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Female long term survivors after allo-HSCT: evaluation and management

Dana Shanis, MD[1], **Melissa Merideth, MD, MPH**[2,3], **Tajana Klepac Pulanic, MD, MSC**[4], **Bipin N Savani, MD**[5], **Minoo Battiwalla, MD, MS**[6], and **Pamela Stratton, MD**[1]

[1]Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Schriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

[2]Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

[3]Intramural Office of Rare Diseases, Office of the Director, National Institutes of Health, Bethesda, MD

[4]Community Health Center East, Zagreb, Croatia

[5]Hematology and Stem Cell Transplantation Section, Vanderbilt University Medical Center, Nashville, TN

[6]Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD

Abstract

Female long term survivors of allogeneic hematopoietic stem cell transplantation incur a significant burden of late effects. Genital GVHD, HPV reactivation, ovarian failure and infertility, sexual dysfunction and osteoporosis are concerns that can significantly impact quality of life. This review examines the risk, pathogenesis, clinical presentation and implications of these common complications. Recommendations are provided for evaluation and management of these late effects, and other obstetric and gynecologic issues that may arise in this patient population.

As allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) survivorship increases, the focus of care has shifted to the identification and treatment of long-term complications that may affect quality of life. Preventive gynecologic care as well as early detection and treatments are important aspects to reducing morbidity and mortality in female long-term survivors after allo-HSCT. In particular, chronic graft-versus-host disease (GVHD) of the genital tract may be symptomatic and can impact intimacy. Other aspects of post-HSCT gynecologic health common to all reproductive-aged women may have unique considerations in women post-HSCT. These include assessment for and prevention of HPV-related cervical dysplasia, contraception, infertility, pregnancy issues, sexual health, and for those who have undergone premature ovarian failure, menopausal health including hormone therapy. With survivorship has come a shift in survivorship care from large transplant

For first proofs and reprint requests please contact: Mail address: Pamela Stratton, MD, Head, Gynecology Consult Service, Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Schriver* NICHD, NIH, Bldg 10, CRC, Room 1-3140, 10 Center Dr. MSC 1109, Bethesda, MD 20892-1109, Phone: (301) 496-9079, Fax: (301) 480-6703, strattop@mail.nih.gov.

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centers to community health care providers. As a result, many gynecologists and primary care physicians are assuming the post-HSCT gynecologic care of female long-term survivors.

This article addresses post-HSCT gynecologic surveillance and care and, when appropriate, frames this care in the context of comprehensive gynecologic care that the HSCT patient may have received in the pretransplant period and during transplant.

Genital Graft versus host disease

Risk

Female genital GVHD affects the vulva and vagina and is reported in 25 to 49% of allo-HSCT survivors[1,2] Vulvovaginal chronic GVHD (cGVHD) presents a median of 7 to 10 months after allo-HSCT[1–3], but vaginal GVHD can develop years later, with the latest reported cases eight years after HSCT[3–5]. Delayed onset suggests a need for long-term gynecological follow-up. The lag between vulvar and vaginal GVHD offers an opportunity for targeted vaginal mucosal prophylactic measures to prevent the need for surgery for vaginal stenosis[2]. Female genital cGVHD is more common after peripheral blood stem cell transplantation (PBSCT) than bone marrow transplantation (BMT)[6]. Vaginal synechiae, severe genital cGVHD, is associated with sclerotic skin cGVHD, the most severe type of skin GVHD[3]. Identification and treatment of genital cGVHD has been hampered by underreporting of symptoms, presumptive management directed at infectious or menopausal etiologies without gynecologic examination[7] or severe illness interfering with gynecology referral.

Pathogenesis

Genital GVHD was first described by Corson et al in 1982. Five women presenting with hematocolpos caused by stenotic vaginal GVHD were successfully treated with surgery followed by topical estrogen and dilators[8]. Genital GVHD is often recognized either by women or their providers in the context of coexisting cGVHD in other organs, especially skin and oral mucosa[1–3]. However, genital GVHD can be the initial GVHD manifestation in up to 27%[1].

