

Graft-versus-Host Disease: Genitals

Celebrating a Second Chance at Life Survivorship Symposium

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At the conclusion of this workshop, attendees will understand

- Who is at risk of developing genital GVHD after transplant
- Signs and symptoms of genital GVHD in men
- Signs and symptoms of genital GVHD in women
- Treatment options for genital GVHD including both pharmacological and non-pharmacological therapies for men and women.

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Genital GVHD: A Case Report

- 46-year-old woman diagnosed with AML, married and mother of five children, underwent a stem cell transplant with donor cells in 2008. Since then, she suffers with GvHD in various locations, namely, eyes, intestines, vulva, and vagina.
- Says the patient: “Genital GvHD caused dryness and pain that prevented me from having a normal sex life, as well as emotional problems and frustration.”
- She was treated with steroid cream and cyclosporine cream inserted into the vagina. She was advised to use dilators, in addition to the creams, to treat vaginal scarring.
- After a year, her genital GvHD symptoms were significantly decreased, and her sexual relationship was restored.
- Says the patient: “I’m finally healthy inside and out. I’m a healthy and confident wife, mother, daughter, and friend.”

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Potential Sexual Problems after Transplant

- Decreased sexual desire
- Genital GVHD
- Hormonal dysfunction
- Erectile dysfunction (ED)
- Difficult or painful sexual intercourse
- Infertility

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Sexual Problems after Transplant

- Nobody talks about it
- Painful
- Discomfort
- Estrogen deficiency
- Testosterone deficiency
- Premature Ovarian Failure
- cGVHD



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Risk Factors for Sexual Problems after Transplant

RISK FACTORS	EFFECTS	Consequences on sexual function	Possible intervention
Total Body Irradiation	gonadal failure	↓sexual desire, arousal, and orgasm discomfort during intercourse erectile dysfunction in males	Hormonal replacement Erectile dysfunction meds, management of stress and r/ship issues
GVHD	Infertility Vulvar or vaginal dryness Penile dryness Inflammatory changes Vaginal narrowing	Performance stress Pain during intercourse Abnormal ejaculation in males Intercourse becomes impossible	Vulvar/vaginal dryness Penile dryness Lubrication during intercourse Use of vaginal dilators Vaginal low dose estrogen
Medications and drug interactions	Vulvar or vaginal scarring, stenosis antidepressants Antipsychotic medications Beta blocker	Negative effect on sexual desire, arousal and orgasm Vaginal dryness	Consider options of reducing dose, or finding an effective alternative medication
Chronic medical problem	CV complication, diabetes Chronic GVHD Secondary cancer	↓ sexual interest Erectile dysfunction	Treatment of underlying medical problems
Psychological distress	Fatigue Personal well-being and partner r/ship Feeling unattractive	↓ sexual interest, negative effect on libido, arousal and orgasm	Psychotherapy sex therapy

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Genital Chronic Graft-versus-Host Disease (GvHD)

- One-half of patients transplanted with stem cells from a donor (allogeneic transplant) experience impaired sexual function after transplant.
- Develops primarily during the first year after transplant with mild signs at onset.

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Epidemiology

- Under-reported in general
- Female prevalence of 24.9% to 69%
 - Median time of onset is between 7 and 10 months
- Male data is lacking, one study had 20%
 - Median time in same study was 5.9 years**

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Early Detection and Treatment Important

- Early treatment of genital GvHD may halt its progression to severe genital GvHD.
- Men usually return to pre-transplant sexual functioning in 2-3 years
- Women less likely to return to pre-transplant sexual functioning
- Women diagnosed with genital GvHD should have life-long follow up and treatment.

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Hirsch P et al. Transplantation 2012 ,
Mueller SM, et al. Bio Blood Marrow Transplant 2013;
Thygesen KH et al. Bone marrow transplant 2012

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Psychological Impact of Genital GvHD

- Heavy psychological toll
 - Depression
 - Anxiety
 - Feeling of inadequacy
 - Body image issues



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Impact of Genital GVHD on Relationships

- Strained relationship
- Distorted body image, leading to-
 - Decreased sexual desire
 - Perception that they are less desirable
- Reduction in the quality and quantity of sexual activity
- Impaired sexual function-
 - In women, could exhibit as lack of sexual desire, difficulty achieving orgasm
 - In men, could exhibit as decreased libido, ED, ejaculatory disorders

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Genital GVHD in Women

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Vulvo-Vaginal GVHD (VVGvHD)

- Genital GVHD is the most common cause of vulvo-vaginal symptoms post-transplant, even in children
- Untreated inflammation and fibrosis (scarring) in the vulva and vagina may lead to total vaginal stenosis (narrowing/closing of the vagina)
 - Significantly impacts the quality of life
 - Interferes with sexual intimacy
- Early identification and treatment of genital cGVHD reduces pain by healing eroded mucous membranes in the vagina.

