Early Detection of Vulvovaginal Graft-Versus-Host Disease: An Integrative Review

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2021.12.7.6

Abstract

Introduction: Vulvovaginal graft-vs.-host disease (VVGvHD) is a condition caused by a T-cell mounted immune response after allogeneic hematopoietic stem cell transplant (alloHSCT), which can lead to sclerotic changes of the external genital organs. A common complication of alloHSCT, VVGvHD is underreported and underdiagnosed in female patients. Without detection and treatment, VVGvHD can progress to complete obliteration of the vaginal canal requiring surgical intervention in severe cases. **Design:** This review summarizes findings to assist providers in detecting and treating VVGvHD. It utilized PubMed, Scopus, and CINAHL databases. Inclusion criteria consisted of female patients, a history of stem cell transplantation, and a history of VVGvHD. Studies not published in English and dated more than 15 years were excluded. After the evaluation of 333 articles, 10 were included based on relevance and applicability. Limitations of this review included small sample sizes, retrospective nature of articles, and lack of randomized control trials. **Findings:** Early identification of VVGvHD requires identifying the rate of occurrence and risk factor profile, recognizing the presenting symptoms, improving VVGvHD assessment techniques, ascertaining when to biopsy, and establishing clinically targeted surveillance programs. **Conclusion:** For female patients who have undergone alloHSCT, targeted surveillance for early identification of VVGvHD results in earlier treatment initiation. Subsequently, this can improve sexual health, partner relationships, and quality of life in patients after stem cell transplant.

Hematopoietic stem cell transplantation (HSCT) is a medical procedure used to treat a multitude of conditions, such as malignant, nonmalignant, congenital, and acquired illnesses. Stem cells may be collected from either unrelated (allogeneic) or self (autologous) sources and occurs by way of bone marrow, peripheral blood, or umbilical cord (Jacobson

J Adv Pract Oncol 2021;12(7):725–737

et al., 2019). Graft-vs.-host disease (GvHD) is a condition caused by a T-cell mounted immune response after allogeneic HSCT (alloHSCT). Donor T cells react against receptor proteins, most importantly human leukocyte antigens. Graft-vs.-host disease most commonly affects the skin, gastrointestinal tract, lungs, and liver, but all organs have the potential to be involved. It is a main contributor to morbidity and mortality in patients who have undergone alloHSCT. For example, generalized GvHD has a 30% to 88% prevalence in transplant patients (Cizek et al., 2019; Jacobson et al., 2019; Machado et al., 2019; Stratton et al., 2007).

Vulvovaginal GvHD (VVGvHD) is a subtype of GvHD and specifically involves the vulvovaginal region. It is a common complication of alloHSCT that is often underreported and underdiagnosed in female patients. Delayed diagnosis may be attributed to various factors such as the coexistence of hypoestrogenism, misunderstanding of the disease, patient or provider embarrassment, or synchronous GvHD symptoms that compete for priority or urgency (Jacobson et al., 2019). Failure to identify and treat VVGvHD may lead to sclerotic changes of the external genital organs and result in complete vaginal obstruction (Cizek et al., 2019; Jacobson et al., 2019). Patients with VVGvHD are at a higher risk of opportunistic genital infections such as human papillomavirus (Da Silva Lara et al., 2010).

Approximately 8,000 alloHSCTs are performed in the United States annually (Kornik & Rustagi, 2017). A growing number of women are receiving alloHSCT and many will experience vulvovaginal symptoms due to GvHD (Jacobson et al., 2019). For patients with VVGvHD, symptoms and physical changes may have a significant negative impact on sexual health, relationships, and quality of life. Without detection and treatment, VVGvHD can progress to complete obliteration of the vaginal canal, which requires surgical intervention (Jacobson et al., 2019).

BACKGROUND AND SIGNIFICANCE

Studies have shown that targeted surveillance for early identification of VVGvHD enables earlier treatment initiation, which can reduce symptoms and long-term complications (Van Dam et al., 2017; Zantomio et al., 2006). To assist in both the diagnosis and staging of VVGvHD, scales and staging systems have been created to help guide providers in determining disease severity. For example, in 2014, the National Institutes of Health (NIH) developed a grading scale of 0 to 3 for absent, mild, moderate, and severe VVGvHD. Spinelli and colleagues (2003) and Stratton and colleagues (2007) developed modified scoring systems from the NIH scale. These three different scales are based on both objective and subjective assessment findings (see Table 1).

Vulvovaginal GvHD can produce mild to severe genitourinary symptoms and contribute to sexual dysfunction. Associated immune dysfunction or the use of immunosuppressant medications leads to an increased risk of cervical and lower genital tract neoplasia and cancer. Immunosuppression also contributes to the development of genital tract infections (Murphy et al., 2019).

The first article discussing VVGvHD was written in 1982. Since that time, there has been a substantial increase in the amount of available literature on VVGvHD. However, there remains a lack of evidence demonstrating the most effective methods for the early detection of VVGvHD. This review identifies interventions and methods that will enhance early detection and treatment initiation.