Genital GVHD most frequently appears in the vulva (68%), or the vulva and vagina concomitantly (26%)[5]. Treatment of only vulvar disease will not prevent development of vaginal GVHD; considering vaginal disease separately and distinguishing between these two sites is important. In one series, 63% of patients required surgery for vaginal GVHD despite aggressive treatment of vulvar cGVHD[1], whereas others instituting regular monitoring avoided surgery[2].

Severity scoring for genital GVHD is described by Spinelli, Stratton and Zantomio with some differences[1–3]. Genital cGVHD is classified into grade I (mild), grade II (moderate), and grade III (severe). Spinelli et al includes leukoplakia, whereas Stratton et al includes reticulated leukoplakia, but considers generalized leukoplakia as a potential sign of human papillomavirus (HPV) disease. Only Zantomio et al's severity grading includes redness, desquamative, or erosive inflammatory vaginal mucosal changes as mild or moderate findings, respectively; noted perhaps because a prospective study design enabled observation of inflammatory lesions before vaginal scarring developed. Stratton and Turner observed that clitoral hood scarring and vulvar architectural changes often were coincident with vaginal scarring and included these changes as evidence of severe genital cGVHD[3,9].

Signs and symptoms/evaluation

Symptoms of genital GVHD include dryness, burning, itching, pain to touch and dyspareunia[3,9,10] Amenorrhea and cyclic pain due to hematocolpos/hematometra or inability to insert a tampon are symptoms of severe genital cGVHD (Table 2). The most common vulvar complaint is burning when urine touches the vulva. Introital dyspareunia is also common and easily distinguished from deep dyspareunia. Introital pain arises from inflammation of the vestibular gland openings (Bartholin's, Skene's), vulvar erosions or fissures and, in the rare complication of labial fusion. Dyspareunia with deep penile penetration occurs in patients with vaginal scarring or shortening. In some, symptoms persist a few days after intercourse as damaged, fragile mucosa heals.

Vulvar signs include patchy or generalized erythema, tenderness on Q-tip palpation of one or more, easily visualized, sometimes erythematous vestibular gland openings, mucosal erosions or fissures, lace-like leukokeratosis, or vulvar architecture changes like labial resorption or clitoral hood agglutination. Vaginal synechiae can appear as filmy webs, arcuate rings, or dense scarring. Cobweb-like filaments are easily lysed during examination. Dense sclerotic changes pull the vaginal walls together narrowing and shortening the vaginal canal. Complete vaginal stenosis prevents cervical cytology testing and can lead to hematocolpos/hematometra in premenopausal women or menopausal women on cyclic hormone replacement[1,8,11]. Vaginal fasciitis, very rare feature, is associated with generalized sclerosing disease[3].

Lichen planus-like features and vaginal scarring or stenosis are sometimes considered diagnostic signs of cGVHD, without additional testing[12]. These changes are similar to those found in vulvar or vaginal lichen planus[13,14].

Examination begins with careful inspection of the vulva, perineum and perianal area for signs of vulvar GVHD and palpation of vestibular gland openings for tenderness with cotton-tipped applicators. Vaginal examination begins with a gentle single digit examination to evaluate for vaginal synechiae followed by a speculum exam to obtain cultures for yeast, *Herpes simplex* virus (HSV), or other pathogens, if indicated. Cervical cytology should be obtained yearly, with colposcopy performed, if indicated by cytology results.

Symptoms of vulvar or vaginal pain and irritation with mild genital GVHD mimic those of genital atrophy from premature ovarian failure after HSCT, but physical findings differ. Patients with genital GVHD are tender to touch and have vulvar erythema or fissures, open, flat sores negative for HSV[10], or vaginal scarring which are not characteristics of menopause.