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Prevalence of Genital GvHD in Women

- Reported prevalence ranges from 24.9% to 69%
- Could be underestimated or under-reported

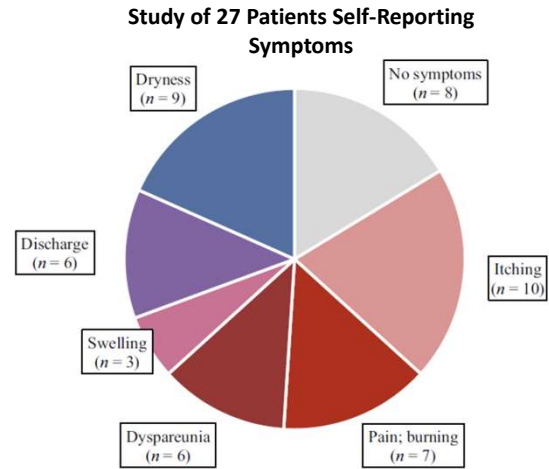
Table 1 – Prevalence of female genital tract graft-versus-host disease.

Author (year)	n	%	Mean age (years)	Donor type	Stem cell source
Spinelli et al. (2003) ¹⁶	213	24.9	31	84.1% sibling 15.9% unrelated	Not mentioned
Spiryda et al. (2003) ¹⁵	501	2	42	50% sibling 50% unrelated	Not mentioned
Zantomio et al. (2006) ⁸	61	35	42	67.2% sibling 32.8% unrelated	34.4% bone marrow 65.6% peripheral blood stem cells
Smith Knutsson et al. (2014) ¹⁷	50	44	47	70% sibling 30% unrelated	18.1% bone marrow 81.9% peripheral blood stem cells
Chung et al. (2015) ¹⁸	180	69	45	Not mentioned	Not mentioned

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Symptoms of Genital GvHD in Women

- Vaginal itching, burning and dryness
- White lines, scarring, adhesions in vagina
- Loss of elasticity in the vagina
- Narrowing of the vaginal canal
- Painful intercourse
- Pain when urinating
- Discharge, swelling
- Patients often have more than one symptom



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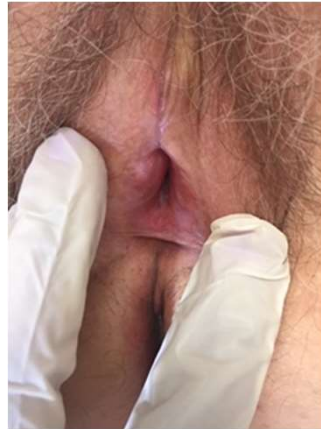
Mild Genital GvHD in Women



Figure 1. Mild genital chronic graft versus host disease. (a) Diffuse erythema and edema of the vulva with reticulated leukokeratosis of the right labial minora and posterior forchette indicated by arrows. (b) Erythematous patches at the introitus indicated with horizontal arrows. Erythematous areas around the opening of Skene's ducts noted with vertical arrows.

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Progression of Genital GvHD in Women



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Adhesions and Fissures Caused by Genital GvHD

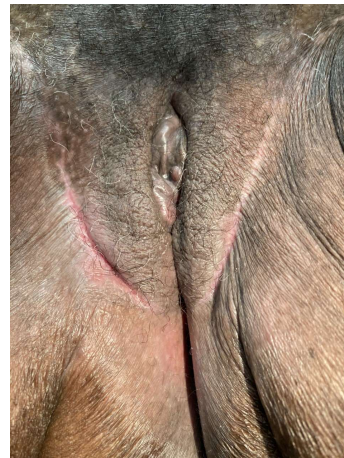


Figure 2. Moderate to severe genital chronic graft versus host disease. (a) Fissuring along the interlabial sulcus may cause burning with urination. (b) Marked architectural atrophy and sclerosis of the labia; tear/fissure at posterior commissure. (c) Clitoral agglutination caused by healing of opposing eroded surfaces of the clitoral hood and labia minora designated by arrow. Labial resorption and diffuse erythema. (d) Narrowed introitus and fusion of labia minora.

