally mediated provoked vestibulodynia
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J Sex Med 2010;7:1716-1719

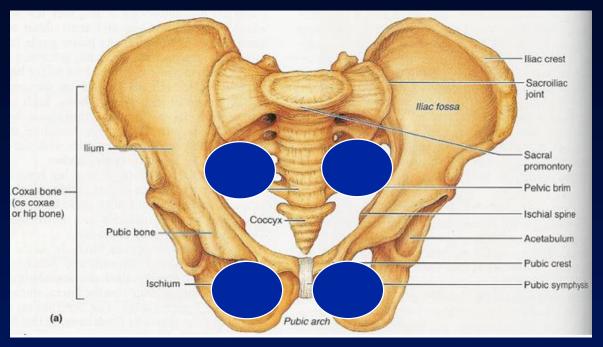
Techniques of Pudendal Nerve Block

Lauri Romanzi, MD

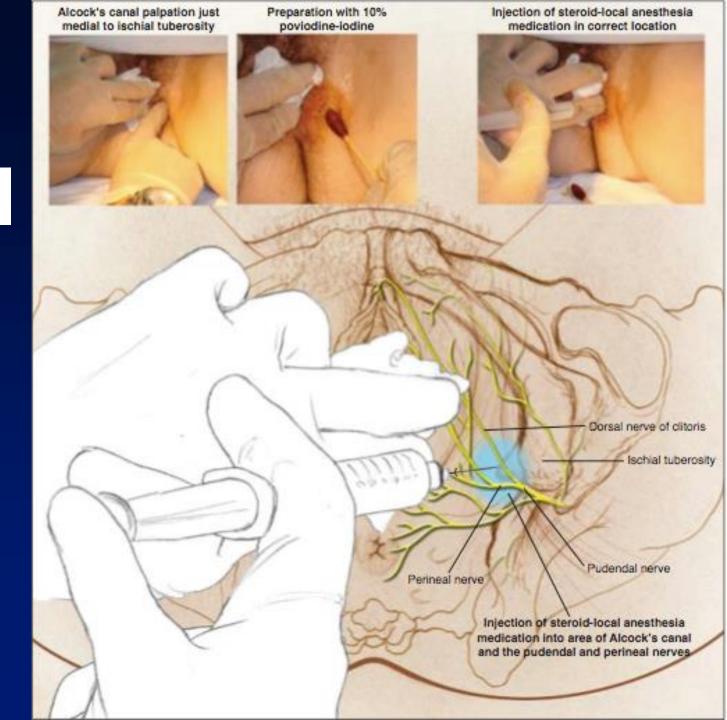
Weill Cornell Medical Center, New York Presbyterian Hospital, New York, NY, USA

"TENS" Transcutaneous
Electrical Nerve
Stimulation.





Pudendal Nerve Blocks



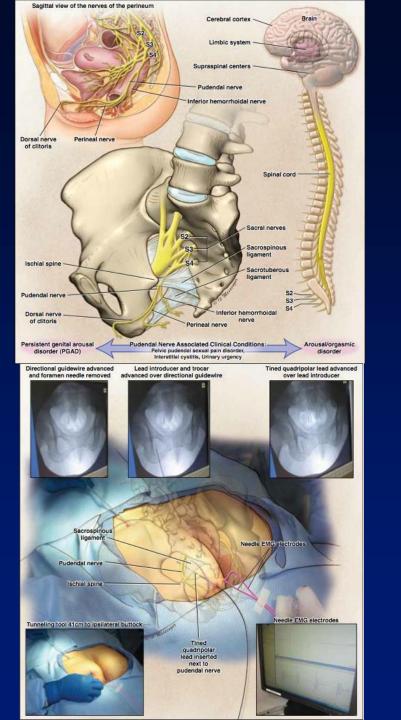


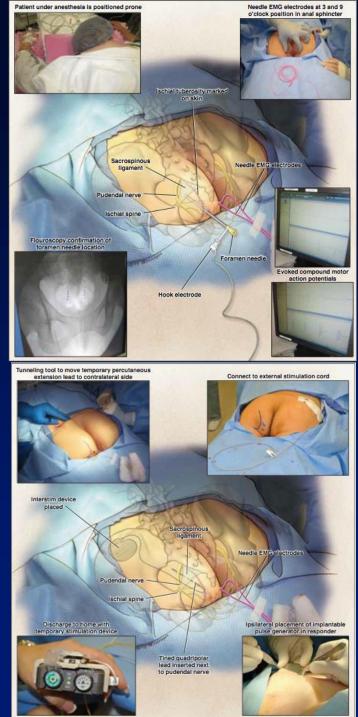












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Candida Infection



Genital herpes is a sexually transmitted disease caused by a herpes virus.

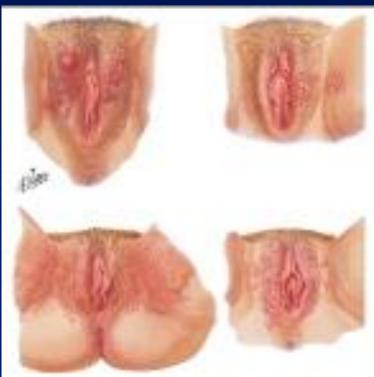
The disease is characterized by the formation of fluid-filled, painful blisters in the genital area.

Herpes may be spread by vaginal, anal, and oral sexual activity. It is not spread by objects (such as a toilet seat or doorknob), swimming pools, hot tubs, or through the air.