Vulvodynia, a chronic pain syndrome, in which gentle q-tip palpation of vestibular glands initiates pain and varying degrees of vestibular erythema, indistinguishable from mild vulvar cGVHD[15]; history of vulvodynia symptoms prior to transplant aid in distinguishing them.

Long-term implications, surveillance and prevention

The key to successful management of genital GVHD is early recognition of genital GVHD and early implementation of topical immunosuppressive and estrogen therapy with concomitant use of dilators, if needed[2,3,16]. Topical steroid therapy is effective in most cases in treatment of genital GVHD. Within 6 to 8 weeks of starting treatment, vulvar erosions and fissures heal and vulvar pain is reduced. For example, a high potency steroid ointment such as clobetasol propionate 0.05% applied in a thin layer to genital GVHD areas, every day at bedtime, usually results in improvement within 2–4 weeks and is tapered to a maintenance dose 2 to 3 times a week. If a less potent topical glucocorticoid such as hydrocortisone cream is used, treatment may be twice a day for a similar time period. If the

response to topical steroids is inadequate, topical cyclosporine or tacrolimus ointment 0.1% can be added[2,17,10].

Topical estrogen application is crucial for improvement of skin integrity resulting from ovarian failure-related genital atrophy and use of topical steroids. Estrogen is applied when erosions and fissures are healed at bedtime every day for 2 weeks and then decrease to one application 2 to 3 times a week.

Treatment of vaginal scarring depends on its severity. After lysing fine scars manually during vaginal examination, an ultralow dose estrogen vaginal ring (2mg; 75mcg/24 hours) can be used to mechanically open opposing sides of the upper vagina and can be replaced every 3 months[3]. If a vaginal estrogen ring cannot be placed, dilators with topical immunosuppressive drugs (steroids, cyclosporine or tacrolimus) and estrogen, such as a pea-sized amount of clobetasol ointment and one half inch of estrogen cream applied to the tip of a dilator, can be successful. Dilator size can be adjusted and used 2 to 3 times a week until the vaginal scarring lessens and a normal vaginal caliber is restored. In our clinical experience, one potential disadvantage of the ring compared to dilators with estrogen cream is formation of new vaginal synechiae below the ring. Dense fibrotic vaginal scars or extensive labial fusion may need surgery[7,11]. After surgery, use of topical immunosuppressive therapy with dilators or sexual intercourse prevents new scarring from developing and maintains vaginal capacity[16].

Human papillomavirus (HPV)-related secondary cancer and disease

Risk

A feared and potentially fatal long-term complications after allo-HSCT is developing a second cancer[18,19]. At 15 years, the risk of second malignancy in a large multicenter, European study was 11.5±2.3% with late mortality attributed to secondary cancer after allo-HSCT in 7%[20]. In a study of nearly 30,000 patients after allo-HSCT, the risk of squamous cell cancer (SCC), which include cervical cancer, is five times higher in patients with a history of cGVHD than in the general population[19].

Cervical SCC in long-term allo-HSCT survivors is reported to have a 13-fold increased risk compared to the general population[21], which is 18.5 fold higher if the patient is older than 34 years. Over 40% of female long-term survivors in our institution had an abnormal cervical cytology, with 20% having high-grade cervical dysplasia[22]. Abnormal cytology testing was detected a median of 51 months after HSCT with prolonged IST for cGVHD associated with the greatest risk[22]. In our clinical experience, use of topical steroids in the treatment of genital cGVHD has also been associated with developing genital warts and dysplasia in both the vagina and vulva. Lower genital tract dysplasia and anogenital condyloma, other manifestations of HPV infection, are also prevalent

Pathophysiology

HPV infection, the most common sexually transmitted infection worldwide, has a reported prevalence in healthy reproductive-aged women ranging from 20–46%; nearly 90% of these infections clear within 2 years.

Both cell-mediated immunity and neutralizing antibodies play a role in the defense against initial HPV infection and viral replication after infection[23]. Helper T-cells are important in B-cell activation and neutralizing antibody formation. Cytotoxic T-cell responses elicited by vaccination appear to play a role in limiting the number of infected cells and lead to an anti-viral cytokine cascade[24], and can be potentiated by existing neutralizing antibodies[23].