METHODS

The literature search included PubMed, CINAHL, and Scopus. Search terms included vagina, vulvovaginal, genital, vulvar, gynecologic, graft-vs.-host disease, and GvHD. Publications used were from November 22, 2004, to November 22, 2019. The search included both abstracts and full text articles and was limited to publications in English. A total of 421 articles were retrieved and after exclusion of duplicates, 333 articles were reviewed. A total of 10 articles met the inclusion criteria (see Figure 1 and Table 2). Studies included female patients, post HSCT, and a diagnosis of VVGvHD. Studies focused on screening, identification, and prevention. An initial appraisal of article validity was completed using "Rapid Critical Appraisal Checklists" by Melnyk and Fineout-Overholt (2011). Articles were rated based on the Johns Hopkins Nursing Evidence-Based Practice Rating Scale (Newhouse et al., 2007).

Table 1. VVGvHD Scoring Systems

	Grade 0	Grade 1	Grade 2	Grade 3
National Institutes of Health	No signs	Mild signs; patient without symptoms	Moderate signs; patient with symptoms and/or discomfort on exam	Severe signs with or without symptoms
Spinelli et al.	NA	General erythema and edema of vulvar structure; patchy erythema of mucous and glandular structures of vulvar vestibule; erythema around opening of vestibular glands	Grade 1 findings plus erosions of mucosal surfaces of the vulva; fissures in vulvar folds	Grade 2 findings, plus agglutination of the clitoral hood; introital stenosis; vaginal synechiae; hematocolpos or complete vaginal closure; fasciitis or spasticity of levator sling
Stratton et al.	NA	Vulvar redness; pain on palpating the labia; small areas of vulvar denudation	Extensive areas of vulvar denudation with or without leukokeratosis and introital stenosis	Vaginal adhesions or complete vaginal closure

Note. VVGvHD = vulvovaginal graft-vs.-host disease. Information from Jagasia et al. (2015); Spinelli et al. (2003); Stratton et al. (2007).

RESULTS

Early identification of VVGvHD included understanding the rate of occurrence (9/10 articles), defining the risk factor profile (7/10 articles), recognizing presenting symptoms (10/10 articles), validating VVGvHD assessment techniques (8/10 articles), determining when to biopsy (6/10 articles), and establishing clinical targeted surveillance programs (4/10 articles). Results are organized by these topics, and Table 3 summarizes the findings. Understanding these factors can assist in the development of a surveillance program.

Rate of Occurrence and Demographics

Nine of the 10 studies reported the rate of occurrence or demographics of VVGvHD among patients (see Table 3). Chung and colleagues (2015) conducted a retrospective review of 180 female bone marrow transplant patients, which assessed the prevalence and symptoms of VVGvHD. Study participants presented with an average age of 45.7 years. Chung and colleagues (2015) found that 69% had systemic GvHD and 35% to 41% of those patients had VVGvHD symptoms.

Cizek and colleagues (2019) completed a retrospective analysis over a 10-year period of 302 pediatric and young adult female patients who underwent HSCT to determine risk factors for presenting symptoms of GvHD. In this study, 5.9% of patients developed VVGvHD. The median patient age was 13.8 years and median day post transplant was 452 days (71–2966 days). In this sample, 47% (n = 9) were identified during a gynecologic exam due to symptoms, 32% (n = 6) were incidentally found during gynecologic examination, 11% (n = 2) were identified during general GvHD management, and 11% (n = 2) were identified incidentally in the operating room.

Hirsch and colleagues (2012) completed a retrospective analysis of female patients (n = 32) undergoing HSCT to assess vulvovaginal symptoms at the time of diagnosis. The authors completed this analysis both before and after the implementation of a systematic intervention for screening VVGvHD. In this study, 19% of women developed VVGvHD at a median age of 40 years.

Smith Knutsson and colleagues (2014) evaluated 42 women post transplant in a cross-sectional population-based study to determine medical history, ongoing medications, and genital signs and symptoms for VVGvHD. In this study, 52% of patients developed VVGvHD at a median age of 47 years.

Smith Knutsson and colleagues (2018) completed a population-based prospective study that analyzed signs and symptoms at diagnosis of VVGvHD with an evaluation of early intervention in 41 women receiving alloHSCT. Vulvovaginal GvHD was diagnosed in 66% of women. Of the women diagnosed with VVGvHD, 85% were diagnosed within the first year post transplant. Diagnosis of genital VVGvHD was made in 56% of women at 12 months, and a diagnosis of extra-