Genital herpes is a disease resulting from an infection by a herpes simplex virus.

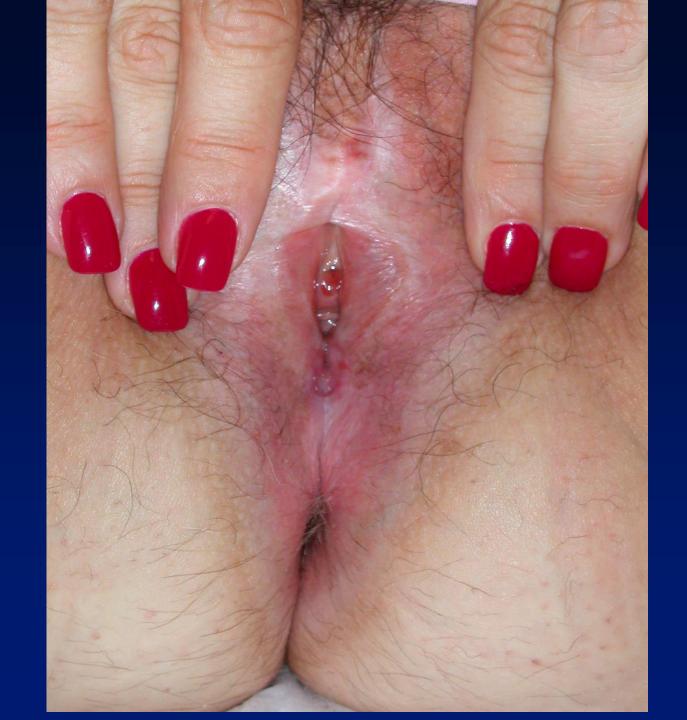
There are eight different kinds of human herpes viruses. Only two of these, herpes simplex types 1 and 2, can cause genital herpes





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- b) altered menopausal hormone integrity vulvovaginal atrophy/genitourinary syndrome of menopause
- c) increased nerve fiber density genetic susceptibility leading to elevated levels of nerve growth factor substances
- d) an injury to, or irritation of, the pudendal nerves that transmit pain and other sensations
- e) abnormal response of tissues to Candida infection, or recognized allergies or non-specific allergies
- f) dermatologic conditions: lichen sclerosus or lichen planus
- g) vulvar granuloma fissuratum
- h) peri-urethral glans pathology
- i) clitorodynia
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Lichen Scleros<u>u</u>s (LS)

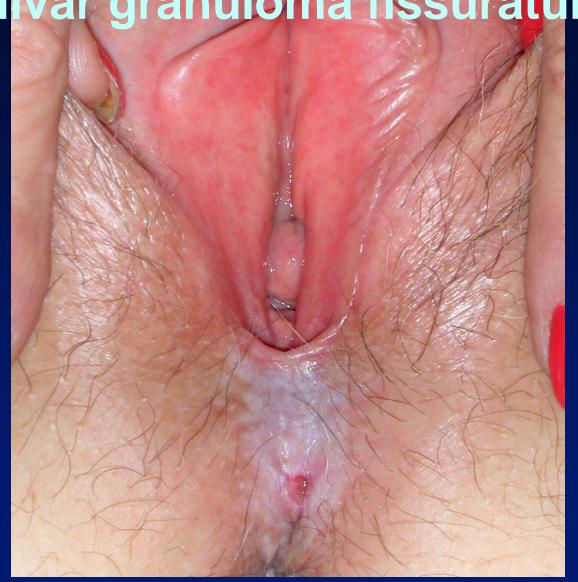


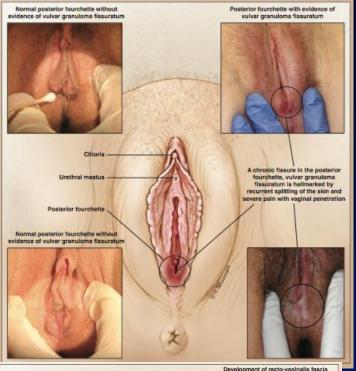
Erosive Lichen Planus

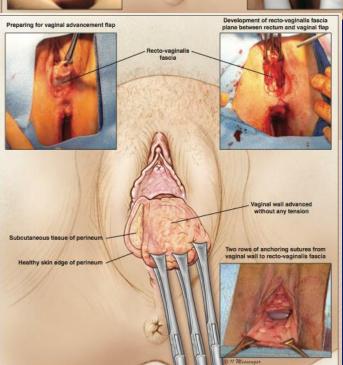


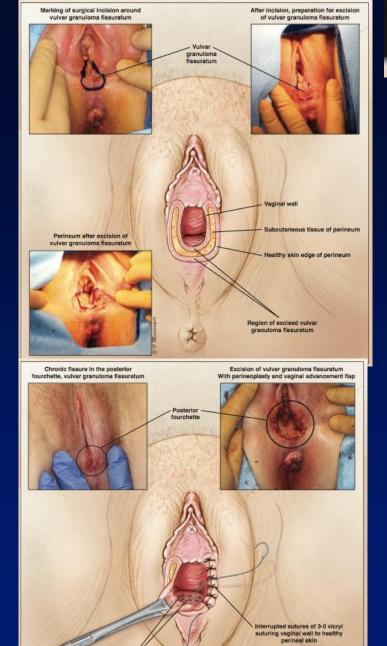
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INTROITAL DYSPAREUNIA Vulvar granuloma fissuratum