Reactivation of latent DNA viruses often occurs in immunocompromised hosts with hepatitis B, cytomegalovirus and various herpes viruses observed to be reactivated after allo-HSCT[25]. Similarly, a loss of HPV seroreactivity among transplant recipients has been reported[26]. Therefore, newly apparent anogenital condyloma and lower genital tract cytologic abnormalities likely represent reactivation of existing HPV infection, rather than acquisition of new infection. Either loss of antibody titers or changes in T-cell immunity to HPV coupled with use of immunosuppression can contribute to reactivation of HPV in the post-transplant population. Consequently, the resulting HPV-related disease may be more common, and more rapidly progressive, as is observed in other immunocompromised populations[27].

Presenting signs and symptoms/Evaluation

The clinical manifestations of HPV infection include genital warts (condyloma accuminata), cervical, vaginal, vulvar and anal intraepithelial neoplasia, and anogenital SCC. Vulvar and anal HPV disease may sometimes cause pruritis; warts may be unnoticed unless they are extensive or exophytic. When located on the cervix, genital warts and other HPV-related disease are asymptomatic mandating regular cervical cytology testing for identifying dysplasia.

Cervical dysplasia related to HPV infection is detected through cervical cytology testing with reflex HPV testing. Most HPV testing uses a Hybrid Capture 2 assay, with probes directed against high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 such that if one type is detected the assay is positive[28]. Colposcopy is warranted for cytology testing documenting atypical squamous cells of undetermined significance (ASC-US) coupled with concurrent positive testing for high-risk HPV types, atypical squamous cells suggestive of a high-grade lesion, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, or cancer. Women with ASC-US on cytology specimens a year apart are considered to have persistent abnormalities and should also undergo colposcopy. Genital HPV disease of the vulva, cervix and vagina is visualized using colposcopy after the topical application of 5% acetic acid; directed biopsy of abnormal areas is recommended.

As part of gynecologic pre-transplant care, most women have cervical cytologic testing with reflex HPV testing and any abnormalities are evaluated and treated. Current EBMT, American Society for Blood and Marrow Transplantation, and Children's Oncology Group guidelines recommend annual screening after transplant[16]. The American College of Obstetricians and Gynecologists recommends more frequent screening with cervical cytology for patients who are immunosuppressed, but does not specify an interval[29].

Prevention

HPV vaccination prior to HPV infection has been shown to reduce the incidence of both cervical cancer and anogenital warts in healthy populations[30,31], and is currently recommended for women 9–26 years, but is not routinely used in women over age 26[32]. The quadrivalent vaccine contains non-living virus-like capsid for HPV 6, 11, 16 and 18, which are found in 70% of cervical cancers and high-grade cervical intraepithelial neoplasia (CIN) and 90% of genital warts[33]. In addition, the vaccine reduces the risk of CIN2–3 and other genital tract neoplasia associated with HPV types not present in the vaccine, but that are responsible for >20% of cervical cancers[34].

Guidelines for vaccinating against vaccine-preventable infections after allo-HSCT have been promulgated, although antibody response may be impaired[35]. Most centers start re-immunizations in patients between 6 to 12 months after transplantation, as some patients

will mount effective responses. While there is no evidence to suggest that inactivated vaccines exacerbate chronic GVHD, vaccination remains controversial because of suboptimal immune response. Vaccination with quadrivalent HPV vaccine is a potentially important, but untested strategy, for reducing the risk of reactivation of HPV infection after HSCT. Vaccination in the year after transplantation could theoretically mitigate reactivation of HPV disease, if an antibody response is generated. At this time, there is no commercially available test to measure response to HPV vaccines. A study assessing whether the quadrivalent HPV vaccine can induce immunity in HSCT recipients in the context of systemic immunosuppression is currently underway at the NIH (ClinicalTrials.gov Identifier: NCT01092195).

