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# Évaluation des complications gynécologiques chez les patientes recevant une allogreffe de cellules souches hématopoïétiques au Centre Henri Becquerel

Marieme Plaziat

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MÉDECINE**

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**Évaluation des complications gynécologiques chez les patientes  
recevant une allogreffe de cellules souches hématopoïétiques au  
Centre Henri Becquerel**

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## **Abbreviation**

**APCs:** antigen presenting cells

**ART:** assisted reproductive technology

**FSH:** follicle stimulating hormone

**GnRH:** gonadotropin releasing hormone

**GvH:** graft versus host

**GvHD:** graft versus host disease

**GvL:** graft versus leukaemia

**HLA:** human leucocyte antigen

**HPV:** human papillomavirus

**HSC:** haematopoietic stem cells

**HSCT:** haematopoietic stem cell transplantation

**IFN- $\gamma$ :** interferon gamma

**IL-2:** interleukin-2

**MHC:** major histocompatibility complex

**NK cells:** natural killer cells

**POF:** premature ovarian failure

**Th1:** type 1 T-helper

**TNF- $\alpha$ :** tumor necrosis factor alpha

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# Introduction

## 1. Haematopoietic stem cell transplantation

### a) **Definition and indications**

Haematopoietic stem cell transplantation (HSCT) may be the preferred treatment for several bone marrow disorders, for certain haematological malignancies which cannot be cured by chemotherapy alone, as well as for other non-malignant disorders of the immune system or bone marrow (1).

The number of HSCT is increasing, reaching now more than 2000 allografts per year in France (2).

This procedure aims at restoring haematopoiesis for patients suffering from bone marrow disease by replacing it with one from a healthy and compatible donor (3).

The donor can either be a sibling or a volunteer listed on a national registry (1).

Haematopoietic stem cells (HSC) can be collected in different ways:

- bone marrow aspiration from a healthy donor, usually from the iliac bone or the sternum
- peripheral stem cells, obtained by cytophoresis (a blood filtration technique which retains only interesting cells)
- placental blood, taken from the umbilical cord at birth (4).

The procedure takes in total between 6 to 8 weeks, divided into different stages: conditioning, transplantation, aplasia period and monitoring. It requires hospitalization in a protected environment.

### b) **Procedure**

The first stage of HSCT is called "conditioning". It consists of destroying the recipient's diseased bone marrow, and therefore its immune cells, to prevent rejection of the transplant. This requires treatment with more or less intensive chemotherapy, sometimes supplemented by total body irradiation (3).

There are several types of conditioning regimens with varying intensity (myeloablative or non-myeloablative). The indication is based on the characteristics of the patient (age, medical history), his pathology and the graft (5,6).

The second stage is transplantation, where the patient receives the donor haematopoietic stem cells intravenously.

Immediately after transplantation, there is a period of aplasia, which is an inadequate production of different blood cell lineages by the bone marrow as a result of rarefaction of haematopoietic stem cells. This phase is essential for the installation of new HSCs from the donor in the recipient to gradually reconstitute haematopoiesis.

The efficacy of the transplant is characterised by the presence de novo of myeloid lineage cells. In addition, the immune system is subsequently reconstituted so that the donor's lymphocytes (T and NK lymphocytes) recognise the recipient's malignant cells as foreign and exert anti-tumour activity. This effect is called graft versus leukaemia (GvL).

Once the bone marrow becomes functional again, this is known as overcoming aplasia. However, effective bone marrow function takes several months to become optimal (5). The effectiveness of the transplant depends on several parameters, in particular the HLA

compatibility of the donor and the recipient, the type and severity of the disease and the recipient's state of health (2).

The last stage of HSCT is monitoring: provided a good HSCT result and correct oral medication, the patient can be released from isolation and the follow-up can be externalized. All this is accompanied by immunosuppressive treatments to prevent the recipient organism from developing an immune response against the graft and thus optimize engraftment.

### **c) Complications**

HSC transplantation can lead to various complications with significant morbidity and mortality. The incidence and severity of these complications are related to the characteristics of the recipient patient (age, medical history, type of haemopathy) as well as to the transplantation modalities (type of conditioning, origin of the graft, HLA compatibility between donor and recipient, immunosuppressive treatments) (7).

They occur mostly in the early post-transplantation phase (between D0 and D100) and are often the direct consequences of conditioning (e.g. mucositis and other mucosal damage, veno-occlusive disease, haemorrhagic events), immunosuppression (e.g. bacterial, viral or fungal infections) and immunological complications (e.g. acute graft-versus-host reactions). Late complications (those occurring more than 100 days after transplantation) are mainly associated with prolonged immunosuppression and may result in reactivation of some viruses, development of secondary cancers and chronic Graft versus host disease (GvHD) (3,8–10).

## **2. Acute GvH reaction**

### **a) Definition and physiopathology**

The GvH reaction is the consequence of an expected but exaggerated inflammatory response mediated by the donor's lymphocytes present in the recipient patient. In fact, the recognition of a "foreign" environment will stimulate the donor's immunity (11).

In 1966, Billingham identified three conditions necessary for GvHD to occur:

- the transplanted graft must contain immunocompetent cells
- the recipient must be unable to reject the transplanted cells
- the recipient must express tissue antigens that are not present in the donor and could therefore be recognized as foreign (12).

A study led by Sackstein in 2006 allowed a revision of Billingham's postulate by introducing an additional condition for the development of GvHD: the donor's lymphocytes must be able to migrate to the target tissues of GvHD (13).

There are 2 types of GvHD: acute and chronic. Classically, acute GvHD occurs within 100 days of allograft transplantation and chronic GvHD occurs after 100 days. Currently, the distinction between these 2 entities is rather clinical than temporal, as delayed forms of acute GvHD ("late-onset acute GvHD") and borderline forms ("overlap syndrome") have been described.

The onset of acute GvHD involves several stages. First, the host tissues are damaged by the underlying pathology and/or the conditioning regimen of the allograft. This leads to the secretion of danger signals (pro-inflammatory cytokines), the activation of host antigen presenting cells (APCs) and an increase in the expression of major histocompatibility complex



(MHC) antigens. As a result, the donor's T lymphocytes recognize a “foreign” environment, which favors their activation and proliferation. This will trigger biochemical cascades that induce the production of numerous pro-inflammatory cytokines, particularly Th1 cytokines (IFN- $\gamma$ , IL-2 and TNF- $\alpha$ ) in the context of acute GvHD. Ultimately, all of this will induce a complex cascade of cellular (cytotoxic T lymphocytes and NK cells) and inflammatory mediators that work together to destroy the target (host) tissue (11).

### **b) Clinical manifestations**

The 3 main organs involved in acute GvHD are the skin (81%), the liver (50%) and the digestive system (54%). Based on Glucksberg's classification, acute GvHD is clinically graded from I (mild) to IV (very severe) according to the extent and severity of damage to these 3 organs (3,14).



**Figure 1** – examples of acute cutaneous GvHD lesions. Photographs from the GFIC-GM (Groupe Francophone des Infirmier(e)s et de Coordination de Greffe de Moelle) website, accessed 24.07.07.

### **c) Epidemiology and prognostic**

The incidence of acute GvHD is highly variable and directly related to the degree of HLA protein mismatch between donor and recipient. It is approximately 30-40% in geno-identical transplants and 50% in pheno-identical transplants.