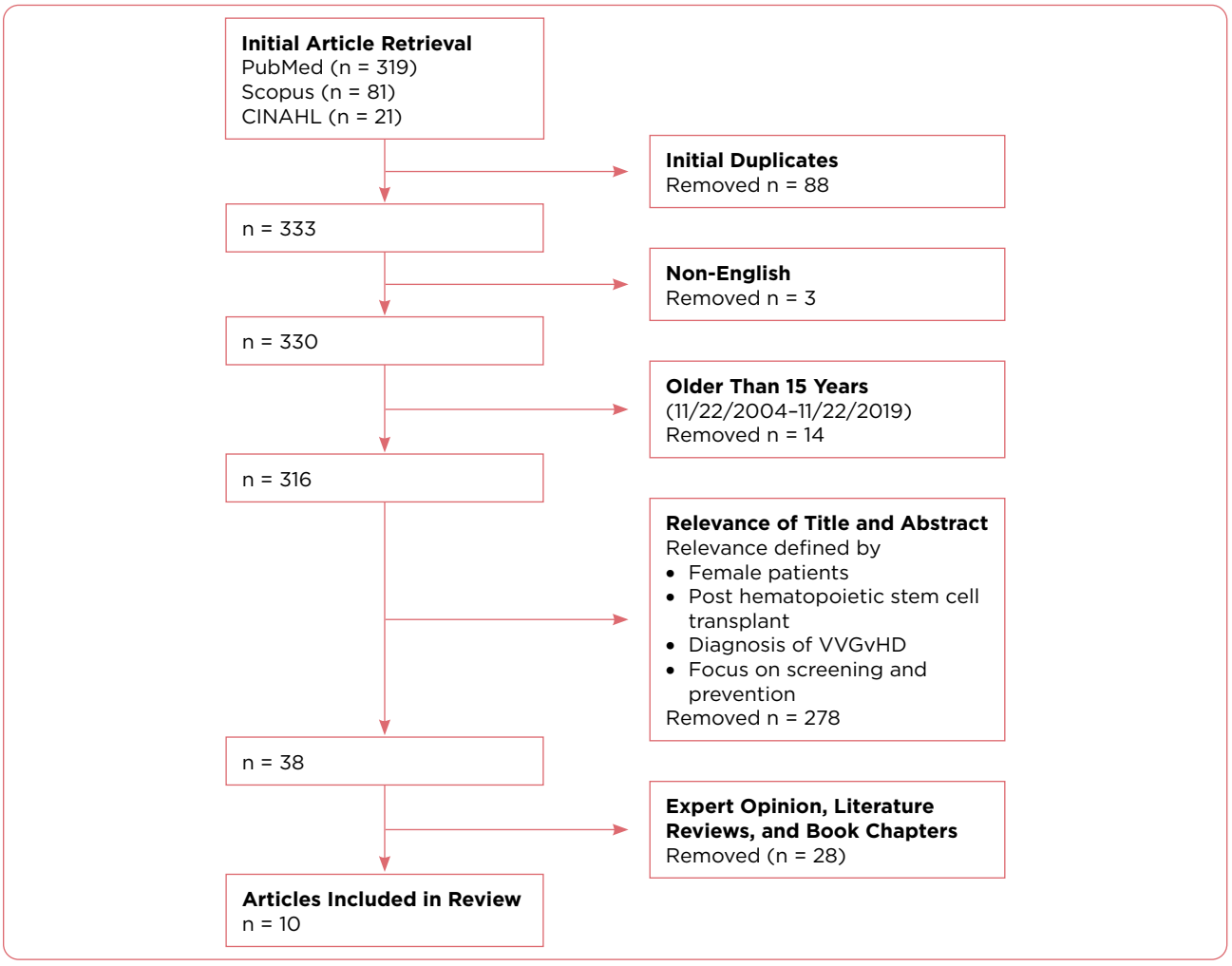

Figure 1. Article selection flow chart (Moher et al., 2019). VVGvHD = vulvovaginal graft-vs.-host disease.

genital VVGvHD was made in 66% of women at 36 months. Median time to first displayed sign or symptom was 6 months.

Scrivani and colleagues (2017) completed a prospective case study to interpret clinical data such as underlying disease, transplant regimen, genital symptoms, sites of disease, and follow-up of women with VVGvHD. This was a small sample of 5 women with a median age of 45. The women were 23 months to 18 years post transplant. Four patients (80%) had labial fusion and active chronic GvHD. Three patients (60%) had severe and sclerotic GvHD.

Stratton and colleagues (2007) completed a retrospective analysis of histories, laboratory tests, examinations, and treatment for adult women (n = 33) referred for gynecologic evaluation post transplant. In this study, 88% showed signs of VVGvHD. Patients ranged in age from 9 to 63 with a median age of 43.

Van Dam and colleagues (2017) completed a mixed-method study involving the evaluation of a VVGvHD clinic in a general tertiary hospital. A total of 81 females ages 2 to 66 years (median 38) were included. The patient population was a mix of both allogeneic (70) and autologous (11) transplants. Vulvovaginal GvHD was found in 54% of the patients.

As a part of genital tract management program evaluation, Zantomio and colleagues (2006) completed a retrospective record review of 61 women who underwent HSCT between May 1999 and June 2004. Incidence of VVGvHD was found to be 35% at year 1 and 49% at year 2. Median patient age was 42 (19–63), and median onset was at 9 months post HSCT.