Ovarian failure, Infertility, Pregnancy, and Sexual Health

Risk

Most women undergoing allo-HSCT are in their reproductive years, and more than 90% of these women experience ovarian failure after radiation and myelo-ablative conditioning chemotherapy for HSCT[36,37]. The likelihood of permanent ovarian failure and post-transplantation infertility is affected by the patient's age, pubertal status, conditioning chemotherapy, and radiation dose and location[37–39]; Table 1. Myeloablative regimens employing high-dose total body irradiation (TBI) with the equivalent of direct ovarian radiation >10Gy have the greatest risk with nearly all post-pubertal females undergoing HSCT developing ovarian failure[40,41]. Use of alkylator-based cytoreduction, especially high doses of busulfan and cyclophosphamide, and increasing age are additional risk factors[38,39,42], with all 68 women over age 25 years undergoing marrow transplantation with cyclophosphamide and TBI preconditioning in one study experiencing permanent premature ovarian insufficiency[36]. The source of stem cells does not appear to be a factor but a double transplant procedure is associated with a lower fertility rate than a single transplant[43].

The risk of premature ovarian insufficiency after TBI increases with increasing age[44]. Radiation doses of 6 Gy are sufficient to cause irreversible ovarian injury in most patients treated after age 40, while 2–3 times this dose is required to precipitate ovarian failure in irradiated children[45,46]. Radiation-induced pelvic damage is dependent upon dose, schedule and age at treatment[44] and includes impairment of ovarian as well as uterine function particularly when the prepubertal uterus has been exposed to irradiation[44].

In the past, fertility has been greatly impaired by myeloablative conditioning prior to transplant. The largest series reporting pregnancies in HSCT patients (19,412 allogenic and 17,950 autogenic patients) included 312 pregnancies in 232 (0.6%) of patients or partners of patients[40]. In addition to decreased fertility, pregnancies of allograft patients have an increased rate of low birth weight, preterm delivery and cesarean section deliveries compared to the general population. Patients with decreased uterine volume after TBI are at increased risk for spontaneous abortion, even with the use of donor oocytes and *in vitro* fertilization[44] although birth defects have not been reported[47]. Additional pregnancy complications reported after TBI include intrauterine growth restriction, abnormal placentation and uterine rupture[48,49]. Although some studies show no increased risk of spontaneous abortion (miscarriage)[40,50], other studies report an increased risk[16,44].

While sporadic pregnancies have been reported after transplant[40,51], reduced-intensity HSCT is reported to be more effective in preserving fertility than myeloablative transplantation[47]. Gonadotropin-releasing hormonal (GnRH) agonist-induced ovarian suppression is used to protect ovarian function of women during alkylating chemotherapy[52] and is shown to reduce the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer[53]. Whether this strategy will be effective in

women undergoing HSCT is not known. While Jonathan Tilly has explored the role of HSCT in preserving ovarian function after chemotherapy in a mouse model, these findings have not translated to humans[54].

For those whose menses return months or years after treatment, transient ovarian failure is common in the first year after treatment[55,56]: Table 1. Not only does ovarian dysfunction along with other endocrine dysfunction arise after chemotherapy, but chronic disease and use of immunosuppressant agents to prevent GVHD also likely contribute. Ovarian damage may ultimately result in premature menopause (before the age of 40), even among those who resume menses; risk factors for premature menopause are similar to those for acute ovarian failure[57,58].

Most affected women not only experience amenorrhea and menopausal symptoms but are at increased risk of cardiovascular disease, osteoporosis, dementia, and sexual dysfunction[59,60] with the youngest transplant patients with ovarian failure most likely to report an impaired sense of well-being and lower quality of life scores[56]. Sexual dysfunction affects 80% of female survivors of allo-HSCT long-term with women reporting no significant improvement in sexual function five years post-transplant[61]. Not only does systemic GVHD contribute to fatigue and perception of unattractiveness, but the occurrence of genital GVHD can contribute to dysfunction. Issues with sexual activity often persist even when other measures of physical and emotional well-being return to normal after treatment[61,62].