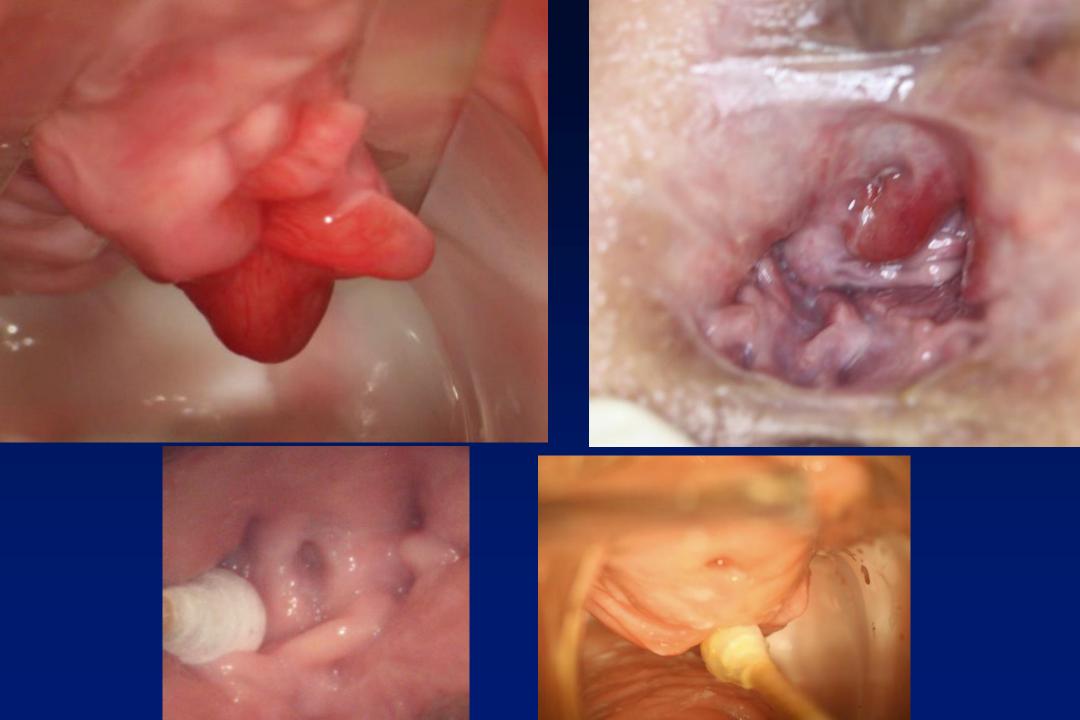


Two rows of interrupted 2-0 vicryl anchoring sutures securing vaginal advancement flap to recto-vaginalis fascia

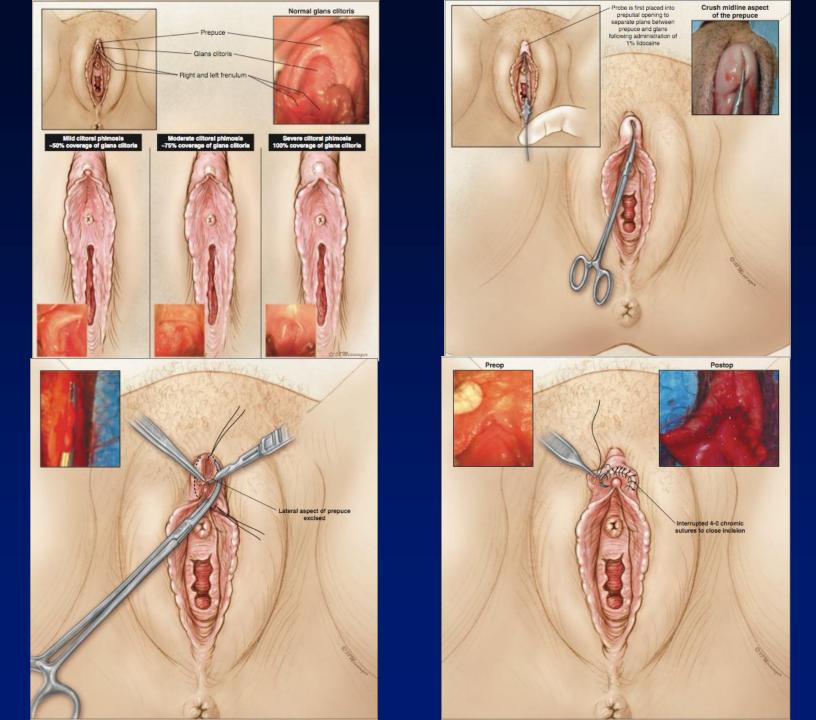
Surgical Techniques

Perineoplasty and Vaginal Advancement Flap for Vulvar Granuloma Fissuratum

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Pelvic Congestion Syndrome Presenting as Persistent Genital Arousal: A Case Report

