

Gynecological chronic graft-versus-host disease: screening, diagnosis, and treatment. Brazilian Society of Cell Therapy and Bone Marrow Transplantation consensus

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Section editor: Fernando Barroso Duarte 

Received: Mar. 14, 2026 • Accepted: Jun. 05, 2026

ABSTRACT

Objectives: To provide an updated review of the diagnosis, preventive measures, screening, and treatment of genital involvement in chronic graft-versus-host disease (cGVHD). **Methods:** A literature review was conducted using the PubMed and Google Scholar databases in January 2026. **Results:** The review addresses risk factors, clinical manifestations and classification, preventive strategies, and the treatment of both acute manifestations and late complications of genital cGVHD. **Conclusion:** Genital cGVHD is a common complication among women undergoing hematopoietic cell transplantation (HCT), with varying degrees of severity. We recommend gynecological follow-up for patients of all ages, beginning in the pre-transplant period, including educational and preventive measures as well as counseling on warning signs to enable early diagnosis and prompt treatment of genital cGVHD, thereby preventing long-term sequelae.

Keywords: Allogeneic stem cell transplantation; Chronic graft-versus-host disease; Female genitals; Human papilloma virus; Late follow-up; Treatment.

INTRODUÇÃO

Chronic graft-versus-host disease (cGVHD) shows variation in incidence according to published studies, with reports ranging from 24.9% to 69%.^{1,2,3,4,5,6} However, this prevalence is probably underestimated since only patients with self-reported symptoms were included, and there may be underreporting.³

In a Brazilian prospective cohort with systematic gynecological follow-up, the incidence of genital sequelae among women who undergo allogeneic hematopoietic cell transplantation (HCT) was 27.5% (n = 11/40), supporting the notion that approximately one-third of patients may develop the disease, and extensive monitoring leads to early diagnosis and intervention.⁶

The average time for the onset of gynecological symptoms ranges from 7 to 10 months after transplant; however, late onset, after 1 year, is not uncommon. Delayed diagnosis, in the absence of systematic evaluation of the genital organs, risk factor analysis, and preventive recommendations, is common for oligosymptomatic patients with inactive sexual activity.^{2,8}

The pre-transplant clinical evaluation of women includes recommendations regarding vulvovaginal cGVHD, focusing on early manifestations and complications, as well as the preventive role of gynecological examination to limit serious gynecological complications, which can become irreversible with a significant impact on life quality.⁹

Risk factors for genital cGVHD

The main risk factor for genital involvement in cGVHD is the use of peripheral blood grafts, which has been associated with an approximately threefold higher risk than bone marrow grafts.¹⁰ The incidence of genital cGVHD does not seem to be affected by the type of conditioning, donor type, parity, age or presence of a vaginal infection at the time of transplantation.⁸ However, surveillance should be reinforced when there is involvement of the oral mucosa, conjunctival mucosa, or extensive skin areas, since genital cGVHD frequently occurs together with skin and oral cGVHD.¹⁰

Clinical manifestations

Symptoms affect the vulva alone in 68% of cases, and the vulva and vagina are affected in 26%, with lesions on the vulva generally preceding those on the vagina. Isolated vaginal involvement is less common and is often asymptomatic; therefore, limiting sequelae are more frequently seen.⁹

Genital cGVHD presents symptoms including dysuria, a feeling of dryness and burning in the vulva, sensitivity of the vulvar vestibule and vaginal introitus to touch or washing, genital bleeding following sexual intercourse, and dyspareunia.^{6,7,11,12}

If the vagina is affected, 25% of patients report a discharge of serous fluid (especially during early stages), but mild forms can be asymptomatic and detected only in a gynecological examination.³

Vulvar and vaginal dryness is experienced by up to 80% of women with genital cGVHD, and dyspareunia affects up to 50% of them, with a marked negative impact on sexual activity.³ Pain at the vaginal introitus is caused by inflammation of the vestibular glands (Bartholin and Skene glands), vulvar erosions or fissures, and, less commonly, labial fusion. Patients with synechiae or vaginal shortening experience deep dyspareunia. Amenorrhea and pelvic pain, particularly amenorrhea in women with cyclic hormonal replacement, suggest the possibility of vaginal synechiae or internal and/or external cervical stenosis, leading to hematocolpos and hematometra, respectively; these may also be considered serious symptoms.^{13,14}