Pathophysiology

The ovary consists of sex steroid-producing granulosa and theca cells, and a fixed number of germ cells, some of which develop into oocytes. Over time, the number of follicles decreases by atresia and recruitment for ovulation such that once the number of follicles decreases to the threshold for that woman, menopause occurs. Therefore, any process causing injury to the ovarian cells, will hasten the onset of menopause.

A complex interplay between follicles, granulosa and theca cells are required in the maturation of a dominant follicle and secretion of female hormones. Chemotherapy-induced injury to granulosa cells can lead to insufficient estrogen production, lack of oocyte maturation[63] and is evident by a significant decrease in circulating levels of anti-mullerian hormone and inhibin B, hormones produced by granulosa cells, after treatment[39,64]. In addition, histologic evaluation of ovarian tissue in these women shows a reduction in the number of developing follicles[38,65]. Alkylating agents are not cell cycle-specific, and therefore can cause injury to both granulosa cells as well as non-dividing oocytes[65].

GnRH agonists may preserve ovarian function, but the mechanism is not fully understood. These agents may attenuate the effects of chemotherapy by decreasing utero-ovarian perfusion, suppressing the hypothalamic-pituitary-ovarian axis, or activating GnRH receptors, protecting undifferentiated germ-line stem cells or up-regulating intragonadal antiapoptotic molecules such as sphingosine-1-phosphate[53].

Presenting signs and symptoms/Evaluation

Since ovarian failure is a likely outcome, reproductive-aged women undergoing allo-HSCT are counseled about the expected signs and symptoms of menopause. Women are advised to avoid pregnancy using a reliable method of birth control with minimal side effects while they are taking transplant-related medications, and assessed for engraftment and disease recurrence.

Primary ovarian failure presents with amenorrhea, reduced estradiol levels and elevated gonadotropins (FSH>30 U/L)[62]. Affected women tend to have exaggerated menopausal

symptoms including hot flashes, sleep disturbances, vaginal dryness, dyspareunia, mood disturbances and musculoskeletal pain[66]. The most common complaints are decreased desire and lack of lubrication[60,61,67], resulting in dyspareunia and increased time to orgasm[61]. On physical examination, women with acute ovarian failure have pale, dry vulvar and vaginal mucosa, and decreased rugation of vaginal mucosa. Menstrual abnormalities may or may not be present when there is decreased ovarian function; however, amenorrhea occurs with complete ovarian failure. Amenorrhea after menses have returned after treatment prompts a pregnancy test since fertility can occur in some patients[51]. Thyroid abnormalities can present with amenorrhea and are common in post-transplant patients, so thyroid function tests are also warranted.

Long term implications, surveillance and management

At the time of transplant, women likely use hormonal therapies for control of menorrhagia and contraception (Table 2). Whether the short-term use of either GnRH agonists or depo medroxyprogesterone acetate around transplant contributes long-term to loss of bone mineral density is not known; this frequent post-transplant complication arises primarily from endocrine dysfunction after transplant as well as hypoestrogenism and use of steroids[16]. Some avoid prescribing oral contraceptive pills (OCP) in women in the early post-transplant period because of risk of thromboembolism, as studies have shown high dose progestins may increase this risk[68]. Others have concerns about whether OCP are absorbed in the setting of mucositis and GVHD[16]. Recommendation to avoid pregnancy likely results in use of OCP or other hormonal methods for some time after transplant.

Options for preservation of fertility have improved and become part of the discussion prior to onset of treatment. These options include pretreatment hormonal stimulation and harvesting of oocytes for fertilization/cryopreservation and GnRH agonist treatment[16,53,69]. Oocyte or ovarian tissue cryopreservation remains experimental.