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Discuss Management with Your Provider

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Management of Genital GvHD in Women

- Early recognition and treatment is important
- Gynecologic consultation should be requested by all patients, even when there are no symptoms



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Genital GVHD Score Helps Determine Treatment

Table 1. Clinical score of genital chronic graft-versus-host disease adjusted from National Institutes of Health 2005 consensus criteria.

Score 0	Score 1	Score 2	Score 3
Asymptomatic independent of signs	Symptomatic ^a with mild signs ^b ; no effect on coitus or minimal discomfort at gynecologic examination	Symptomatic ^c with moderate signs ^d ; mild dyspareunia or discomfort with gynecologic examination	Symptomatic ^e with advanced signs ^f ; pain with coitus or inability to insert vaginal speculum

Clinical scoring is used to classify the impact of chronic graft-versus-host disease on affected organ by combining signs and symptoms into one of four categories (score 0–3).

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Treatment	Preventive/supportive measures	Recommended monitoring
Changes involving the vulva Correction of estrogen deficiency with topical estrogen PLUS High potency topical steroid ointment	Surveillance for estrogen deficiency-Rx POF Intermittent dilator use for non-sexually active pts	Genital exams at 3-6 months after transplantation or sooner based on symptoms , then at least annually Consider gynecologic exam at a minimum of every 3 months for pts with known active genital cGVHD
Tacrolimus oint 0.1% alone or in addition to topical steroid	Vulvar hygiene to minimize irritation	Cervical cytology annually Consider HPV vaccine
Changes involving vaginal mucosa As above PLUS	Use of non irritating personal lubricants	IF A PT HAS A FLARE- rule out infection and allergic or irritant contact dermatitis
Intravaginal estrogen Intravaginal steroids Tacrolimus cream/suppository 0.1%(2mg tacrolimus per 2 g suppository)	Simple emollient to the vulva- Aquaphor®	
Dilator therapy	Surveillance for infection and secondary malignancy	
Vaginal stenosis/synechiae (fibrosis) As above PLUS	Education of patients on signs and symptoms	
Surgical intervention for lysis or reconstruction Dilator therapy to prevent recurrence		

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Should you avoid penetrative sex while you have genital GVHD?

- You can have penetrative sex if you are comfortable. Some patients use 2-5% topical lidocaine prior to intercourse
 - Intercourse or vaginal dilation twice a week recommended to prevent adhesion and vaginal stenosis
 - Fine scar can be lysed manually with digital exam or intercourse

Zantomio D et al. Bone marrow Transplant 2006.

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Topical Medication for Women with Genital GvHD

- Vaginal
 - Hydrocortisone acetate rectal suppositories (25 mg)
 - Hydrocortisone acetate 10% foam/compounded
 - Intravaginal clindamycin 2% plus steroid
- Clobetasol ointment
 - 2x daily for 6 weeks
 - Daily for 6 weeks
 - 2-3 times weekly
- Estrogen /DHEA
 - Daily for 2 wks, then 2-3 x a week
 - Compounded DHEA/Intrarosa®

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Topical Genital GvHD Medication for Women

Table 2. Local treatment schedule of genital chronic graft-versus-host disease.

Ointment	Week						
	1–4	5–8	9–10	11–14	15–18	19–22	23 ^a
Estrogen ^b	Twice a week	Twice a week	Twice a week	Twice a week	Twice a week	Twice a week	Twice a week
Tacrolimus 0.1% ^c	Every other day	Every other day					
Tacrolimus 0.03% ^c			Every other day	Twice a week	Twice a week	Once a week	Once a week
Clobetasol 0.05% ^c	Every other day	Twice a week	Twice a week	Twice a week	Once a week	Once a week	Not used
Vaginal dilator ^d	Once a week to twice a day						

^aMaintenance treatment.

^bVulvar and vaginal estriol or estradiol—daily use for 2 weeks before maintenance treatment twice a week; or estradiol vaginal ring (7.5 µg/24 h).

^cKeep the amount as low as possible (0.25–0.5 cm).

^dGentle painless use includes lubricant, slow insertion, waiting for muscular contractions to relax before continuing insertion and leaving the dilator in place.