On physical examination, findings are similar to erosive lichen planus and may include erosions, glassy hyperemia in the vestibule, openings of the Skene glands with increased painful sensitivity (early-stage), and interlabial fissures.^{10,11}

The involvement of other mucosae may increase the risk of genital involvement and, therefore, women with oral and/or ocular involvement should undergo gynecological examination even when asymptomatic. If a gynecologist is not available, then an external examination should be performed by a clinician; vaginal involvement may be underdiagnosed.¹⁰

In advanced stages, findings include destruction of the vulvar architecture due to adhesions involving the labia minora with agglutination between them as well as at the furcula and narrowing of the vaginal introitus; adherence leads to a buried clitoral prepuce. There may be reduced elasticity, vaginal channel shortening, as well as synechiae, especially in the vaginal fornices, with obstruction or impossibility of performing a complete visualization of the cervix for oncotic cytology collection, partially or completely compromising sexual intercourse.¹

Histological confirmation is recommended only in the absence of diagnostic manifestations of cGVHD in other organs. In both early and late stages with functional sequelae, estrogen deficiency due to chemotherapy-induced ovarian failure needs to be appropriately addressed so that the physical examination findings of cGVHD are not mistaken for signs of hypogonadism.^{1,15}

Clinical classification of female genital cGVHD

According to the clinical scoring system for organ evaluation described in Table 1, genital involvement can be classified as mild, moderate, or severe, with active investigation for asymptomatic cases.^{10,17}

Table 1. Management of cGVHD in the female genital tract.

Intervention type	Score
Vulvar discomfort	
Avoid chemical and mechanical irritants (soaps and intimate hygiene products)	B4
Wash the genital area with warm water, allow for air circulation, and clean from front to back.	B4
Apply an emollient to the vulva	B4
Water-based lubricants	B4
Vulvovaginal symptoms and low estrogen levels	
Topical estrogen – 0.5 g of estriol 1 mg/g (cream) or estradiol 10 mcg (vaginal tablets)	B4
Encourage regular sexual intercourse for sexually active women	B4
Advise the use of vaginal dilators two to three times a week for women with vaginal narrowing, stenosis, or obliteration	B4
Topical therapy for vulvovaginal cGVHD	
Hydrocortisone 25 mg in vaginal suppositories	B4
Clobetasol propionate gel 0.05% for the vulva	B4
Betamethasone ointment for the vulva	B4
Tacrolimus 0.1% ointment for the vulva and cream for the vagina (cool)	B2B
Surgical therapy	
Surgical lysis of adhesions with or without vaginal reconstruction, followed by 6 months of corticosteroid therapy in a tapering regimen, and the use of dilators	B4
Pediatric considerations	
Although data on the incidence of genital lichen sclerosis in childhood are scarce in the literature, treatment, recognition of the same valid risk factors as in adults, and early detection and care through guidance from the mother or caregiver can prevent late diagnoses and irreversible complications.	

Source: Elaborated by the authors.

Jagasia et al.¹⁰ developed a consensus for GVHD's diagnosis and a severity score, adapted and published by Kornik et al.,¹⁷ suggesting active research on asymptomatic cases.

In a Brazilian study, most patients (63.6%) presented mild and moderate signs of genital cGVHD, including interlabial fissures and lichen-like lesions, while a minority (9.1%) presented severe signs of genital cGVHD, with fusion of the labia minora and majora.⁶

Preventive measures

Early systemic or topical estrogen therapy corrects ovarian failure caused by medication use during the conditioning phase and maintains the physiological characteristics of the genital tract, facilitating early detection of cGVHD symptoms.¹⁷ In addition, educating women about cGVHD increases awareness of this complication, its early onset, and possible sequelae.³