J Sex Med 2008;5:504-508

Catherine Thorne, MBBS,* and Bronwyn Stuckey, FRACP*†

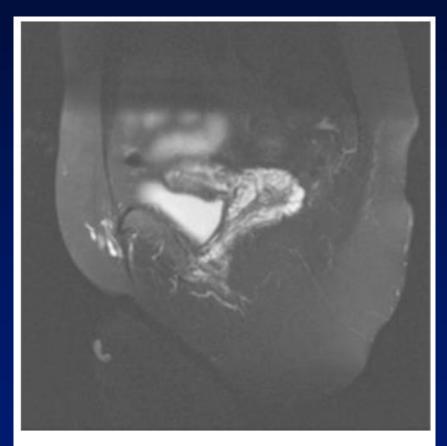
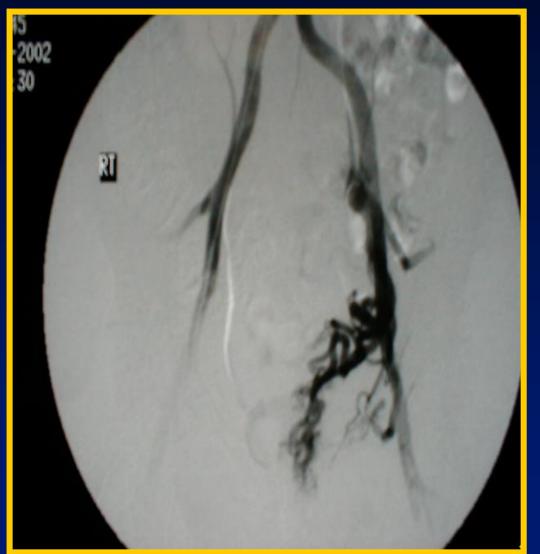


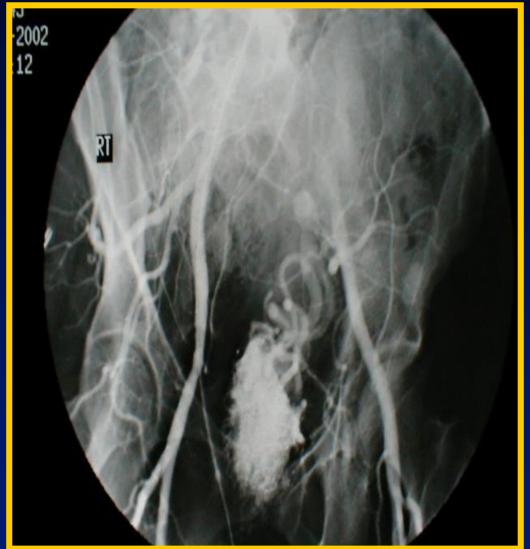
Figure 1 Magnetic resonance imaging scan with contrast enhancement shows extensive varices involving the entire vaginal wall, contiguous with the prominent parametrial veins. Varicosities are also seen in the anterior abdominal wall and in the anterior thigh.



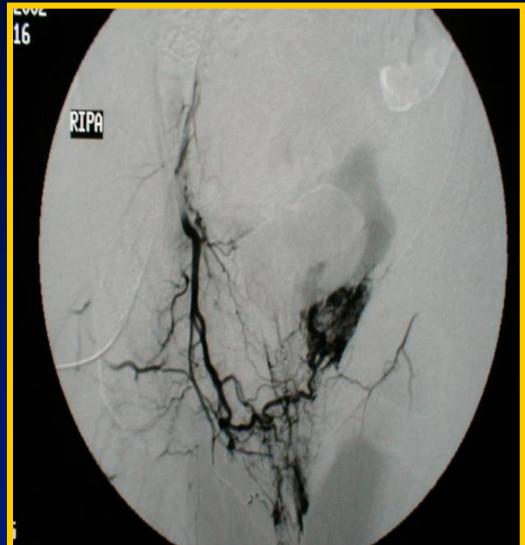
Figure 2 Venogram of the left ovarian vein shows retrograde flow and pelvic varices before embolization (left) and after embolization using stainless steel coils and 3% ethoxysclerol (right).