Severe GvHD has a poor prognosis, with long-term survival of 25% for grade III and 5% for grade IV (3,11,14).

#### **d) Therapeutic means**

Immunosuppressive treatment is given systematically as a preventive measure after transplantation. It consists of a combination of methotrexate and cyclosporine.

If acute GvHD occurs, the standard treatment is corticosteroid therapy at a dose of 2 mg/kg per day. However, a significant number of acute GvHD cases are resistant to corticosteroids. Despite a variety of proposed therapeutic approaches, second-line treatments for steroid-resistant acute GvHD are not standardized (3,14,15). Recently, a drug targeting the JAK1/JAK2 kinases, ruxolitinib, has shown efficacy in refractory forms of the disease (16).

### **3. Chronic GvH reaction**

#### **a) Definition and physiopathology**

In contrast to acute GvHD, the pathophysiology of chronic GvHD is poorly understood. Some studies have shown that in chronic GvHD, the thymus is damaged by the underlying pathology, the consequences of conditioning, but also by the presence of acute GvHD. Thymic epithelial cells, which are responsible for presenting antigens to T lymphocyte progenitors, are damaged. These changes induce aberrant thymic development. Indeed, the presentation of self-antigens by thymic cells to the newly formed T lymphocytes becomes defective, leading to a lack of selection of these lymphocytes and thus to the emergence of autoreactive T lymphocytes.

The importance of autoreactivity is suggested by the clinical manifestations of chronic GVHD, which often resemble those of autoimmune diseases, suggesting a similar pathophysiology (14,17)

#### **b) Clinical manifestations**

The clinical manifestations of chronic GvHD are numerous and polymorphic, potentially involving multiple sites. Despite the wide variability of symptoms, a fibrotic nature of organ lesions is readily apparent. The onset of chronic GvHD may be progressive (as a continuation of acute GvHD), quiescent (after a period of resolution of acute GvHD) or de novo (without prior acute GvHD).

There are several types of clinical criteria for chronic GvHD:

- Diagnostic criteria, the presence of which is sufficient to establish the diagnosis of chronic GvHD (e.g. poikiloderma, lichen planus sclerosus)
- Discriminatory criteria requiring histological confirmation (e.g. skin depigmentation)



**Figure 1** – examples of chronic cutaneous and buccal GvHD lesions. Photographs from the GFIC-GM (Groupe Francophone des Infirmier(e)s et de Coordination de Greffe de Moelle) website, accessed 24.07.07.

The definitive diagnosis of chronic GvHD requires the exclusion of other possible diagnoses such as infection, drug effects, malignancy and residual post-inflammatory damage and scarring.

The clinical classification of chronic GvHD is complex. It includes the number and type of organs involved and the severity of the lesions observed (National Institute of Health classification).

Overall, the diagnosis of chronic GvHD is therefore based on specific signs, the degree of organ damage (mild, moderate, severe) and/or histological confirmation, rather than on the time of onset after transplantation (> 100 days), as was previously the case. Indeed, there may be an overlap syndrome of clinical features in which diagnostic or characteristic features of chronic GvHD and acute GvHD occur simultaneously (e.g. erythematous rash, nausea, vomiting, diarrhea, hepatic dysfunction, etc.) (3,12,14)

### **c) Epidemiology and prognostic**

Chronic GvHD is a serious condition that occurs in approximately 50% of long-term survivors and is life-threatening in 5% of cases (3,18)

Several risk factors for the development of chronic GvHD have been described, such as the age of the recipient, the type of donor, the source of the haematopoietic stem cells, the presence of acute GvHD and the prophylaxis used (17,18)

### **d) Therapeutic means**

As with acute GvHD, treatment of chronic GvHD is based on corticosteroid therapy. A combination with a calcineurin inhibitor (mainly cyclosporine) may be considered in cases of severe GvHD, progression of the disease on maximum corticosteroid therapy or risk of poor tolerance to corticosteroids. If this is not sufficient to control the disease, second-line treatments

are used. However, there is no consensus on what should be done, and different therapeutic options may be suggested considering the organs involved, the patient's testimony, the possible presence of active infection, the cost and survival profile of each option, potential drug interactions, and patient preference and compliance (8,15,18).

The treatments are essentially administered orally, but it should be noted that the topical route is important in mild chronic GvHD and depending on the site of damage (cutaneous, ocular, oral) (19).

As organ infections are a major cause of mortality in chronic GvHD due to immunodeficiency, antibiotic prophylaxis is indicated for these patients (3,8).

In parallel with systemic treatment of chronic GvHD, multidisciplinary care in collaboration with organ specialists is necessary to optimize patient monitoring.

#### 4. Vulvovaginal GvHD

##### **a) Definition**

Genital GVHD is a rare complication of HSCT (20). It is estimated to occur in approximately 10 to 50% of long-term female survivors (21–23).

It is by far the most common cause of vulvovaginal symptoms after HSCT, even in children, resulting in significant morbidity (20,24). This condition often occurs in the context of another coexisting GvHD location, particularly the skin and oral mucosa (20,25). However, in almost 25% of cases, genital GvHD may be the only manifestation of GvHD (26).

It was in 1982 that Corson's team (27) was the first to expose this entity, in 5 patients who had undergone an allograft of HSC. Several subsequent studies have made it possible to better describe the clinical aspects of this disease, genital GvHD still remains too underestimated and therefore untreated (20,28).

Several reasons have been cited that could explain this under-recognition of GvHD.

First of all, the genital symptoms associated with GvHD are not specific (dryness, dyspareunia, itching, burning, pain when touched, dysuria). Then, in most centers, early and systematic gynecological follow-up after HSC allograft is not carried out. Finally, genital GvHD does not constitute a potentially fatal complication (unlike other locations) and the embarrassing nature of genital discomfort could lead patients and doctors not to discuss such symptoms during follow-up (22).

Therefore, screening, preventive gynecological care, and the implementation of early treatments are important aspects to reduce the morbidity and mortality of long-term surviving women after allogeneic HCT transplantation (22,26).

##### **b) Clinical manifestations and classification**

Since the first publication on gynecological GvHD by Corson et al. in 1982, this entity has been well recognized. The diagnosis is essentially based on clinical examination and description of symptoms, but histological confirmation may be recommended in case of diagnostic doubt to rule out another gynecological pathology (20,29).

Symptoms include vaginal dryness, burning, itching, pain when touched, and dyspareunia (20,26). Vulvovaginal GvHD can sometimes be asymptomatic and detected only by clinical examination (30).

A classification of genital GVHD is currently used to describe the lesions observed (25,29,31):

- Grade I: erythema and edema of vulvar structures
- Grade II: erosions/fissures or vulvar petechiae (interlabial furrows and the frog)
- Grade III: hooding of the clitoris, loss of vulvar relief, fusion of the labia minora, synechia of the posterior fork or anterior corner of the labia minora
- Grade IV: partial or complete vaginal synechia, sclerosis of the vaginal mucosa

Physical signs of minimal or moderate disease (grade I or II) may be confused with genital atrophy linked to premature ovarian failure, generally associated with chemotherapies during graft conditioning (20,26).

Vulvovaginal GVHD usually occurs within a median of 7 to 10 months after allogeneic HCT transplantation, but the first symptoms may appear up to 2 years after transplantation (20,29,32).