Table 2. Evidence Table on Detection and Treatment of VVGvHD

No.	Author and year	Methodology	Sample, sample size, setting, and country of origin	Main findings/outcomes	Limitations	Evidence
1	Chung et al. (2015)	Retrospective analysis	• BMT patients referred for a gynecologic consultation • n = 180 • City of Hope Medical Center, Duarte, California	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Surveillance programs	• Retrospective nature: Could not measure severity of vulvovaginal symptoms and possible population bias	Level III/ good
2	Cizek et al. (2019)	Retrospective analysis	• Transplantation follow-up and diagnosis of vvGvHD • n = 19 • Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Surveillance programs	• Small study population • Retrospective nature with possible population bias	Level III/ good
3	Da Silva Lara et al. (2010)	Case study	• HSCT female patients complaining of coital pain • n = 5 • Sao Paulo University, Ribeirao Preto, Brazil	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Necessity of biopsy and biopsy techniques • Surveillance programs	• Low level of evidence: case study • Small sample size	Level 5/ low
4	Hirsch et al. (2012)	Retrospective analysis	• Female patients with vvGvHD who underwent alloHSCT between 2000–2010 followed by gynecologist • n = 32 • Hospital Saint-Louis, Paris, France	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Necessity of biopsy and biopsy techniques • Surveillance programs	• Retrospective selection bias • Lack of systematic biopsy realized • Small sample size	Level III/ good
5	Smith Knutsson et al. (2014)	Cross-sectional population-based study	• Females post alloHSCT • n = 42 • Sahlgrenska University Hospital, Gothenburg and Trollhattan, Sweden	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Necessity of biopsy and biopsy techniques • Surveillance programs	• Small sample size	Level III/ medium
6	Smith Knutsson et al. (2018)	Population-based prospective study	• Females receiving alloHSCT in 2005–2010 • n = 41 • Sahlgrenska University Hospital, Gothenburg, Sweden	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • Surveillance programs	• Small sample size	Level III/ medium

Note. BMT = bone marrow transplant; HSCT = hematopoietic stem cell transplant.

Table 2. Evidence Table on Detection and Treatment of VVGvHD (cont.)

No.	Author and year	Methodology	Sample, sample size, setting, and country of origin	Main findings/outcomes	Limitations	Evidence
7	Scrivani et al. (2017)	Prospective case study	• Women post HSCT • n= 5 • NIH intramural clinical trial, Bethesda, Maryland	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Surveillance programs	• Small sample size	Level V/ low
8	Stratton et al. (2007)	Retrospective observational study	• 1999–2006 females with vulvar symptoms or undergoing evaluation for chronic GvHD post-HSCT • n = 33 • Clinical Center of the NIH, Bethesda, Maryland	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Necessity of biopsy and biopsy techniques • Surveillance programs	• Retrospective nature; population bias • Small sample size	Level III/ medium
9	Van Dam et al. (2017)	Mixed method: literature review/case report/cross-sectional study	• Females ages 2–66 post-HSCT 2009 to 2015 • n = 81 • Hadassah Medical Center, Jerusalem, Israel	• Defining the risk factors/rate of occurrence • vvGvHD objective assessment techniques • Surveillance programs	• Small sample size • One clinic location	Level V/ good
10	Zantomio et al. (2006)	Mixed method: Prospective surveillance program/ retrospective audit	• Females post alloHSCT 1999–2004 engrafted with donor cells and in remission for at least 6 mo post-HSCT • n = 61 • Royal Melbourne Hospital, Melbourne, Australia	• Defining the risk factors/rate of occurrence • Identifying presenting symptoms • vvGvHD objective assessment techniques • Surveillance programs	• Surveillance program altered disease progression • Retrospective bias	Level III/ medium

Note. BMT = bone marrow transplant; HSCT = hematopoietic stem cell transplant.

Table 3. Results Summary

Author and year	Occurrence	Risk factors	Signs and symptoms[a]	Assessment techniques	Biopsy	Surveillance programs
Chung et al. (2015)	41%	N/A	+: 42% asymptomatic	N/A	N/A	N/A
Cizek et al. (2019)	5.9%	Matched unrelated donor, chronic GvHD, POI	+	Incidental, Stratton scale, genital exam, history and chart review	N/A	N/A
Da Silva Lara et al. (2010)	N/A	N/A	+	N/A	May be useful	N/A
Hirsch et al. (2012)	19%	AlloHSCT, chronic GvHD	+	Spinelli Scale	Limited value	Less severe disease with early consultation; mandatory evaluation day +100
Smith Knutsson et al. (2014)	52%	Sibling donor, age, steroid use, chronic GvHD	+	Genital exam, photo documentation, NIH criteria	Obtained in minority of patients	N/A
Smith Knutsson et al. (2018)	66%	Diagnosis, sibling donor, conditioning	+	Genital exam, photo documentation, NIH criteria	Limited value (biopsy plus distinctive sign)	Follow-up at 3, 6, 9, 12, 18, and 24 months
Scrivani et al. (2017)	N/A	N/A	+	Genital exam	Reported patient refusal	N/A
Stratton et al. (2007)	88%	HSCT	+	Genital exam	Not useful	N/A
Van Dam et al. (2017)	54%	HSCT	+	Genital exam	N/A	VVGvHD clinic visit every 2–4 months, improved QOL and sexual health
Zantomio et al. (2006)	49%	AlloHSCT, peripheral source, myeloablative regimens	+	Spinelli Scale	N/A	Early intervention program