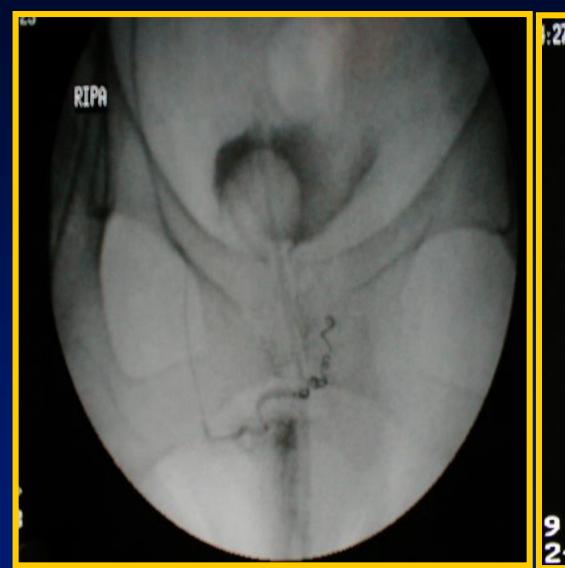
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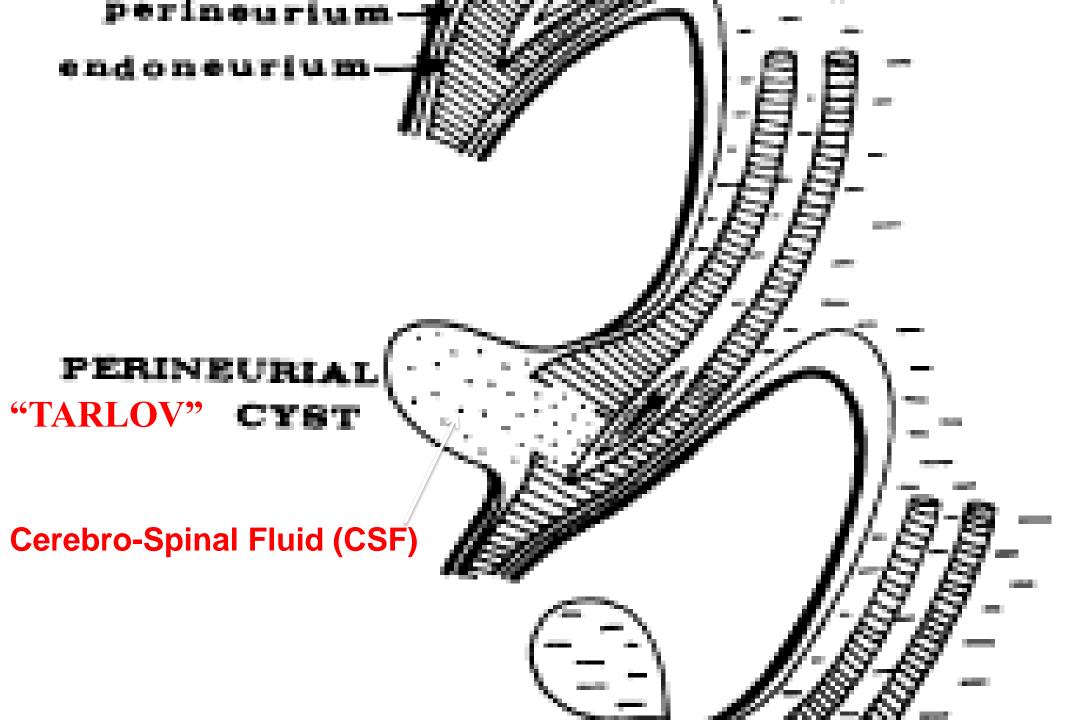