### **c) Epidemiology**

The incidence of vulvovaginal GvHD is approximately 25 to 49% depending on studies (20,26). It is most often only vulvar (68%), or simultaneously vulvovaginal (26%). It can be concomitant with GvHD located in other organs, but in approximately 25% of cases, it can be the only location of this condition (26). The main GvHD diseases associated with genital lesions are: mouth (59%), skin (44%), eyes (44%), liver (19%) and lungs (19%) (20,22,24). The severity of gynecological symptoms does not seem to be correlated with the severity of GvHD of other organs (20).

Regarding the risk factors for developing genital GvHD, studies have shown that the source of stem cells was the only independent risk factor. Indeed, cells from peripheral blood are associated with a higher risk than those from bone marrow. It is considered that the conditioning regime can also influence the occurrence of genital GvHD in the case of myelo-ablative conditioning, but without significance. There is no evidence that donor source, GvHD prophylaxis, donor sex, recipient or donor age influenced the risk of genital GvHD independent of stem cell source. Likewise, extra-genital GvHD is not a risk factor for developing genital GvHD (20,21).

### **d) Therapeutic means**

The key to effective management of genital GvHD is early diagnosis of the pathology (18,26). In early GvHD, topical treatment (cream and egg) with hyaluronic acid and estrogens is used first (if there are no contraindications) (20–22,30,31). If this is not sufficient, corticosteroid therapy (cream, foam, eggs) (20,21,29,33), or even topical immunosuppressive treatment (cream) in case of progression of the disease (20,21).

It should be remembered that corticosteroid therapy and systemic immunosuppressive treatment are introduced as part of the overall treatment of patients. This also helps to control the vulvovaginal damage (30).

Vaginal stenosis is first treated by manual elevation in cases of mild synechiae, then by surgery in cases of significant vaginal stenosis (21,31).

To prevent their formation, it is recommended to continue having sexual intercourse. If this is not possible, the regular use of vaginal dilators, more or less induced by creams containing hyaluronic acid, estrogens, corticosteroids or immunosuppressants, can help maintain vaginal capacity (18,20,21,26).



**Figure 3** – example of vaginal dilators

Patients with premature ovarian failure should receive hormone replacement therapy in addition to GvHD treatment (29).

## 5. Other gynecological complications post-allograft of HSCs

### a) **Definitions and context**

In addition to vulvovaginal GvHD, there are other gynaecological complications that may occur after allogeneic HCT transplantation. These include chemo-induced meno-metrorrhagia, premature ovarian failure, impaired fertility, sexual dysfunction and abnormal pap smears and induced HPV lesions. In addition, we also chose to study the incidence of post-transplant osteoporosis because it is associated with the gynaecological complications described above.

Specific monitoring is therefore essential to optimise the overall care of these patients. (34)

### b) **Chemo-induced bleeding**

Menometrorrhagia accounts for about 5% of haematological complications after allogeneic HSC transplantation. Indeed, severe thrombocytopenia may induce bleeding and complicate its management. The presence of menstrual cycles can also cause menometrorrhagia. It is therefore essential to induce therapeutic amenorrhoea before the start of conditioning chemotherapy and throughout treatment. Several options are available: estrogen-progestin treatment, microprogestin or a GnRH analogue. In certain situations, transfusion of platelets and red blood cells may be indicated. In the case of significant menometrorrhagia that is resistant to hormonal treatment, surgical treatment should be considered (endometrectomy or, exceptionally, hysterectomy) (34).

### c) **Cervicovaginal smear abnormalities and induced HPV lesions**

Human papillomavirus (HPV) is a sexually transmitted virus. There are over 80 strains of the virus. The presence of certain genotypes in the reproductive tract can cause cervical cancer. In immunocompetent people, HPV is cleared spontaneously. 91% of patients are cured within 24 months.

In immunocompromised patients, the HPV clearance process is severely impaired due to loss of immunity. After HSC transplantation, an increase in HPV infection is observed in one third of long-term survivors. Careful gynaecological follow-up must be established in these patients to monitor HPV-induced cervical lesions (26,35–37).

#### **d) Premature ovarian failure**

Premature ovarian failure (POF) is a common consequence of HSC transplantation, affecting approximately 90% of premenopausal patients. It is mainly related to the type of conditioning protocol. In fact, myeloablative regimens, with or without concomitant body irradiation (especially to the pelvis), have a very high risk of developing POF (26,38–40). The source of the transplanted stem cells does not seem to be a risk factor (26,39,41).

The follicle, the functional unit of the ovary, is composed of sex steroid-producing cells, the granulosa and theca cells, and a fixed number of germ cells, some of which will develop into oocytes. The number of follicles decreases over the cycles due to ovulation and follicular atresia up to a certain threshold, at which point menopause occurs. If the ovarian cells are attacked or destroyed by haemophilic treatments (chemotherapy, body irradiation), we therefore observe a more rapid onset of menopause (26,40,41). In addition, the younger a patient is, the greater her follicular reserves are. The ovaries of children and adolescents are therefore relatively resistant to damage from treatment, unlike the ovaries of adult women (26,38–42).

Given the young age of many patients, it is indicated that premenopausal women begin hormone replacement therapy as soon as POF is diagnosed. This can compensate for oestrogen deficiency, correct menopausal symptoms and prevent cognitive decline and osteoporosis (8,26,39). In the case of body irradiation, ovarian transplantation can be suggested beforehand, allowing ovarian function to be preserved in most young girls and adolescents (40). Recovery of ovarian function may be possible after treatment (26,39,40).

Therefore, gynaecological follow-up of these patients is necessary to detect POF early after HSC transplantation and to mitigate its physical and psychological consequence (8,39,41,42).

#### **e) Fertility disorder**

As mentioned above, changes in ovarian function are often seen during conditioning protocols prior to HSC transplantation. Therefore, POF may lead to loss of fertility (26,34,43–45). Although spontaneous pregnancies have been reported after HSC transplantation, this remains a rare phenomenon and causes obstetric complications, such as: risk of cesarean section, premature births, low birth weight. Therefore, fertility preservation must be offered to any patient of childbearing age before treatment begins.

There are several techniques for doing this :

-Cryopreservation of eggs or embryos. This method may require a first phase of follicular stimulation or may be carried out during a natural menstrual cycle. The oocytes or embryos are then preserved and can be reused for assisted reproduction.

-Cryopreservation of ovarian tissue followed by transplantation of the tissue after treatment. It is the method of choice for prepubertal and adolescent girls or patients requiring immediate chemotherapy, as there is no need for follicular stimulation. Restoration of ovarian function is seen in the months following autotransplantation. (26,34,38,39,43,46,47)

#### **f) Sexual disorder**

The presence of a change in sexuality is widely described in the few studies of patients' quality of life after systemic treatment of haematological malignancies (48–50). It affects about 80% of women after allogeneic HSC transplantation, with no significant improvement in sexual function 5 years after transplantation. Sexual dysfunction rarely has a direct impact on physical health, but can cause significant emotional distress (26,48,51).

The different types of sexual dysfunction that patients experience include lack of sexual desire, difficulty achieving orgasm and dyspareunia. Paradoxically, sexual satisfaction during intercourse is preserved (51).

The causes are multifactorial and interdependent, including the treatments used, dryness, vaginal atrophy, dyspareunia and reduced libido seen in POF and genital GvHD (48,50).