Note. GvHD = graft-vs.-host disease; POI = primary ovarian insufficiency; alloHSCT = allogeneic hematopoietic stem cell transplant; QOL = quality of life.
[a]Signs, symptoms, and exam findings: dyspareunia, vulvar pain, vestibular gland pain, pruritus, vaginal discharge, dysuria, vaginal dryness, and a sensation of vaginal narrowing; pain with sexual activity, tampon insertion, or pain during manual/speculum examination; erythema, red and white spotting, telangiectasia, vulvar/labial adhesions and fusions, loss of architecture in the labia minora and clitoris, skin erosions/ulcerations/fissures, atrophic vaginal mucosa, mucosal paleness, abnormal vaginal discharge, vulvar skin hyperpigmentation, vulvar skin dryness/scaling, plaques, vaginal strings, vaginal stenosis, and vaginal obliteration.

Risk Factors

Seven out of 10 studies discussed associated risk factors for VVGvHD (Table 3). Patients impacted by VVGvHD involved primarily recipients of alloHSCT for hematologic malignancy (Chung et al., 2016; Zantomio et al., 2006), although two of the studies also included the assessment of VVGvHD in autologous transplant recipients and in patients with a primary diagnosis other than a hematologic malignancy (Stratton et al., 2007; Van Dam et al., 2017).

The presence of chronic GvHD in another organ was a common risk factor. In the Cizek and colleagues (2019) study, most patients had a matched unrelated donor and underwent transplant for a

nonmalignant condition. Authors reported that primary ovarian insufficiency may overlap with the presentation of VVGvHD. Other risk factors included chronic GvHD, especially oral, lung, and liver. Similarly, Stratton and colleagues (2007) found that 79% of patients with VVGvHD were being treated for GvHD in a differing organ. Nearly all patients with VVGvHD had active chronic GvHD of the skin, mouth, and eyes. In the Hirsch and colleagues (2012) article, all patients received alloHSCT primarily for the treatment of hematologic malignancy (29). Again, the authors found most patients (72%) had chronic GvHD in another organ, predominantly in oral, eyes, skin, liver, and lung.

In the Smith Knutsson and colleagues (2014) study, researchers drew associations between VVGvHD, sibling donors, and age. Older age was associated with higher rates of VVGvHD (p = .07) as was HSCT from a sibling (p = .002). Systemic corticosteroid use for the treatment of extragenital GvHD was positively correlated with VVGvHD (p = .001). In a later study, Smith Knutsson and colleagues (2018) found no association between VVGvHD and hematologic diagnosis or donor (sibling/unrelated). Zantomio and colleagues (2006) reported that a peripheral stem cell source for transplant was associated with a higher risk of developing VVGvHD as compared to bone marrow (p = 0.017). Donor source (sex or age) and GvHD prophylaxis did not impact VVGvHD outcomes.

Conditioning regimens were not associated as a risk factor in either the Smith Knutsson and colleagues (2018) or Zantomio and colleagues (2006) studies. Examples of conditioning regimens include nonmyeloablative (fludarabine and cyclophosphamide) chemotherapy, myeloablative chemotherapy (fludarabine and melphalan, busulfan and cyclophosphamide, busulfan and cyclophosphamide and etoposide), and myeloablative chemotherapy with total body irradiation (cyclophosphamide with total body irradiation and etoposide with total body irradiation; Zantomio et al., 2006). In the Zantomio and colleagues (2006) study, myeloablative regimens appeared to have increased risk, but the results were nonsignificant (p = 0.155).

Identifying Presenting Signs and Symptoms

All articles included in this review discussed patient signs and symptoms of VVGvHD. Cizek and colleagues (2019) reported that 42% of their patients were asymptomatic at time of diagnosis of VVGvHD, but the remainder of patients experienced a plethora symptoms, such as interlabial and clitoral hood adhesions (89%), loss of architecture of the labia minora and clitoral hood (42%), and skin erosions/fissures (37%). In Smith Knutsson and colleagues' (2014) study, patients frequently described dryness, pain, smarting pain (p < .5), and dyspareunia (p = .001).

Chung and colleagues (2016) found that 69% of patients had generalized GvHD, 41% had dyspareunia, and 35% had vaginal stenosis. Patients with VVGvHD were more likely to have vaginal stenosis (p <.0001), more likely to have used a vaginal dilator (p = .0008), but less likely to have urinary incontinence. The authors concluded that patients diagnosed with GvHD were at a higher risk for genitourinary symptoms (Chung et al., 2016). Stratton and colleagues (2007) also state most patients complained of pain during urination and pain that prevented sexual intercourse.