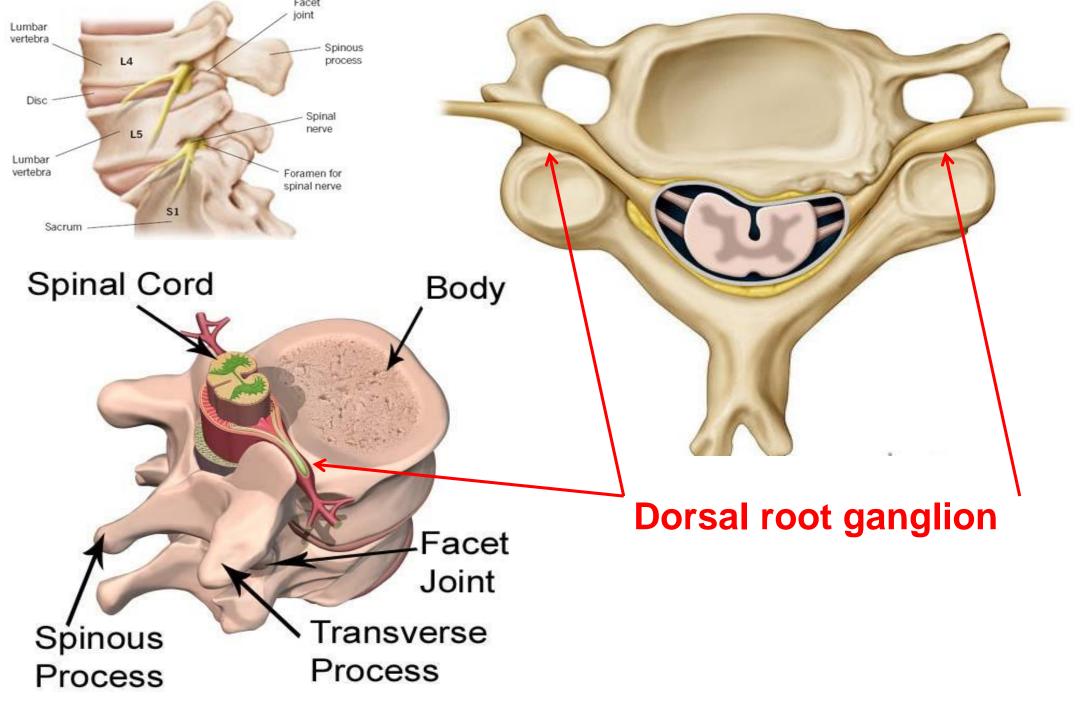




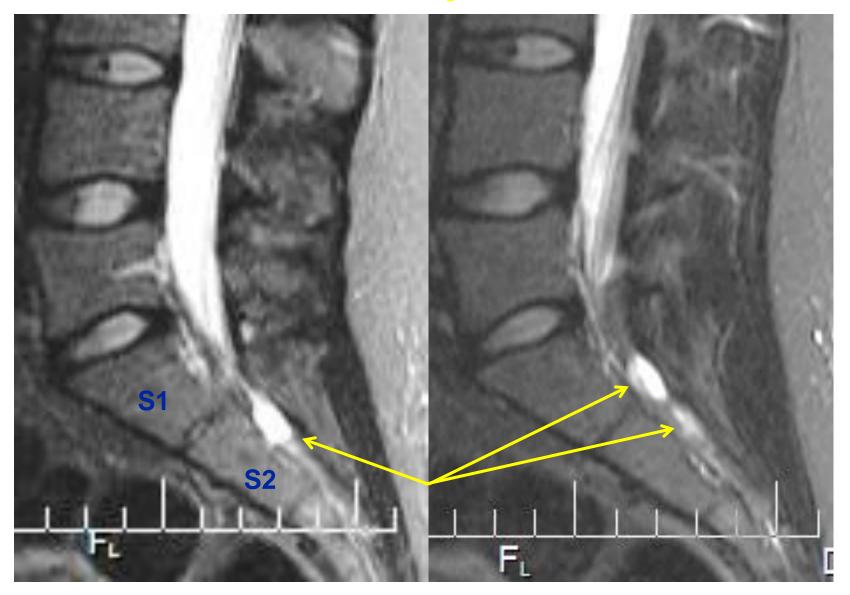


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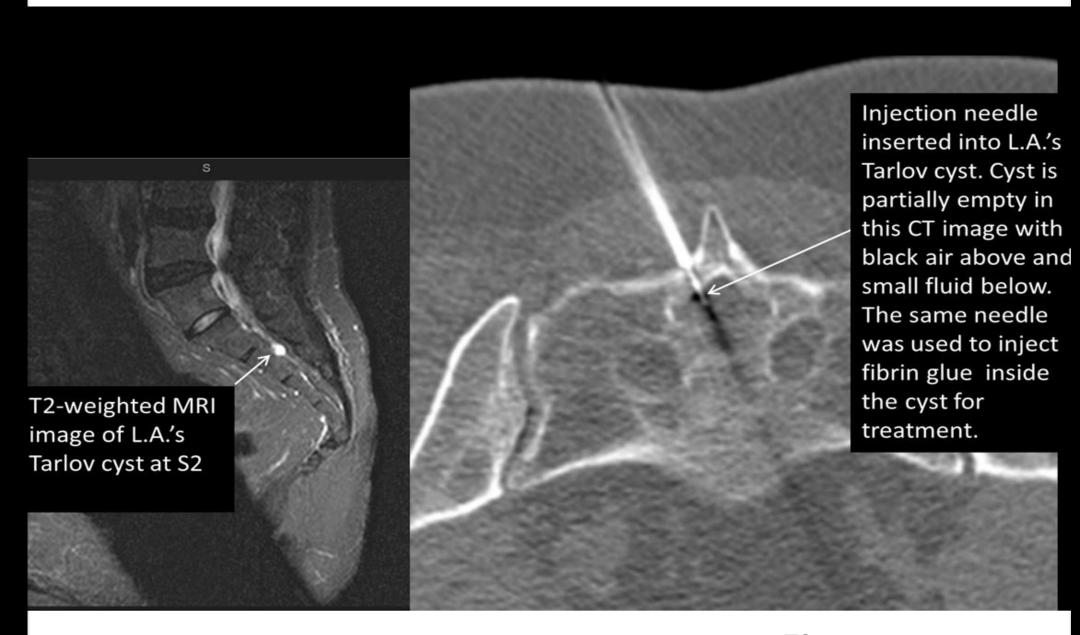




Tarlov cysts

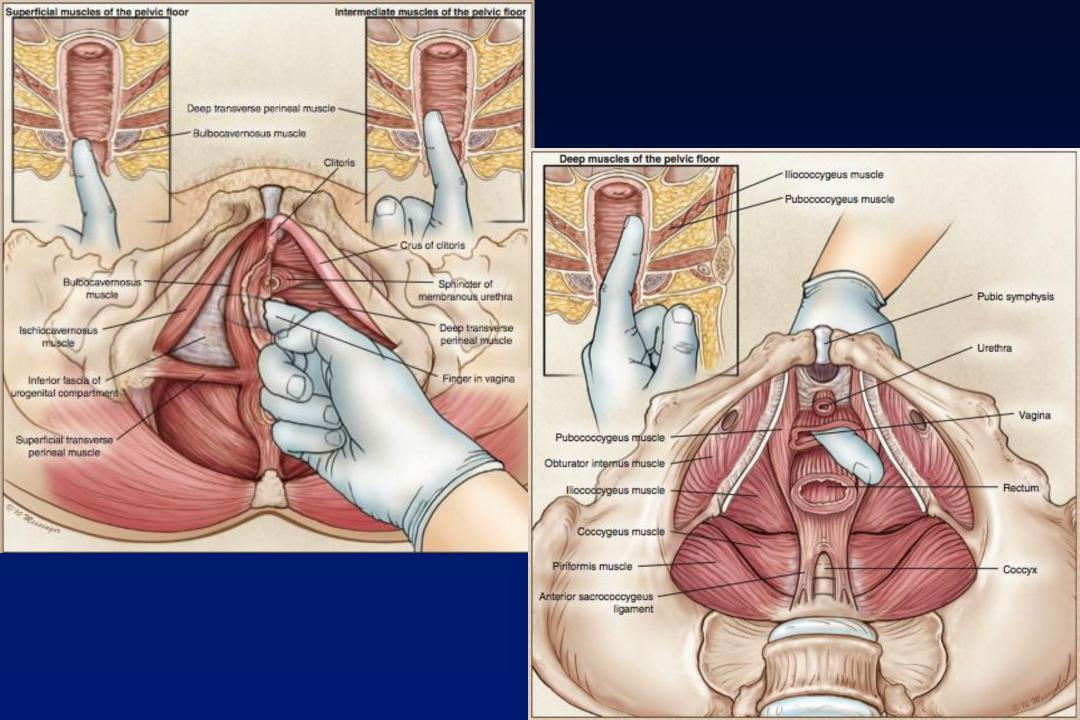


Sagittal





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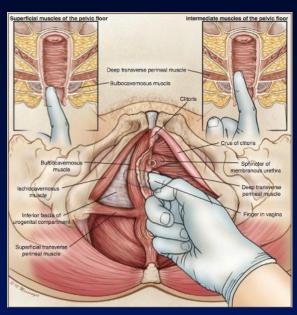