The conditioning phase involves the administration of chemotherapeutics and/or radiotherapy that induce acute ovarian insufficiency, resulting in hypoestrogenism and genital atrophy that can lead to symptoms potentially mimicking early signs of cGVHD. When a woman does not receive contraceptives for hormonal blockade or uses a gonadorelin analog, vaginal suppositories of 0.5 g of topical estriol cream (1 mg/g) or 0.5 mg should be used and applied two to three times a week throughout the transplant phase; they should continue until systemic hormonal therapy is initiated or, in case of contraindication, continuously. By improving atrophy of the vulvovaginal epithelium, this approach may facilitate the resumption of sexual activity, given that dyspareunia and shortening of the vagina can occur in genital cGVHD, allowing early diagnosis of cGVHD lesions.⁷ Lubricated condoms reduce friction-related discomfort and prevent contamination by different organisms with pathogenic ability (bacteria, fungi, and agents that cause STIs) during sexual intercourse.¹⁸

Initial treatment

Vulvar and vaginal introitus lesions are very sensitive erosions, even to the touch of intimate clothing. In this phase, topical corticosteroids such as clobetasol propionate 0.05% are indicated and should be applied until the

erosions resolve. Warm water compresses or baths before applying the corticosteroid help absorption. The topical administration of 1 mg/g estriol in the vulvar vestibule stimulates the trophism of the epithelium and may improve complaints of vaginal dryness.¹⁵ Protective measures, such as topical emollients and moisturizers, sitz baths or warm water compresses, and viscous lidocaine application, also relieve discomfort, especially during sex.^{10,15}

Involvement of the vaginal mucosa may be characterized by the formation of ulcers, loose synechiae, and fluid vaginal discharge. Hydrocortisone suppositories (25 mg), once or twice daily, should be continued until early re-evaluation in 15 to 30 days. Additionally, the use of 0.5 mg estriol 1 mg/g in suppositories or in cream form is recommended to counteract atrophy induced by hypoestrogenism and exacerbated by corticosteroids. To prevent vaginal synechiae formation, patients are encouraged to maintain sexual intercourse if sexually active or to use vaginal dilators.^{5,19,20}

One reported approach is the use of a vaginal cream consisting of a 200 mg oral cyclosporine suspension diluted in an oily base, which was applied twice a day for 4 weeks, followed by a tapering regimen for 2 months with the suspension.¹⁵ Healing of vaginal erosions was noted after 2 weeks, and the concomitant use of dilators prevented surgical intervention for stenosis in four of the 11 women studied. Seven women who had a surgical correction of synechiae and vaginal stenosis continued to use the medication postoperatively and were able to engage in sexual intercourse within 6-12 weeks. One patient remained refractory to both clinical and surgical treatment because of thick synechiae.

Another calcineurin inhibitor with conflicting outcomes is tacrolimus 0.1% ointment or cream for vulvar and vaginal use, respectively. Its use would have the advantage of reduced damage to genital trophism, but it is poorly tolerated because of its irritating effect on the mucosa.⁹ When indicated, tacrolimus can be used for refractory disease in cases of corticosteroid therapy failure. The application of tacrolimus in the form of a chilled cream alleviates burning and discomfort.

Finally, topical treatment with corticosteroids and estrogen appears to decrease progression from mild to severe lesions, thus preventing surgical treatment. Thus, the earlier the treatment, the lower the risk of sequelae.¹⁸

Late complications treatment

Late complications, such as adhesions and occlusions in various segments of the genital tract, can be surgically treated while maintaining more intensive topical use of steroids and estrogen in the postoperative period.²¹⁻²³

In the presence of stenosis of the internal or external cervical in women who develop collections in the cervical canal and uterine cavity (hematometra), procedures such as dilation and drainage, or hysterectomy in cases of complete cervical burial, may be required.²⁴

Sexuality

Women undergoing HCT develop various sexual problems that are often not addressed with their physicians and negatively impact their quality of life. Dyer et al.²⁶ observed that 66% of women reported sexual difficulties, including decreased libido in 61.6% of them. These dysfunctions have multifactorial causes and may be related to medications, depression, estrogenic and androgenic deficiency, decreased energy, and low self-esteem.²⁴ Systemic cGVHD, especially with genital involvement, negatively affects the quality of life through dyspareunia and sequelae impairing sex life. Rehabilitation with attention to triggering factors and a multidisciplinary approach that values and seeks to address complaints is important for the overall well-being of these women.^{6,12,26}