The use of topical estrogens and vaginal lubricants may improve symptoms. Appropriate care is recommended in the context of premature ovarian failure or proven genital GvHD. Communication within the couple, but also with health professionals, is essential to identify this dysfunction early and ensure continued sexual activity (26,48,51).

#### **g) Osteoporosis**

Loss of bone mineral density is common after allogeneic HSC transplantation. More than half of long-term survivors develop osteopenia (T-score between -2.5 and -1) or osteoporosis (T-score  $\leq$  -2.5). It is therefore recommended that bone densitometry of transplant patients be monitored regularly during treatment.

Risk factors for the occurrence of bone demineralisation include attacks on bone cells during graft conditioning, prolonged exposure to corticosteroids in the treatment of GvHD and the presence of hypogonadism resulting from POF.

Calcium and vitamin D supplementation, treatment of hypogonadism with hormone replacement therapy, and regular physical activity may prevent the development of osteopenia or even osteoporosis. If possible, a reduction in the dose of corticosteroids should be considered to prevent bone loss.

Once osteoporosis has been diagnosed, the standard treatment is the introduction of bisphosphonates to improve bone density and reduce the risk of fracture (8,9,36).

### **6. Purpose of the study**

As mentioned above, vulvovaginal GvHD is a little-known pathology, generally poorly investigated and diagnosed, despite its frequent occurrence (between 10 and 50% of women who have undergone allogeneic HSC transplantation).

Given the contextual elements related to the lack of training of caregivers and the absence of adequate reference on these existing and potentially serious complications, our study aims to evaluate the gynaecological complications of allogeneic haematopoietic stem cell transplantation, in particular the occurrence of vulvovaginal GvHD.



## **Material and methods**

### **1. Study type and population recruitment**

We conducted a retrospective, observational and single-center study at the *Centre Henri Becquerel* in Rouen between 1<sup>st</sup> November 2017 and 30<sup>th</sup> April 2024. We recruited all female patients who had undergone HSC allograft transplantation at the *Centre Henri Becquerel* since its accreditation to perform HSC allograft transplantation, in 2008. Within this population of interest, we included in our project all patients who had at least one medical gynaecological consultation at the *Centre Henri Becquerel* between 2017 (start of medical gynaecological activity) and 2024 and who did not oppose to the re-use of medical data for cancer research purposes. Conversely, patients who did not have a gynaecological follow-up visit during their treatment were excluded from the study.

The primary objective was to assess the incidence of vulvovaginal GvHD following allogeneic haematopoietic stem cell transplantation.

The secondary objectives of the study were to evaluate the efficiency of treatments for genital GvHD and to evaluate the occurrence of other gynaecological complications: chemo-induced menometrorrhagia, cervical smear abnormalities and induced HPV lesions, premature ovarian failure and osteoporosis, impaired fertility, sexual dysfunction.

Since November 2017, female patients at the *Centre Henri Becquerel* who have already received an HSC transplant or for whom the indication has been raised are almost systematically offered a gynaecological consultation during their follow-up. Ideally, this medical examination took place before the start of the transplant, but if this was not possible, it could take place during or at the end of the treatments. During the appointment, verbal information about vulvovaginal GvHD and other gynaecological complications was discussed, and an information leaflet covering key points raised during the consultation was provided. A routine gynaecological examination was carried out, with updating of gynaecological screening tests, if necessary (cervical smear or HPV test, mammography), prescription or renewal of contraception and screening for genital GvHD lesions.

A typical prescription with treatments to improve vulvovaginal trophicity (hyaluronic acid and estrogen) was given to all patients as a preventive measure. Hygiene and dietary instructions were also provided, with advice to maintain sexual activity if possible for the duration of the allograft in order to prevent the onset of GvHD (for vaginal synechiae prevention).

In case of proven GvHD, the lesions found were graded according to the clinical classification described above. Treatment was carried out by organising medical check-ups. The same process was followed when other gynaecological complications were detected: management of chemo-induced menometrorrhagia, monitoring of cervical smear/HPV test abnormalities, proposal of hormone replacement therapy in cases of POF and treatment of osteoporosis, suggestion of fertility preservation in case of decline in ovarian reserve, management of sexual dysfunction.

Recruitment took place from April 2023 to April 2024 included. The study was conducted by the *Centre Henri Becquerel* in Rouen.

### **2. Experimental plan**

All female patients who underwent allogeneic HSCT at the *Centre Henri Becquerel* and received at least one gynaecological consultation at the *Centre Henri Becquerel* (as of November 2017) were included in the study.

The occurrence of genital GvHD was clinically assessed during the gynaecological visit at the CHB during follow-up. The effectiveness of GvHD treatment was assessed clinically according to the evolution of the lesion's classification.

Other gynaecological complications were evaluated according to clinical, biological, and imaging criteria. All data were collected by chart review.

### 3. Statistical analysis

The study population was described using the usual parameters: mean, median, quartiles and extreme values for quantitative variables, and numbers and percentages for qualitative variables.

The overall analysis is mainly descriptive, with some comparisons made according to vulvovaginal GvHD status on certain characteristics. As Chi2 tests (or Fisher's exact test) were used for categorical/qualitative variables, non-parametric Wilcoxon or Student's t-tests were used for quantitative variables (considering the normal or non-normal distribution of these variables).

### 4. Ethical and regulatory issues

Due to the retrospective nature of our study, we did not need to request informed consent from patients. The synopsis of this study did not need to be validated by the Data Protection Committee, as all patients signed an informed consent form at the start of treatment, allowing us to use their computerised medical records.

## Results

### 1. Description of the study population

Since the accreditation of this treatment, 202 patients have received an HSC allograft at the *Centre Henri Becquerel* and 110 of them met the inclusion criteria of our study (54.45%).

The characteristics of the patients are described in **Table 1**.

One patient received a second allograft for relapse during the study period. The mean age at transplantation was 48.2 years. The most common diagnosis was acute myeloid leukaemia (48.18%, n=53), followed by myelodysplastic syndrome (10%, n=11) and acute lymphocytic leukaemia (8.18%, n=9).

Gynaecologically speaking, 57 patients (52.78%) were menopausal, 1 (0.92%) had POF of unknown aetiology prior to transplantation, and 1 had a history of total inter-adnexal hysterectomy in whom the menopausal status was unknown (no hormonal assays were performed). None of the postmenopausal patients had received hormonal treatment for menopausal symptoms. Only the patient with POF had hormone replacement therapy prior to transplantation.