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Maintain Vaginal Canal

- Prevent formation of adhesions and vaginal stenosis
 - In non-sexually active patients, dilators treat, prevent
 - Scarring
 - narrowing and shortening of vagina
- Vaginal self-examination 2 times a week
 - Self dilation
 - Intercourse



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Treatment for Moderate to Severe Genital GvHD

- Estrogen vaginal ring to mechanically dilate
 - Estring® every 3 months
- Coat dilator with immunosuppressive creams and topical estrogen/DHEA
- Surgical procedure *plus*
 - Topical immunosuppressant coated dilator
 - Sexual intercourse



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Supportive Therapies

- Pelvic floor physical therapy
 - Ask transplant team for a referral
 - PelvicRehab.com
- Consult a sex therapist for non-penetrative sexual intimacy options
 - Request referral from transplant team
 - American Association of Sexuality Educators, Counselors and Therapists
 - aasect.org/referral-directory
- Behavioral health therapist

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Improving Your Sexual Relationship

- Talk to gynecologist about hormone therapy in vulva and vagina to improve lubrication and to make sex less painful
- Use lubricants or extra-lubricated condoms
- Discuss your difficulties with your partner; this is a couple's problem, not one partner's problem
- Keep intimacy and affect intact, not necessarily with penetrative sex

Genital GVHD in Men

Symptoms of Genital GvHD in Men

- A decreased desire to have sex
- Redness/rash on penis
- Ulcers on the penis
- Inflammation of the penis and/or scrotum
- Narrowing of the urethra
- An inability to ejaculate

S.M. Mueller et al. / Biol Blood Marrow Transplant 19 (2013) 1574e1580

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Male Presentation: cGvHD of Genitalia

- A change in skin color on the head of the penis
- Redness, white lines, burning or pain on the head of the penis
- Difficulty or pain when retracting the foreskin
- Scarring or adhesions on the foreskin
- Scarring on the meatus



Figure 1. Examples of post-transplantation inflammatory genital skin changes. (A) Inflammatory (noninfectious) balanoposthitis with reddish “cayenne-pepperspots” on the glans penis and partial phimosis. (B) Shiny plaques on the glans penis and the inner layer of the foreskin. (C) Lichen sclerosuslike skin changes with erythematous and whitish sclerotic areas on the foreskin. (D) Phimosis

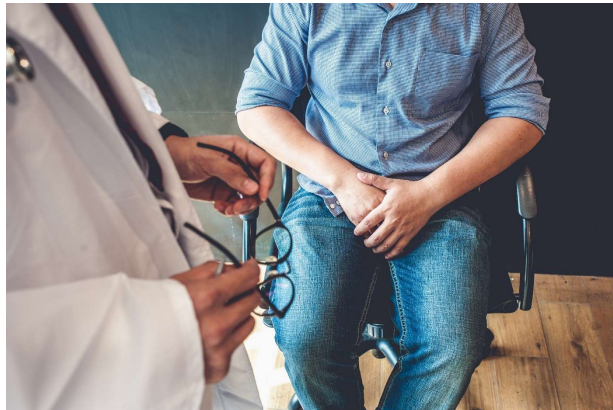
S.M. Mueller et al. / Biol Blood Marrow Transplant 19 (2013) 1574e15801576

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Treatment of Genital GvHD in Men

- Once/twice daily high potency topical steroid ointment
- Genital Lichen sclerosis may benefit from topical calcineurin inhibitor (Tacrolimus)
- Circumcision in cases of phimosis (tight foreskin) or insufficient response
- Male Hypogonadism (low testosterone)
 - testosterone replacement therapy (TRT)

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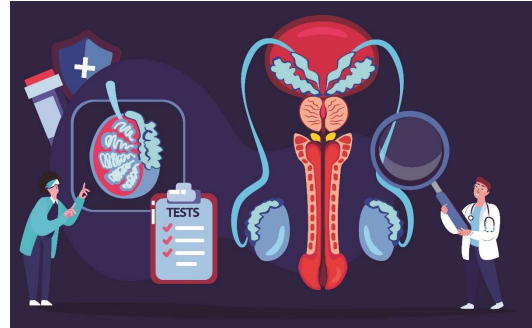


Discuss Management with Your Provider

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Genital GvHD Management in Men

- Early recognition and treatment is important
- Urologic consultation should be requested by all patients, even when there are no symptoms



Key Points to Remember

- Check yourself frequently for symptoms of genital GvHD
- If you are having symptoms that may be genital GvHD, ask for a gynecologist or urologist referral
- Wash genital area only with warm water and soap
- Don't use perfumed products in the genital area
- Wear loose cotton or cotton-lined undergarment
- Supportive therapy



QUESTIONS?



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LET US KNOW HOW WE CAN HELP YOU



Visit our website: bmtinfonet.org

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