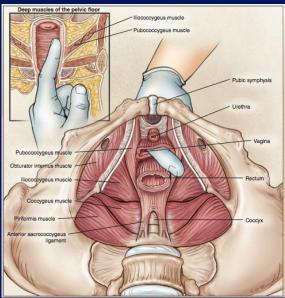
Hypertonic Pelvic Floor Muscle Dysfunction

Increased tone causes a decrease in blood flow and oxygen to the muscles of the pelvic floor. This leads to a build up of lactic acid.

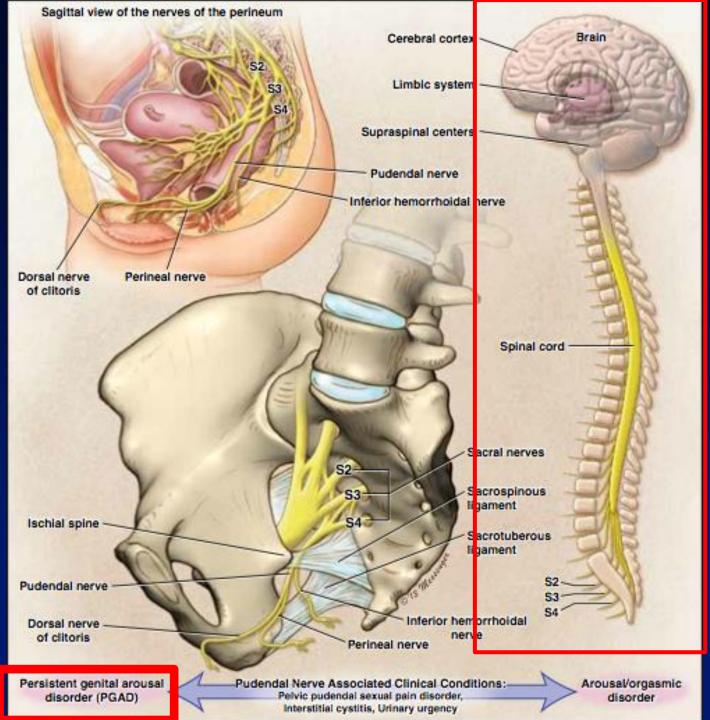
Symptoms include: generalized vulvar pain or burning, tenderness where the muscle insert (4,6,8 o' clock on the vestibule) which causes severe introital dyspareunia, urinary symptoms (frequency, hesitancy, incomplete emptying) constipation, hemorrhoids, and rectal fissures

Physical exam reveals erythema where the muscles insert at the vestibule, multiple trigger points, muscles weakness and an inability to hold a sustained contraction.





Increased peripheral pudendal nerve sensory afferent input



Central sexual arousal reflex center that is overly excited and under inhibited

High Excitation, Low Inhibition Sexual Dysfunction

SEX THERAPY

Strategies to reduce anxiety
Conservative measures such as
heating pad, warm bath, yoga and
acupuncture

PHYSICAL THERAPY

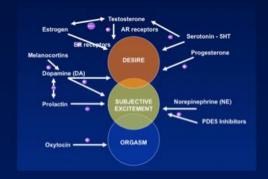
Pelvic floor relaxation strategies to reduce stress or anxiety that is associated with skeletal muscle pelvic floor relaxation

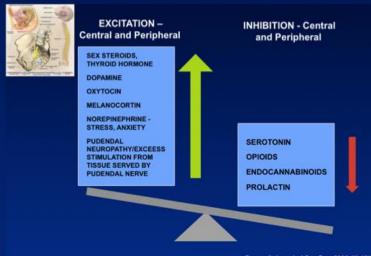
Pharmacologic Agents That Decrease Neurotransmission – (Local Anesthesia, Tricyclic Antidepressants, Calcium Channel Blocking Agents, Sodium Channel Blocking Agents, Anticonvulsant Agents)

Lidocaine – topical 1-5%
TCA – Amitriptyline – 25 – 150 mg
TCA – Nortriptyline – 25 – 100 mg
TCA – Desipramine – 25 – 300 mg
Ca+ - Gabapentin – 100 – 2400 mg
Ca+ - Pregabalin – 25 – 300 mg
Na+ - Carbemazepine – 100 – 400 mg
Na+ - Oxcarbazepine – 150 – 2400 mg
Lamotrigine – 25 – 200 mg

Non-Pharmacologic Strategies That Decrease Neurotransmission

TENS/Inferential Stimulation
Sacral Neuromodulation – Interstim
Pudendal Neuromodulation – Interstim
Pudendal Nerve Block – local anesthesia
and steroid
Electroconvulsive Therapy (ECT)





Bancroft J, et al. J Sex Res. 2009;46:121-142.