## STUDY POPULATION

<b>Age</b>	
N (MD)	110 (0)
mean ( $\pm$ standard deviation)	48.20 ( $\pm$ 14.76)
median [q1;q3]	50.00 [36.0; 61.0]
min ; max	14.00 ; 72.00
<b>Genital activity</b>	
N (MD)	104 (6)
No	14 (13.46%)
Yes	90 (86.54%)
<b>Menopause</b>	
N (MD)	108 (2)
No	51 (47.22%)
Yes	57 (52.78%)
<b>Diagnostic</b>	
N (MD)	110 (0)
Aplasic médullaire	5 (4.55%)
Other diagnostic	11 (10.00%)
ALL	9 (8.18%)
AML	53 (48.18%)
CLL	1 (0.91%)
CML	3 (2.73%)
CMML	1 (0.91%)
Hodgkin's lymphoma	4 (3.64%)
Non-Hodgkin's lymphoma	4 (3.64%)
Multiple myeloma	4 (3.64%)
MDS	11 (10.00%)
MPS	4 (3.64%)
<b>Other</b>	
N (MD)	11 (0)
0	0 (0.00%)
EBV infection	1 (9.09%)
Plasmacytoid dendritic cell leukaemia	1 (9.09%)

T-cell prolymphocytic leukaemia	1 (9.09%)
Acute undifferentiated leukaemia	1 (9.09%)
CML + ALL	1 (9.09%)
Follicular lymphoma	1 (9.09%)
Angioimmunoblastic T-cell lymphoma	3 (27.27%)
Primary myelofibrosis	1 (9.09%)
Secondary myelofibrosis	1 (9.09%)

**Table 1:** Clinical characteristics of the study population  
*ALL: acute lymphoblastic leukaemia / AML: acute myeloid leukaemia / CLL: chronic lymphocytic leukaemia / CML: chronic myelogenous leukaemia / CMML: chronic myelomonocytic leukaemia / MDS: myelodysplastic syndrome / MPS: myeloproliferative syndrome / MD : missing data*

83.75% (n=67) of patients had a normal pretransplant pap-smear and 63.64% (n=35) had a negative HPV test when it was performed.

Regarding bone, 32.97% of patients had osteopenia and 13.19% had osteoporosis before transplantation (**Table 7**).

## 2. Occurrence of vulvovaginal GvHD reaction

In total, of all patients included (n=110), 29 developed vulvovaginal GvHD after transplantation (26.36%). Of these 29 patients, 8 had grade I GvHD (29.63%), 3 had grade III (11.11%), and 16 had grade IV (59.26%).

The time to onset of GvHD was late in 96.43% of cases, i.e., after the 100th day after allograft transplantation (**Table 5**).

There was no significant difference in age, menopausal status, genital activity, and initial diagnosis (**Table 7**).

	STUDY POPULATION
<b>GvH</b>	
N (MD)	110 (0)
No	81 (73.64%)
Yes	29 (26.36%)
<b>Onset time</b>	
N (MD)	28 (1)
NC	0 (0.00%)
Early	1 (3.57%)
Late	27 (96.43%)
<b>Grade of GvH</b>	
N (MD)	27 (2)
I	8 (29.63%)

III	3 (11.11%)
IV	16 (59.26%)

**Table 5: Occurrence of vulvovaginal GvHD**

In addition, a significant association was found between the occurrence of gynaecological GvHD and oral, ocular and hepatic GvHD (**Table 6**).

	STUDY POPULATION	PATIENTS WITHOUT VULVO-VAGINAL GVHD	PATIENTS WITH VULVO-VAGINAL GVHD	P-VALUE
<b>Cutaneous GvHD</b>				0.088
N (MD)	110 (0)	81 (0)	29 (0)	
No	41 (37.27%)	34 (41.98%)	7 (24.14%)	
Yes	69 (62.73%)	47 (58.02%)	22 (75.86%)	
<b>Digestive GvHD</b>				0.984
N (MD)	110 (0)	81 (0)	29 (0)	
No	89 (80.91%)	65 (80.25%)	24 (82.76%)	
Yes	21 (19.09%)	16 (19.75%)	5 (17.24%)	
<b>Pulmonary GvHD</b>				0.077 (fisher)
N (MD)	110 (0)	81 (0)	29 (0)	
No	103 (93.64%)	78 (96.30%)	25 (86.21%)	
Yes	7 (6.36%)	3 (3.70%)	4 (13.79%)	
<b>Integument GvH</b>				0.264 (fisher)
N (MD)	110 (0)	81 (0)	29 (0)	
No	109 (99.09%)	81 (100.00%)	28 (96.55%)	
Yes	1 (0.91%)	0 (0.00%)	1 (3.45%)	
<b>Oral GvHD</b>				0.01
N (MD)	110 (0)	81 (0)	29 (0)	
No	79 (71.82%)	64 (79.01%)	15 (51.72%)	
Yes	31 (28.18%)	17 (20.99%)	14 (48.28%)	
<b>Ocular GvHD</b>				0.004
N (MD)	110 (0)	81 (0)	29 (0)	
No	87 (79.09%)	70 (86.42%)	17 (58.62%)	
Yes	23 (20.91%)	11 (13.58%)	12 (41.38%)	
<b>Hepatic GvHD</b>				0.046
N (MD)	110 (0)	81 (0)	29 (0)	
No	91 (82.73%)	71 (87.65%)	20 (68.97%)	
Yes	19 (17.27%)	10 (12.35%)	9 (31.03%)	

**Table 6: Description of non-gynaecological GvHD and comparison following the presence of vulvovaginal GvHD**

### 3. Treatment efficiency

82.76% (n=24) of patients with vulvovaginal GvHD benefited from topical treatments based on estrogens, but also hyaluronic acid in 75.86% (n=22) of patients and corticosteroids in 58.62% (n=17) of cases. Although the 110 patients received anti-GvHD prophylaxis immediately after transplantation, 51.72% (n=15) of our patients had to be reintroduced to oral immunosuppressive therapy specifically for the treatment of GvHD and oral corticosteroids in 41.38% (n=12) of cases. 11 patients received additional physical treatments: use of vaginal

dilators (n=6/29) and surgery (n=5/29). Of the patients who underwent surgery, 5 underwent vaginal synechia removal, including 1 with additional vaginal lipofilling. In 93.10% of cases, GvHD treatments resulted in resolution of the lesions (**Table 8**).

<b>STUDY POPULATION</b>	
<b>Topical hyaluronic acid treatment</b>	
N (MD)	29 (0)
No	7 (24.14%)
Yes	22 (75.86%)
<b>Topical oestrogen treatment</b>	
N (MD)	29 (0)
No	5 (17.24%)
Yes	24 (82.76%)
<b>Topical corticosteroid treatment</b>	
N (MD)	29 (0)
No	12 (41.38%)
Yes	17 (58.62%)
<b>Oral corticosteroid treatment</b>	
N (MD)	29 (0)
No	17 (58.62%)
Yes	12 (41.38%)
<b>Topical immunosuppressant treatment</b>	
N (MD)	29 (0)
No	28 (96.55%)
Yes	1 (3.45%)
<b>Oral immunosuppressant treatment</b>	
N (MD)	29 (0)
No	14 (48.28%)
Yes	15 (51.72%)
<b>Dilator treatment</b>	
N (MD)	29 (0)
No	23 (79.31%)
Yes	6 (20.69%)

<b>Surgical treatment</b>	
N (MD)	29 (0)
No	24 (82.76%)
Yes	5 (17.24%)
<b>Treatment efficacy</b>	
N (MD)	29 (0)
No	2 (6.90%)
Yes	27 (93.10%)

**Table 8:** Different therapies for patients with vulvovaginal GvHD

#### 4. Other gynaecological and bone complications

6.48% (n=7) of patients had menometrorrhagia after HSC transplantation (**Table 7**).

After HSC transplantation, a non-significant increase in the presence of HPV and cervical lesions was observed (**Table 7**). Pre-transplant, the HPV test was positive in 2 patients and the pap-smear, if performed, was abnormal in 4 patients. Post-transplant, the HPV test was positive in 8 patients and the pap-smear was abnormal in 27 patients: 8.70% (n=6) of LSIL, 17.39% (n=12) of ASCUS, 7.25% (n=5) of HSIL, 5.80% of ASCH (n=4).