Common symptoms as reported by multiple studies of VVGvHD in this review include: dyspareunia, vulvar pain, vestibular gland pain, pruritus, vaginal discharge, dysuria, vaginal dryness, and a sensation of vaginal narrowing (Cizek et al., 2019; Da Silva Lara et al., 2010; Hirsch et al., 2012; Scrivani et al., 2017; Smith Knutsson et al., 2014, 2018; Stratton et al. 2007; Van Dam et al., 2017; Zantomio et al., 2006). Patients also reported pain with sexual activity, tampon insertion, or pain during manual/speculum examination (Cizek et al. 2019; Hirsch et al., 2012). Exam findings reported by multiple studies include erythema, red and white spotting, telangiectasia, vulvar/labial adhesions and fusions, loss of architecture in the labia minora and clitoris, skin erosions/ulcerations/fissures, atrophic vaginal mucosa, mucosal paleness, abnormal vaginal discharge, vulvar skin hyperpigmentation, vulvar skin dryness/scaling, plaques, vaginal strings, vaginal stenosis, and vaginal obliteration (Cizek et al., 2019; Da Silva Lara et al., 2010; Hirsch et al., 2012; Smith Knutsson et al., 2014, 2018; Scrivani et al., 2017; Stratton et al., 2007; Zantomio et al., 2006).

Objective Assessment Techniques

Eight of 10 articles discussed assessment techniques for VVGvHD (Table 3). Assessment in-

volved the use of staging scales to help determine severity of disease at diagnosis. Additionally, primary examination was done by genital area–directed examinations with or without speculum examinations (Scrivani et al., 2017; Stratton et al., 2007; Van Dam et al., 2017; Zantomio, 2006).

In the Cizek and colleagues (2019) retrospective study, VVGvHD was diagnosed incidentally as part of gynecologic evaluation for primary ovarian insufficiency, fertility, menstrual management, or in the operating room. The diagnosis was based primarily on clinical exam. The researchers documented history and symptoms through detailed chart review and applied the Stratton Scale to grade severity (Stratton et al., 2007). Nine patients underwent a gynecologic exam, and five patients in this study underwent a speculum examination. (Cizek et al., 2019).

In Zantomio and colleagues' (2006) study, 20 patients were assessed as having mild to moderate VVGvHD, while nine patients were ranked as severe using criteria similar to the Spinelli Scale (see Table 1). In the Hirsch and colleagues (2012) retrospective analysis using the Spinelli Scale, 50% of patients had grade 1 disease, 9% had grade 2 disease, and 41% percent had grade 3 disease. Conversely, studies without screening and surveillance methods reported higher rates of occurrence with later-stage VVGvHD. In the Cizek and colleagues (2019) study using the Stratton Scale, 17 out of the 19 patients were identified as grade 3 (Table 1). In the Stratton and colleagues (2007) study, the majority (20/29) had grade 2 or grade 3 VVGvHD. In Smith Knutsson and colleagues' (2014) study, all patients were seen within the gynecology department at a median of 80 months post transplant. A gynecologic examination with a structured documentation system of all vulvovaginal signs was completed. Photographic documentation was also utilized. Scoring in this study was completed using NIH criteria, and 90% of VVGvHD patients were scored at a stage 3 (Table 1).

In Smith Knutsson and colleagues' (2018) study, NIH criteria was utilized for staging. Gynecologic examination with structured documentation of vulvovaginal signs was completed, and photographic documentation was utilized. This study revealed that a score of 0 was most often seen 9 months post alloHSCT and a score of 1 to 3 was seen at 12 to 18 months. Additionally, in Scrivani and colleagues (2017) study, some patients had early presentation within 100 days post transplant, while others had delayed presentation; one patient was diagnosed 8 years post transplant.

Necessity of Biopsy and Biopsy Techniques

Six out of 10 articles in this review discuss the necessity of biopsy in patients to help establish a diagnosis of VVGvHD (Table 3). Da Silva Lara and colleagues (2010) completed a case study of five women post alloHSCT reporting coital pain to determine if genital biopsy would help differentiate GvHD and hypoestrogenism. Biopsies revealed findings indicative of but not specific for GvHD. However, the authors reasoned that coupled with clinical symptoms, biopsy can contribute to accurate diagnosis of the disease. The researchers concluded that genital biopsy may be important to differentiate VVGvHD from other disease processes such as hypoestrogenism (Da Silva Lara et al., 2010).

In Hirsch and colleagues' (2012) study, vulvovaginal biopsy in 12 patients was compatible with histology of chronic GvHD. Smith Knutsson and colleagues (2014) reported that biopsies were obtained in a minority of patients. This study suggested that biopsy may be of limited value, because biopsy may be indicated in select patients with symptoms but without diagnostic genital signs. Similarly, in Smith Knutsson and colleagues' (2018) study, patients were diagnosed with a distinctive VVGvHD clinical sign or symptom, biopsy plus distinctive sign, or distinctive sign plus chronic GvHD in another organ. Scrivani and colleagues (2017) make note of patient biopsy refusal but also reported treatment for diagnosis differentials illuminated by biopsy are similar and did not impact plan of care. Stratton and colleagues (2007) found that biopsy confirmation was utilized in only one case and affirmed that biopsy may be difficult based on pain and sensitivity in the vulvovaginal area.