Hormone replacement therapy (HRT) in long-term survivors with ovarian failure improves vasomotor and urogenital menopausal symptoms, and increases measures of psychological well-being, but has little effect on sexual desire and dissatisfaction[70–72]. Testosterone failed to increase libido in cancer survivors who were not on estrogen therapy[72]. The patient's psychological status and the quality of her relationship with her partner have a large effect on sexual function[73]. Behavioral therapies that encourage communication and expression of patient's fears of feeling unattractive or rejected, and directly address relationship conflicts are most likely to be effective. Given the young age of many transplant patients, higher doses of estrogen and progesterone may be needed to reach physiologic levels compared to women who undergo naturally-occurring menopause. There is no clear recommendation for the management of ovarian failure and contraception in women after allo-HSCT: the risks and benefits of hormone therapy are individualized based on the severity of menopausal symptoms, underlying disease status, contraindications to hormones, such as history of clot or active liver disease[56]. Women under age 35 have not yet reached peak bone mass and may benefit from hormone therapy to acquire bone mass. Hormone therapy is likely to be continued for many years in these young women, so the lowest dose that relieves symptoms is advised. Continued surveillance and screening, and need for continuing hormones is addressed intermittently[56]. There may be a role for stopping therapy every few years to assess the hypothalamic-pituitary-ovarian axis[74].

In menopausal patients with contraindications to systemic HRT, placebo-controlled trials suggest SSRIs or SNRIs reduce hot flashes by over 50%, leading to a reduction in sleep disturbances and psychological complaints, with an increase in energy[75]. Exercise, acupuncture, and herbal remedies have failed to demonstrate a consistent improvement in

symptoms[76,77,78]. Concern about harmful side effects of some herbal remedies, as well as inability to insure proper dosing limit recommending their use[79].

While the likelihood of recovery of ovarian function after myeloablative transplantation is very low, patients regain partial or complete function months to years after treatment[36,51,80]. As non-myeloablative preconditioning becomes more common with allo-HSCT for malignant and nonmalignant disorders, preservation of menstrual cycle and reproductive function have increased, allowing for higher rates of spontaneous pregnancies without complications such as preterm deliveries[47,81].

With increasing pregnancies in post-transplant survivors, new challenges are emerging in monitoring these pregnancies. Since allo-HSCT recipients have donor-derived red blood cells, lymphocytes and DNA in circulation, many of the usual prenatal test results are affected. These tests include serological tests for syphilis, rubella, HIV and hepatitis B, hematological tests such as mean cell volume, blood group and hemoglobin pattern, and DNA screening[82].

As more young women are undergoing allo-HSCT and surviving for many years, the magnitude of the obstetric and gynecologic problems faced by this patient population is becoming more evident. Early detection and treatment of gynecologic issues such as chronic GVHD can significantly improved quality of life issues, as can detection and treatment of other late effect complications such as HPV reactivation, sexual dysfunction and osteoporosis. Table 2 provides evaluation and management recommendations for the plethora of gynecologic issues faced by patients post-HSCT, both at the time of transplant and in long-term follow-up. More trials are needed to assess the clinical potential of GnRH agonist in limiting ovarian dysfunction and preservation of fertility, the natural history of ovarian failure and the outcomes of long-term hormone replacement in these patients. Given the complexities involved with testing in this patient population and setting, it is important for the obstetrician-gynecologist and hematologist-oncologist to work together.