15.09% (n=16) of patients underwent colposcopy (1 patient died prior to colposcopy), which revealed a high-grade cervical lesion in 4.63% of cases (**Table 9**). The 5 patients with a high-grade cervical lesion all underwent conisation, including 1 patient with a secondary total inter-adnexal hysterectomy for a high-grade lesion on non in sano margins.

<b>STUDY POPULATION</b>	
<b>Colposcopy</b>	
N (MD)	106 (4)
No	90 (84.91%)
Yes	16 (15.09%)
<b>Cervical biopsy</b>	
N (MD)	108 (2)
None	98 (90.74%)
Benign	5 (4.63%)
High grade	5 (4.63%)
<b>Vaginal biopsy</b>	
N (MD)	108 (2)
None	106 (98.15%)
Low grade	1 (0.93%)

Benign	1 (0.93%)
<b>Vulvar biopsy</b>	
N (MD)	108 (2)
None	107 (99.07%)
Benign	1 (0.93%)

**Table 9:** Post-transplant investigations in the event of an abnormal cervical smear

There was also no significant difference between the presence of HPV and the presence of immunosuppressive treatment in our study (**Table 10**).

	<b>PATIENTS NOT TREATED WITH ORAL IMMUNOSUPPRESSANTS</b>	<b>PATIENTS TREATED WITH ORAL IMMUNOSUPPRESSANTS</b>	<b>P-VALUE</b>
<b>Post-transplant smear abnormality</b>			0.008 (fisher)
N (MD)	11 (3)	14 (1)	
Normal	3 (27.27%)	12 (85.71%)	
ASCH	1 (9.09%)	0 (0.00%)	
ASCUS	3 (27.27%)	2 (14.29%)	
HSIL	2 (18.18%)	0 (0.00%)	
LSIL	2 (18.18%)	0 (0.00%)	

**Table 10:** Association between oral immunosuppressant use for vulvovaginal GvHD and post-transplant smear abnormalities

*ASCUS: Atypical Squamous Cell of Unknowned Significance/ LSIL: low-grade squamous intraepithelial lesions / HSIL: high-grade squamous intraepithelial lesions / ASCH: Atypical squamous cells cannot exclude HSIL*

53.33% (n=16) of patients under 40 years old developed POF after transplantation. 31.25% (n=5) of them received oral hormone replacement therapy such as the estrogen-progestin pill or a combination of oestradiol and dydrogesterone; and 37.50% (n=6) of them received percutaneous hormone replacement therapy (**Table 7**).

12 premenopausal patients benefited from fertility preservation prior to transplantation. One patient did not have this option due to an altered ovarian reserve balance prior to transplantation, and another patient had fertility preservation but was unable to use her frozen ovarian cortex fragments prior to transplantation.

After transplantation, the average AMH dose was 0.80 ng/ml and the average of antral follicle count was 1.75 for both ovaries.

4 patients became pregnant after transplantation: one with ART thanks to oocyte donation, 3 spontaneous pregnancies. This resulted in 2 live births, 1 voluntary abortion, 1 pregnancy terminated in the 1st trimester (**Table 11**).



## STUDY POPULATION

Pre-transplant fertility preservation	
N (MD)	51 (0)
0	36 (70.59%)
1	12 (23.53%)
NC	3 (5.88%)
Post-transplant AMH dose	
N (MD)	7 (44)
mean ( $\pm$ standard deviation)	0.80 ( $\pm$ 0.52)
median [q1;q3]	1.00 [0.5; 1.1]
min ; max	0.01 ; 1.36
Occurrence of post-transplant pregnancy	
N (MD)	49 (2)
0	42 (85.71%)
ART	1 (2.04%)
NC	3 (6.12%)
Spontaneous	3 (6.12%)
Outcome of pregnancy	
N (MD)	51 (0)
Terminated pregnancy	1 (1.96%)
IVG	1 (1.96%)
Live birth	2 (3.92%)
NC	47 (92.16%)

**Table 11:** Post-transplant fertility in premenopausal women

*FP: fertility preservation / AMH: anti-mullerian hormone/ ART: assisted reproductive technology / NC: not concerned / IVG: voluntary termination of pregnancy*

Patients with vulvovaginal GvHD have more sexual dysfunction such as vaginal dryness (27.85% vs 62.07%,  $p=0.001$ ) and dyspareunia (21.52% vs 62.96%,  $p<0.001$ ). The presence of libido dysfunction is not significantly different between patients with and without vulvovaginal GvHD (**Table 7**).

Before transplantation, 30 patients (32.97%) had osteopenia and 12 patients (13.19%) had osteoporosis. After transplantation, 4 additional patients developed osteopenia and 8 osteoporosis. There was no association between the presence of osteopenia/osteoporosis and the presence of genital GvHD (**Table 7**).

## **Discussion**

Our study showed that about a quarter of patients who underwent allogeneic HSCT developed vulvovaginal GvHD. For half of them, the disease was of late onset (> 100 days) and the lesions were grade IV. These results clearly demonstrate the need for appropriate care for all women undergoing HSC transplantation. This must include early detection, preventive and/or curative treatment and personalized monitoring.

In most cases, topical treatments with hyaluronic acid and estrogen are sufficient to prevent or control the disease. If needed, escalating therapy with systemic treatments or even vaginal dilators or surgery is indicated.

These results are in line with the literature. In fact, a review of the Canadian literature published in 2019 (52) reports a prevalence of vulvovaginal GvHD of 19 to 35%, with a late onset depending on the study. Furthermore, in the prospective study by Machado et al. (53), 27.5% of the included patients developed genital GvHD, also mainly with late onset. Approximately 63% of the patients developed grade I vulvovaginal GvHD, whereas in our study the majority developed grade IV. We can explain this difference by the fact that the patients in our study did not all have regular gynaecological follow-up. There was no systematic screening for symptoms of genital GvHD and they were ultimately referred for consultation when symptoms became severe. Also, the implementation of personalised treatment adapted to the grade of GvHD allowed one of the lesions to disappear, as our study showed. Finally, a significant association was also found between the presence of genital and ocular GvHD (53).

As for other gynaecological complications, we found a low number of patients with menometrorrhagia, as expected. This is due to the presence of chemo-induced thrombocytopenia associated with graft conditioning, but also to the persistence of menstrual cycles. To avoid this effect, it is therefore recommended that amenorrhoea be induced in any premenopausal patient before transplantation (34).

We also observed a tendency to develop HPV-induced lesions, although this was not significant in our results. The lack of significance may be due to the low power of our study. This association between the presence of vulvovaginal GvHD and an increased risk of HPV-induced lesions was also shown in a single-centre longitudinal American study (OR = 5.7, 95% CI = 1.90-17.16, P = 0.002), as well as an increased risk of developing severe genital dysplasia (CIN II-III/VIN II-III; OR = 13.1, 95% CI = 1.59-108.26, P = 0.017) (54).