Surveillance Programs

In-depth approaches to surveillance programs were discussed in four out of 10 articles (Table 3). Studies with screening and surveillance programs found higher rates of occurrence with larger pa-

tient percentages in the mild to moderate disease categories (Hirsch et al., 2012; Zantomio et al., 2006). The Hirsch and colleagues (2012) study compared patients occasionally seen in a specialized gynecology clinic to a group of all patients seen around day 100 post transplant. In patients diagnosed with grade three disease, median consultation took place at day 232 post transplant. In patients with grade one disease, median consultation took place at day 111. This documented program completed systematic gynecologic follow-up performed by a trained gynecologist, which showed an improved detection of the disease. Gynecologic follow-up was completed on post transplant day 100, every 3 months, and extended for years even if the patient did not have symptoms (Hirsch et al., 2012).

In the study by Smith Knutsson and colleagues (2018), 56% of women were diagnosed with VVGvHD at 12 months, and 66% of women were diagnosed with VVGvHD at 36 months. This study recommends regular gynecologic evaluation during the first 3 to 18 months post alloHSCT. A protocol is recommended for a gynecologic exam three to four times in the first year post transplant and every 6 to 12 months after. In summary, this clinic suggests systematic follow-up at months 3, 6, 9, 12, 18, 24, 30, and 36 (Smith Knutsson et al., 2018).

In the study by Van Dam and colleagues (2017), the VVGvHD clinic was an interprofessional collaboration between the medical director, nursing staff, and a gynecologist. Patients attended the clinic every 2 to 4 months depending on symptom severity. Nurses would complete initial screening and education. Patients would then be referred to a gynecologist if symptoms warranted treatment. Additionally, patients were referred to a physiotherapist to strengthen pelvic muscles and a sex counselor if needed. This clinic recommends follow-up every 2 to 4 months depending on symptoms (Van Dam et al., 2017).

In the study by Zantomio and colleagues (2006), a patient self-management program consisted of topical vaginal estrogen with hormone replacement, regular gynecologic review, and self-maintenance with dilator or intercourse. Most women attended regular appointments and responded positively to the appointments. Due to early intervention, no patients required surgical intervention with the program for severe VVGvHD. The lack of severe disease in this study may be attributed to the early intervention program. Essential aspects of a surveillance program in this study included pretransplant VVGvHD education, baseline sexual function assessment, self-surveillance, topical and/or systemic estrogen, VVGvHD surveillance, consideration of testosterone levels, and cervical cytology.

DISCUSSION

In the articles reviewed, 5.9% to 88% of patients were found to have VVGvHD (Cizek et al., 2019; Stratton et al., 2007). Such a wide distribution may be attributed to a multitude of factors such as pediatric vs. adult studies, retrospective nature of the studies, and early intervention programs vs. no early intervention.

Several authors found that VVGvHD is a disease process that fluctuates with periods of remission and relapse or progression. This cycle of disease denotes the need for long-term assessment and follow-up (Scrivani et al., 2017). Smith Knutsson and colleagues (2018) and Van Dam and colleagues (2017) both suggest surveillance programs that bring patients back post transplant at approximately day +100 then every 3 months for at least 3 years depending on symptoms. Vulvovaginal GvHD may have a late onset of symptoms. An important finding of this review is that many patients present asymptomatically (Cizek et al., 2019). This strengthens the recommendation for interval-based screenings for all female patients who have received alloHSCT. It is important to note that adolescent and young adult patients are less likely to undergo a sexual health discussion with health-care providers (Stratton et al., 2007).

Da Silva Lara and colleagues (2010) note the importance of evaluating genital symptoms to establish VVGvHD but conclude that biopsy may be useful when trying to determine VVGvHD from symptoms due to hypoestrogenism. Biopsy may be done to confirm the diagnosis of VVGvHD if needed, especially if there are no observable genital signs to match the patient complaints of genital symptoms. In the literature reviewed, biopsy was required in a minimal number of patients to establish an accurate diagnosis. Histologic findings may

reveal generalized changes commonly associated with GvHD (Hirsch et al., 2012; Lara et al., 2010).

Studies in this review showed that VVGvHD should be systematically assessed in early specialized consultation (Hirsch et al., 2012). The feasibility of self-vaginal examination should be discussed with all patients prior to transplant in an educational session. Patients should also be taught the importance of self-vaginal examination. It is important for patients to be educated on how to use vaginal lubricants and dilators. Chung and colleagues (2016) state the prevalence of vaginal dilator use was higher in their patient population. Prevention is the most important step in controlling the evolution of VVGvHD. Interprofessional consultations with physiotherapists, sex counselors, psychiatrists, and others may be considered based on the patient (Zantomio et al., 2006).