Several guidelines have been published on gynecological care in women undergoing HCT, with only minor differences among them. All emphasize the importance of menstrual flow suppression during the conditioning phase until platelet counts normalize, and counseling about the possibility of hormonal and reproductive function impairment after conditioning. They suggest guidance on the first signs of genital cGVHD, periodic gynecological examination, even in asymptomatic women, with screening for precursors of cervical cancer – HPV/DNA testing or Pap smear, hormonal treatment for early ovarian failure, and sexual

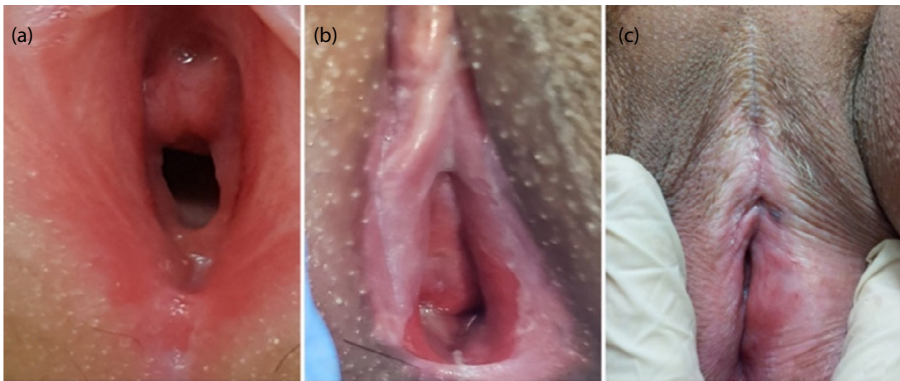
dysfunction management. In addition, they discuss the need to evaluate pediatric patients not only when there is concern for cGVHD but also for pubertal development, as hypogonadism, due to loss of estrogen, can preclude normal development of secondary sex characteristics.^{1,5-7,9,10,15,17,26-32.}

Finally, the role of a gynecologist in HCT centers, as a member of the multidisciplinary team, is crucial to cover all phases, contributing towards total recovery and quality of life for transplanted women.³³ Table 2 summarizes the main care for managing cGVHD in the female genital tract. The pictures below illustrate different lesion patterns as referenced on the mentioned table (Figs. 1-3).

Table 2. Diagnosis and grading of GVHD – National Health Guidelines¹⁵.

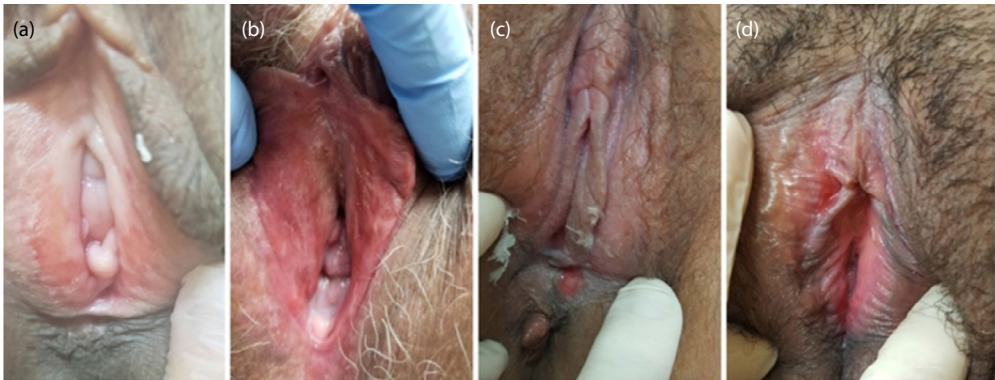
	E0	E1	E2	E3
Genital female	No signs	Mild signs and symptoms ^a with or without discomfort on examination ^b (Fig. 1)	Moderate signs and may have symptoms with or without discomfort on examination ^b (Fig. 2)	Severe signs with or without symptoms (Fig. 3)
		Any of the following: erythema on vulvar mucosal surfaces (Fig. 1a), vulvar lichen planus-like features (Fig. 1b), vulvar lichen sclerosis-like features ^c (Fig. 1c)	Any of the following: Erosive (Fig. 2a), inflammatory (Fig. 2b), changes of the vulvar mucosa, ^d ulcers ^d (Fig. 2c), fissures in vulval folds ^d (Fig. 2d)	Any of the following: labial fusion, ^c clitoral hood agglutination, ^c (Fig. 3a), vaginal scarring, ^c fibrous vaginal banding (Fig. 3b), vaginal shortening (Fig. 3c), synechia, dense sclerotic changes, complete vaginal stenosis (Fig. 4c)