Then remember that POF is amenorrhoea lasting more than 4 months in a woman under 40 years of age with an FSH dose > 40 IU/l. In our study, half of the patients under 40 years of age developed POF after HSC transplantation and all other related treatments. These results differ from those found in the literature. In fact, it is described that 90% of premenopausal patients develop POF after allograft (55). The difference in results can be explained by the fact that transient amenorrhoea due to chemotherapy or the initiation of antigonadotropic treatment (for its contraceptive and preventive effect on chemo-induced menometrorrhagia) is generally present early after transplantation. This makes it difficult to detect POF. Some of our patients were enrolled in the study shortly after transplantation, so we were not able to detect certain late complications. The presence of POF should therefore be assessed in cases of persistent amenorrhoea at least 2 years after the start of transplantation. In addition, our study showed that POF and the conditioning protocols can affect fertility. To achieve pregnancy after treatment of the primary disease, it would be prudent to offer fertility preservation to premenopausal patients who request it.

We also found that the presence of POF and the use of GvHD treatments induce a decrease in bone mineralisation, explained by conditioning, prolonged exposure to corticosteroids and the presence of hypogonadism due to POF. The study by Savani et al. on a cohort of patients recruited at least 3 years after transplantation shows an incidence of bone demineralisation of 73.4% (41.8% for osteopenia and 31.6% for osteoporosis) (56). Regular monitoring with bone densitometry and appropriate treatment of osteopenia or osteoporosis must therefore be part of the overall care of our patients.

Finally, patients who have developed vulvovaginal GvHD have more sexual dysfunction, such as vaginal dryness and dyspareunia, than those without this reaction (57).

The strength of our study lies in the objective measurement of most of the parameters analysed (biological results, bone densitometry, imaging, etc.), which makes it easy to extrapolate our results to the population concerned. However, the study has several limitations. Firstly, it is a retrospective and single-centre analysis. The sample size is limited due to the small number of allografts performed annually at the CHB, but also because initially patients with an HSC allograft were not systematically offered gynaecological follow-up at our centre. The medical gynaecological activity developed at the end of 2017 and increased significantly from 2019. This justifies the number of missing data, as not all information regarding the occurrence of gynaecological GvHD, treatment and complications of this procedure were always recorded due to lack of follow-up. We should also note a possible bias in the classification of vulvovaginal GvHD. When reading the files, the grade of GvHD was not always mentioned, but it could be assumed from the description of the lesions observed.

GvHD is therefore a reaction that can affect the genitals. Other conditions after HSCT are explained by the state of immunosuppression, prolonged prophylactic or curative corticosteroid therapy and ovarian cytotoxicity of the treatments. We are now seeing an increase in overall survival after HSC transplantation. It is therefore important to pay attention to the quality of life of patients after treatment by limiting the occurrence of complications as much as possible. This would mean systematising the gynaecological monitoring protocol during an HSC transplant, which is already in place at our centre, to optimise care. Our study is therefore a preliminary study that allows us to take stock of the gynaecological consequences of HSC transplantation, but it is underpowered and contains numerous biases. It would therefore be important to carry out the same work prospectively, including more patients and carrying out a gynaecological follow-up of all the patients included, to overcome the bias associated with the lack of data. It would also be interesting to replicate this study after the *Centre Henri Becquerel* gynaecological follow-up protocol has been systematised, to see if early detection of lesions would limit the occurrence of certain complications.

## **Conclusion**

HSC transplantation is a treatment associated with several organ complications, especially gynaecological ones. This is due to the state of chronic inflammation, immunosuppression, and associated therapies (corticosteroids, immunotherapy, chemotherapy). Vulvovaginal GvHD is a poorly understood condition and is therefore under-recognised. Other gynaecological complications of HSC transplantation include chemo-induced menometrorrhagia, HPV-induced lesions, POF and osteoporosis, impaired fertility, and sexual dysfunction. It is thus our responsibility as healthcare professionals to inform patients who have undergone HSC transplantation of the potential consequences of this procedure and to offer them gynaecological follow-up tailored to the characteristics of their disease and treatment.

## Appendix

	STUDY POPULATION	PATIENTS WITHOUT VULVO- VAGINAL GVHD	PATIENTS WITH VULVO-VAGINAL GVHD	P-VALUE
<b>Pre-transplant pap smear abnormality</b>				1 (fisher)
N (MD)	80 (30)	65 (16)	15 (14)	
0	67 (83.75%)	54 (83.08%)	13 (86.67%)	
ASCUS	3 (3.75%)	3 (4.62%)	0 (0.00%)	
LSIL	1 (1.25%)	1 (1.54%)	0 (0.00%)	
NC	9 (11.25%)	7 (10.77%)	2 (13.33%)	
<b>Pre-transplant HPV test</b>				1 (fisher)
N (MD)	55 (55)	44 (37)	11 (18)	
No	35 (63.64%)	28 (63.64%)	7 (63.64%)	
Yes	2 (3.64%)	2 (4.55%)	0 (0.00%)	
NC	18 (32.73%)	14 (31.82%)	4 (36.36%)	
<b>Pre-transplant osteoporosis</b>				1 (fisher)
N (MD)	91 (19)	66 (15)	25 (4)	
No	78 (85.71%)	56 (84.85%)	22 (88.00%)	
Yes	12 (13.19%)	9 (13.64%)	3 (12.00%)	
NC	1 (1.10%)	1 (1.52%)	0 (0.00%)	
<b>Pre-transplant osteopenia</b>				0.858 (fisher)
N (MD)	91 (19)	66 (15)	25 (4)	
No	60 (65.93%)	44 (66.67%)	16 (64.00%)	
Yes	30 (32.97%)	21 (31.82%)	9 (36.00%)	
NC	1 (1.10%)	1 (1.52%)	0 (0.00%)	
<b>Post-transplant pap smear abnormalities</b>				0.655 (fisher)
N (MD)	69 (41)	44 (37)	25 (4)	
0	37 (53.62%)	22 (50.00%)	15 (60.00%)	
ASCH	4 (5.80%)	3 (6.82%)	1 (4.00%)	
ASCUS	12 (17.39%)	7 (15.91%)	5 (20.00%)	
HSIL	5 (7.25%)	3 (6.82%)	2 (8.00%)	
LSIL	6 (8.70%)	4 (9.09%)	2 (8.00%)	

NC	5 (7.25%)	5 (11.36%)	0 (0.00%)
<b>Post-transplant HPV testing</b>			0.112 (fisher)
N (MD)	54 (56)	35 (46)	19 (10)
No	35 (64.81%)	19 (54.29%)	16 (84.21%)
Yes	8 (14.81%)	7 (20.00%)	1 (5.26%)
NC	11 (20.37%)	9 (25.71%)	2 (10.53%)
<b>Post-transplant osteoporosis</b>			1 (fisher)
N (MD)	46 (64)	27 (54)	19 (10)
No	31 (67.39%)	18 (66.67%)	13 (68.42%)
Yes	15 (32.61%)	9 (33.33%)	6 (31.58%)
NC	0 (0.00%)	0 (0.00%)	0 (0.00%)
<b>Post-transplant osteopenia</b>			1 (fisher)
N (MD)	46 (64)	27 (54)	19 (10)
No	35 (76.09%)	20 (74.07%)	15 (78.95%)
Yes	11 (23.91%)	7 (25.93%)	4 (21.05%)
NC	0 (0.00%)	0 (0.00%)	0 (0.00%)
<b>Menometrorrhagia</b>			0.383 (fisher)
N (MD)	108 (2)	79 (2)	29 (0)
No	101 (93.52%)	75 (94.94%)	26 (89.66%)
Yes	7 (6.48%)	4 (5.06%)	3 (10.34%)
<b>Infections of the lower genital tract</b>			0.057 (fisher)
N (MD)	108 (2)	79 (2)	29 (0)
No	99 (91.67%)	75 (94.94%)	24 (82.76%)
Yes	9 (8.33%)	4 (5.06%)	5 (17.24%)
<b>Dyspareunia</b>			<0.001 (fisher)
N (MD)	106 (4)	79 (2)	27 (2)
No	61 (57.55%)	55 (69.62%)	6 (22.22%)
Yes	34 (32.08%)	17 (21.52%)	17 (62.96%)
NC	11 (10.38%)	7 (8.86%)	4 (14.81%)
<b>Vaginal dryness</b>			0.001
N (NA)	108 (2)	79 (2)	29 (0)
Non	68 (62.96%)	57 (72.15%)	11 (37.93%)
Oui	40 (37.04%)	22 (27.85%)	18 (62.07%)