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Table 1

Risk Factors and Timing of Ovarian Failure after Hematopoietic stem cell transplantation (HSCT)

	Risk factors
Transient ovarian failure in the two years after HSCT	
•Endocrine disruption	•Adrenal Insufficiency, transient hypo- or hyperthyroidism
•Immunosuppression	•High dose steroids
•Chronic disease	•Severe infection or chronic graft-versus-host disease
Long-term ovarian failure*	
•Pubertal Status	•After puberty
•Age at first treatment	•Older age
• Underlying disease, tendency to infiltrate ovaries	•Lymphoma, acute lymphocytic leukemia
•Type of transplant	•Allogeneic
•Number of HSCT	•Two or more
•Conditioning regimen	•Myelo-ablative
•Chemotherapy regimen	•Chemotherapy prior to transplant
	•Alkylating agents
	•Multiple alkylating agents
•Radiation	•High dose
	• Multiple doses
	• Pelvic or total body
•Graft-versus-host disease	• Long-term Immunosuppression

*Premature menopause – age <40 years has these same risk factors

Table 2

Care and Screening Recommendations for Women Post-Hematopoietic Stem Cell Transplantation

Assessments at the time of transplant

- Ovarian preservation and potential for ovarian failure
  - Address prior to transplant as part of transplant care
  - Options include:
    - Ovulation induction with fertilization and cryopreservation of oocytes
    - GnRH agonist treatment
    - Oocyte or ovarian tissue cryopreservation - experimental
- Contraception
  - Encourage use of effective method with minimal side effects at time of transplant
  - Prescribe contraception while woman being assessed for engraftment, on multiple transplant medications, and at risk of disease recurrence
  - Assess need for continuing contraception annually
  - Obtain pregnancy test in routine follow-up
  - If amenorrhea occurs after menses have resumed
    - Obtain pregnancy test
    - Consider hypothalamic pituitary axis testing

Long-term follow-up assessments

- Bone
  - Dual-energy X-ray absorptiometry (DEXA) at beginning of follow-up period
  - Continue calcium and vitamin D
  - Treat osteoporosis with bisphosphonates or hormone therapy
- Breast
  - Annual clinical breast exam at puberty and mammogram annually starting at age 40
  - Patients who underwent chest radiation begin annual mammography at age 25 or 8 years after treatment
- HPV assessment
  - Inspect vulva, vagina and cervix for evidence of HPV disease
  - Perform cervical cytology testing annually
  - Perform reflex HPV DNA testing for high risk types when cytology report is normal cytology or atypical cells of undetermined significance
  - Refer for colposcopy for cytology reports of atypical cells suggestive of high grade dysplasia or worse
  - Consider HPV vaccination
- STD
  - Perform annual screening based on risk factors
- Vulvovaginal symptoms
  - Assess for vulvovaginal symptoms in the setting of other GVHD
  - Refer for gynecologic evaluation if patient has vulvovaginal symptoms
  - Assess for signs of genital GVHD at annual pelvic exam
  - Consider gynecologic examination every 3 months for patients with severe GVHD or known genital GVHD
  - Treat any genital GVHD with topical immunosuppression, dilators and, if no contraindication, topical estrogens
  - Treat labial fusion or complete vaginal stenosis with surgery followed by dilators, topical immunosuppression, and topical estrogens

- Assess for HPV disease if topical immunosuppression is used

- Hypothalamic pituitary ovarian axis
  - Assess pubertal status with tanner stage at time of transplant
  - Consider ovarian function at annual history and physical
  - Check FSH, LH, estradiol
  - Consider performing transvaginal ultrasound
  - Check TSH when indicated
- Hormone therapy in the setting of ovarian failure
  - Assess contraindications to hormone therapy such as blood clots, liver function abnormalities, severe mucositis compromising absorption, hormone-dependent tumors
  - Consider hormone therapy in women with ovarian failure less than age 35
    - May improve bone mass
    - Likely improve sexual function
- Sexual function
  - Assess for dyspareunia, hypoactive sexual desire, and dysfunction with arousal or orgasm
  - Treat any underlying endocrine or medical conditions
  - Consider vaginal estrogen or lubricants for dyspareunia from atrophic vaginitis
  - Refer to psychologist for individual or couples therapy

GnRH is gonadotropin-releasing hormone; HPV is human papillomavirus; STD is sexually transmitted disease; GVHD is graft-versus-host-disease, FSH is follicle-stimulating hormone; LH is luteinizing hormone; TSH is thyroid-stimulating hormone