Limitations

There continues to be a lack of randomized controlled trials involving patients with VVGvHD. This literature review consists predominantly of retrospective analyses, case studies, and population-based studies. An increasing amount of evidence has been published discussing the risk factors, symptoms, and treatment strategies for women with VVGvHD. Also, there are a growing number of literature reviews regarding the overarching pathophysiology, assessment, and treatment of VVGvHD. At this time, there is a predominance of Level III and below research studies based on retrospective analysis and utilization of case studies. The literature may be influenced by retrospective patient population selection bias. Randomized controlled trials are needed to compare the efficacy of prevention and screening programs.

Implications for Practice

Early VVGvHD detection leads to intervention, which minimizes the risk of severe vulvovaginal symptoms (Chung et al., 2016). Education on VVGvHD should begin prior to transplant. Screening and prevention for VVGvHD should begin prior to transplant with a clinic-based educational session. This may be incorporated into a general pretransplant education session or GvHD educational session. Risk factors associated with the development of VVGvHD include a history of acute GvHD or extragenital chronic GvHD, older age, human leukocyte antigen mismatch, and peripheral blood stem cell grafts (Kornik & Rustagi, 2017). There is an increased need for screening of VVGvHD for all female patients of every age post alloHSCT. Vulvovaginal GvHD assessment should be incorporated into a facility's preexisting post-transplant screening checklist. Vulvovaginal GvHD is a fluctuating condition with frequent exacerbations and improvement, and regular clinic examinations are necessary. Post transplant, providers delivering their care must be prepared to complete gynecologic assessment and education. Providers should ask questions specifically regarding gynecologic health, and consideration should be made for evaluation for alloHSCT patients by a specialist if needed. Vulvovaginal GvHD may manifest over a long period of time, and long-term gynecologic follow-up is required to address the possibility of late-onset symptoms. Patients and providers may not focus on the genital area when considering an intensive procedure such as HSCT. However, if VVGvHD is found and treated early, severe complications may be avoided (Zantomio et al., 2006).

Vulvovaginal GvHD is primarily a clinical diagnosis based on signs and symptoms. National Institutes of Health staging, Spinelli and colleagues (2003), or Stratton and colleagues (2007) scales may be utilized to grade patients based on symptoms and presentation. During assessment, it is important to differentiate between primary ovarian insufficiency and VVGvHD. A biopsy can be performed needed. However, it is important to keep in mind that treatment of differing disease processes may be similar.

When assessing patients, VVGvHD can easily be missed due to nonspecific symptoms and low provider awareness. Patients should be specifically questioned regarding urinary symptoms, vaginal symptoms, and sexual dysfunction. Carpenter (2011) gave an expert opinion on the comprehensive assessment of chronic GvHD including the vulvovaginal site. Assessment techniques should include establishing a methodical assessment approach, periodic assessments for detection, and monitoring to avoid progression. Direct questions should be asked such as, "Do you have vaginal dryness and/or discomfort during sexual activity or

gynecologic examination?" (Carpenter, 2011, pp. 2,682). It is also imperative to assess if vaginal dryness is mild, moderate, or severe. Always examine the genital area during GvHD screening, keeping in mind potential sensitivity issues with speculum examination. Physical exam should include a full examination of the vulva and digital palpation of the vagina. A q-tip may be used to assess the sensitivity of the vestibular glands. Serial wet mounts may be considered, especially if a speculum exam cannot be completed (Kornik & Rustagi, 2017).

Diagnostic differentials should be considered such as estrogen deficiency, irritant dermatitis, atrophic vaginitis, and common infections. Typical therapeutic management of VVGvHD includes topical immunosuppressive therapies, such as clobetasol propionate ointment 0.05% or tacrolimus 0.1%, estrogens, and steroids. Oral therapies may be considered in patients who do not respond to topical treatment. Vaginal moisturizer, such as over-the-counter Replens, may be useful for some patients. Dilators continue to be a crucial part of treatment. The earlier VVGvHD is detected and treatment is initiated, the greater the chance for disease control and reduced need for surgical intervention.

CONCLUSION

Despite the current lack of randomized controlled trials for preventative programs and treatment options, screening and early intervention make a positive impact on vaginal health and sexual functions for female patients post alloHSCT. Clinical interventions should include the development of pretransplant educational programs and VVGvHD screening and treatment clinics. Vulvovaginal GvHD screening may be incorporated into a preexisting GvHD clinic if applicable. The surveillance and treatment of VVGvHD could easily be integrated into preexisting programs. Advanced practitioners are trained and positioned to establish clinics focused on VVGvHD surveillance and management. They are also positioned to assess for patient need and to advocate for their patients regarding the development of such programs.

Directions for Further Research

Further research is needed for the screening and treatment of VVGvHD. Well-designed randomized controlled trials would increase the current treatment options for VVGvHD. Recruiting a sufficient number of females post alloHSCT with VVGvHD may be difficult given small patient populations. A comparison of the differing screening techniques should be performed to identify those with the highest efficacy considering cost and resource utilization. With the current evolution of telehealth, educational and counseling sessions may be able to be conducted remotely. A program that demonstrates enhanced patient outcomes and ease of implementation will increase acceptance by organizational stakeholders and promote initiation of VVGvHD surveillance programs.

Disclosure

The authors have no conflicts of interest to disclose.

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