<b>Libido dysfunction</b>				0.498 (fisher)
N (MD)	105 (5)	79 (2)	26 (3)	
No	94 (89.52%)	71 (89.87%)	23 (88.46%)	
Yes	8 (7.62%)	5 (6.33%)	3 (11.54%)	
NC	3 (2.86%)	3 (3.80%)	0 (0.00%)	
<b>POF</b>				1 (fisher)
N (MD)	30 (2)	23 (2)	7 (0)	
No	14 (46.67%)	11 (47.83%)	3 (42.86%)	
Yes	16 (53.33%)	12 (52.17%)	4 (57.14%)	
<b>Oral hormone replacement therapy</b>				1 (fisher)
N (MD)	16 (0)	12 (0)	4 (0)	
No	11 (68.75%)	8 (66.67%)	3 (75.00%)	
Yes	5 (31.25%)	4 (33.33%)	1 (25.00%)	
<b>Percutaneous hormone replacement therapy</b>				0.118 (fisher)
N (MD)	16 (0)	12 (0)	4 (0)	
No	10 (62.50%)	9 (75.00%)	1 (25.00%)	
Yes	6 (37.50%)	3 (25.00%)	3 (75.00%)	

**Table 7:** Gynecological and bone complications

*ASCUS: Atypical Squamous Cell of Unknowned Significance/ LSIL: low-grade squamous intraepithelial lesions / HSIL: high-grade squamous intraepithelial lesions / ASCH: Atypical squamous cells cannot exclude HSIL / NC: not concerned*

## LA GvH VULVAIRE ET VAGINALE, CE QU'IL FAUT SAVOIR !

### QU'EST-CE QUE LA GvH VULVAIRE ET VAGINALE ?

La réaction de GvH apparaît **lorsque les cellules du donneur attaquent les cellules du receveur au niveau gynécologique** : une inflammation apparaît. Cette GvH n'est pas systématique, mais peut survenir **entre 3 mois et 12 mois après la greffe**. Généralement la vulve est atteinte en premier, puis le vagin.

Sans traitement adapté, **cette GvH occasionne des douleurs, et peut empêcher les rapports sexuels**.

### QUELS SONT LES SYMPTOMES ?

Les patientes peuvent ressentir **des brûlures, une sécheresse vaginale, des douleurs pendant les rapports sexuels ou lorsqu'elles urinent, voire des saignements vaginaux**.

Dès l'apparition d'un symptôme, il faut **consulter le médecin afin de procéder à un examen gynécologique**. En effet, dans les cas les plus graves de GvH vaginale, une fermeture complète du vagin peut survenir.

### QUELS SONT LES TRAITEMENTS ?

- Crèmes et ovules à l'acide hyaluronique
- Crèmes et ovules hormonaux
- Crèmes et mousses corticoïdes
- Crème d'immunosuppresseurs
- Dilatateurs vaginaux
- Chirurgie dans les cas de sténose vaginale complète

## QUE FAIRE POUR LIMITER CETTE RÉACTION DE GvH GYNÉCOLOGIQUE ?

- Faire sa toilette à l'eau, sans savon et sans frotter
- Porter des sous-vêtements en coton
- Utiliser du lubrifiant à base d'eau pour les rapports sexuels
- Maintenir des rapports sexuels réguliers
- Maintenir un suivi gynécologique régulier et prévenir le médecin en cas de symptôme

## QUE FAUT-IL SAVOIR D'AUTRE ?

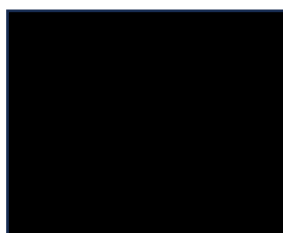
- Ne pas se sentir embarrassée d'en parler au médecin, il est là pour vous aider
- Ne pas tarder à consulter en cas de problème
- Le système immunitaire étant plus fragile : risque plus fréquent d'infections (mycose, herpès, vaginose...), et d'anomalies au frottis (papillomavirus)
- Si vous êtes ménopausée : prendre en charge la carence hormonale

## QUAND FAUT-IL APPELER LE MÉDECIN ?

- En cas de nouveau symptôme au niveau vulvaire et/ou vaginal
- En cas de douleurs, spontanées ou lors des rapports sexuels
- En cas de saignement inexplicable

## EN CAS DE DIFFICULTÉS RESENTIES DANS VOTRE SEXUALITÉ

- N'hésitez pas à contacter le service de Médecine et Soins de support pour une consultation de Sexologie au [REDACTED]



Information leaflet - verso



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## **Abstract**

### **Introduction**

HSC transplantation is a treatment which can be offered to treat bone marrow disease. It can be the cause of various organ complications, particularly gynaecological. Vulvovaginal GvHD is a poorly understood, under-recognised and under-diagnosed complication occurring after transplantation.

### **Purpose**

Evaluation of the incidence of vulvovaginal GvHD reaction after HSC transplantation.

### **Methods**

We conducted an observational, retrospective, single-center study at the *Centre Henri Becquerel* in Rouen. We included all patients who received an HSC allograft at the *Centre Henri Becquerel* and who had at least one gynaecological consultation at the centre between November 2017 and April 2024. All clinical, biological, and imaging data were analysed from computerised medical records.

### **Results**

We included 110 patients in the study. Vulvovaginal GvHD was diagnosed in 26.36% of patients. In 59.26% of cases, GvHD was grade IV. The time to onset of GvHD was late in 96.43% of cases. In 93.10% of cases, GvHD treatments resulted in resolution of the lesions. Regarding other gynaecological complications following allograft transplantation, 6.48% (n=7) of patients had menometrorrhagia; the incidence of HPV and cervical lesions was not significantly increased; 53.33% (n=16) of patients under 40 years old developed POF after transplantation; the average AMH dose was 0.80 ng/ml, and the average of antral follicle count was 1.75 for both ovaries. Patients with vulvovaginal GvHD have more sexual dysfunction such as vaginal dryness (27.85% vs 62.07%,  $p=0.001$ ) and dyspareunia (21.52% vs 62.96%,  $p<0.001$ ). There was no association between the presence of osteopenia/osteoporosis and the presence of genital GvHD.

### **Conclusion**

Vulvovaginal GvHD is a poorly understood pathology and is therefore under-recognised. Other gynaecological complications may occur after HSC transplantation. It is therefore important to inform patients and offer them gynaecological follow-up appropriate to the characteristics of their disease and treatment.

**Key words:** stem cell transplantation / graft-versus-host disease / vulvovaginal graft-versus-host disease / HPV / POF