DOPAMINE ANTAGONIST

Varenicline Tartrate 0.5 mg – 2 mg/day

Hyperthyroidism

Methimazole 5 - 60 mg

Serotonin and Norepinephrine Reuptake Inhibitor Serotonin Reuptake Inhibitor and 5 HT1A Receptor Partial Agonist

> SNRI - Duloxetine - 20 – 120 mg SNRI – Venlafaxine – 75 – 225 mg SNRI – Desvenlafaxine – 50 – 100 mg SRISRPA - Vilazodone – 10 – 40 mg

Opioid Agonist

Tramadol 25 – 200 mg
Tapentadol 25 – 400 mg
Hydrocodone bitartrate and acetominophen – 5/500
Oxycodone and Acetaminophen – 2.5/325 – 10/325

Cannabinoid

Dronabinol - 2.5 - 20 mg

Vascular Causes
Arterial Venous Malformation – Embolization
Congestion Syndrome - Embolization

Neurologic Causes
Cerebral space occupying lesion, CVA
Spinal Cord injury, trauma, surgery

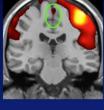
Pharmacologic Causes
DISCONTINUE UNDER SUPERVISION:
Trazodone

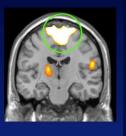
Anti-psychotics - chlorpromazine
Anti-coagulants – heparin
Anti-hypertensives – alpha-blockers
Recreational drugs – cocaine

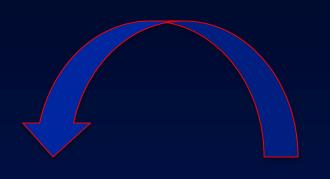
Severe 10/10 PGAD - Pulsating throbbing genital arousal sensations

Persistent Genital Arousal Disorder: during an attack











Normal clitoris projection

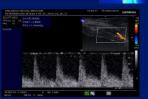
PGAD attack





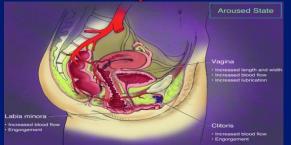






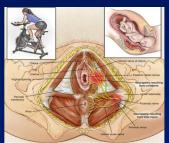




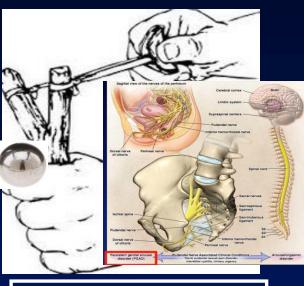










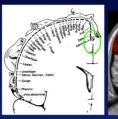


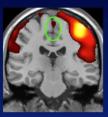
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- 2. Altered menopausal hormone integrity -**Vulvovaginal Atrophy**
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- 5. Abnormal response of tissues to Candida infection, or recognized allergies or non-specific allergies 6. Dermatologic conditions: lichen sclerosus or lichen
- 7. Vulvar granuloma fissuratum
- 8. Peri-urethral glans pathology
- 9. Tarlov Cyst
- 10. Bartholin cyst
- 11. Clitorodynia
- 12. Pelvic Congestion Syndrome
- 13. Endometriosis
- 14. Pelvic Organ Prolapse15. Interstitial Cystitis
- 16. Referral from Hip Disease
- 17. High tone pelvic floor dysfunction

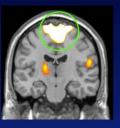


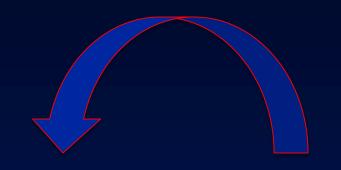
PGAD after Peripheral Treatment

Persistent Genital Arousal Disorder: during an attack







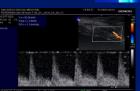




Normal clitoris projection

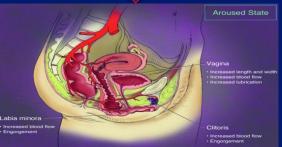
PGAD attack





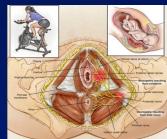




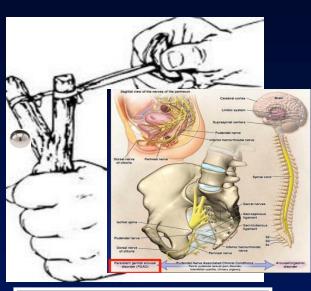












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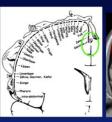
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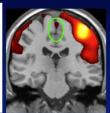
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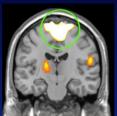


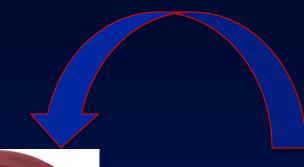
PGAD after Peripheral and Central Treatment













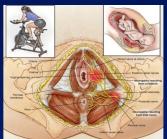
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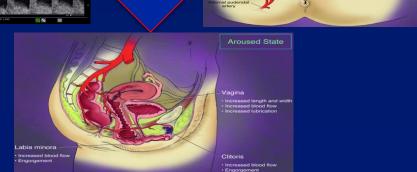






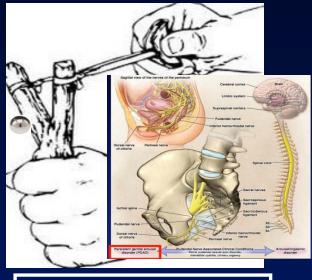












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Effective treatment of PGAD consists of attention to both the peripheral problems and the central problems

PGAD is a dynamic condition - there will be times where the persistent genital arousal symptoms are worse

Hopefully with logical, rational biopsychosocial treatments, the persistent genital arousal symptoms will be more often better