a: Symptoms are not specific and can represent premature gonadal failure or infection; b: To be determined by a specialist or trained medical provider. Discomfort is defined as vulvar pain elicited by gentle touch with a cotton swab in any of the following sites: vestibular glands, labia majora, or minora; c: Diagnostic sign; d: Distinctive sign. Source: Elaborated by the authors.



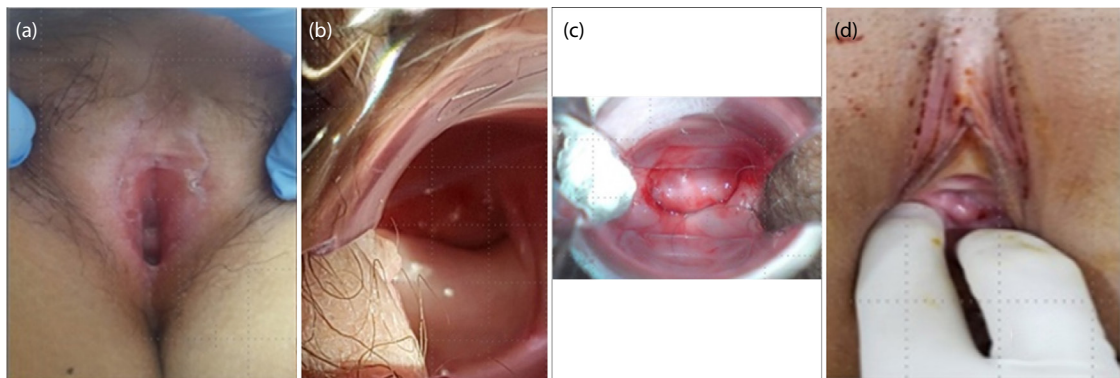
Source: Elaborated by the authors with authorization signed by the patients.

Figure 1. Mild signs and symptoms: (a) erythema on the vulvar mucosal surfaces; (b) lichen planus-like lesions; (c) lichen sclerosus-like lesions.



Source: Elaborated by the authors with authorization signed by the patients.

Figure 2. Moderate signs: (a) erosions; (b) inflammatory changes of the vulvar mucosa; (c) ulcers; (d) fissures in the vulvar folds.



Source: Elaborated by the authors with authorization signed by the patients.

Figure 3. Severe signs with or without symptoms: (a) labial fusion and adhesion of the clitoral prepuce. Vaginal adhesions: (b) vaginal fibrous ring; (c) vaginal shortening; (d) complete vaginal stenosis (1 centimeter deep).

CONFLICTS OF INTEREST

Nothing to declare

AUTHOR CONTRIBUTIONS

Conceptualization: Mauad LMQ, Machado AMN. **Investigation:** Mauad LMQ, Machado AMN. **Methodology:** Mauad LMQ. **Formal Analysis:** Mauad LMQ, Machado AMN. **Data Curation:** Mauad LMQ, Machado AMN. **Project Administration:** Mauad LMQ, Machado AMN. **Funding Acquisition:** Mauad LMQ, Machado AMN. **Writing:** Mauad LMQ, Machado AMN. **Supervision:** Mauad LMQ, Machado AMN. **Final Approval:** Mauad LMQ.

DATA AVAILABILITY STATEMENT

Data will be provided upon request.

FUNDING

This research did not receive any specific funding from public, commercial, or not-for-profit funding agencies.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

No artificial intelligence tools were used in the preparation of this work.

ACKNOWLEDGEMENTS

Nothing to declare.

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