Biol Blood Marrow Transplant 25 (2019) e331–e343

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Reviews

A Practical Guide to Gynecologic and Reproductive Health in Women Undergoing Hematopoietic Stem Cell Transplant

Jeanne Murphy[1,*], Mary McKenna[2,3], Suzanne Abdelazim[3,4], Minoo Battiwalla[5], Pamela Stratton[6]

[1] George Washington University School of Nursing, Washington, District of Columbia
[2] Loyola University Medical Center, Maywood, Illinois
[3] NIH Clinical Center, Bethesda, Maryland
[4] Riverside Regional Medical Center, Newport News, Virginia
[5] Sarah Cannon Research Institute, Nashville, Tennessee
[6] Office of the Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Article history:
Received 7 May 2019
Accepted 30 July 2019

Keywords:
Gynecologic care
Human papillomavirus
Women's health
Allogeneic stem cell transplant

A B S T R A C T

Optimum care of female transplant recipients requires gynecologic care at several stages through the allogeneic hematopoietic stem cell transplantation (HCT) process. Sex-based considerations in women post-HCT span gynecologic sequelae of transplant along with assessment and maintenance of optimal sexual and gynecologic health. Pre-HCT, managing menstruation and abnormal uterine or genital bleeding, considering fertility preservation, and assessing for sexually transmitted infections, including human papillomavirus (HPV)-related disease and cervical cancer, enhance women's health. While inpatient during transplant when women are thrombocytopenic, menstrual bleeding requires suppression. Whenever graft-versus-host disease (GVHD) is assessed, screening for genital GVHD merits consideration. After the first 100 days, periodic assessments include obtaining a menstrual history, assessing ovarian function, and reviewing current hormonal use and contraindications to hormonal methods. Regular assessment for primary ovarian insufficiency, dyspareunia, and intimacy guides provision of contraception and hormone replacement options. As part of ongoing screening for genital GVHD and HPV-related disease, including sexually transmitted infections, periodic pelvic examinations are performed. Once successful long-term survival is achieved, planning for fertility may be considered. This article offers a comprehensive approach to these aspects of gynecologic care of patients throughout the trajectory of HCT and beyond into survivorship. We review the effects of HCT treatment on sexual health, ovarian function, and resulting menstrual changes and fertility challenges. Identification, treatment, and prevention of subsequent malignancies, including breast cancer, are discussed, with a focus on regular assessment of genital HPV disease and GVHD in long-term follow-up.

INTRODUCTION

Gynecologic care throughout hematopoietic stem cell transplantation (HCT) spans all aspects of reproductive and gynecologic health, with a focus on early detection and prevention of disease to reduce morbidity and mortality (Figure 1). Pathobiology of gynecologic issues and complications over the HCT trajectory have been identified, studied, and reviewed over the past several years [1-7]. In this article, we strive to create a primer on gynecologic care of women undergoing HCT. Fertility preservation is desirable but practical only for a minority of women. Without menstrual suppression, thrombocytopenia-associated menorrhagia can be a consequence of the conditioning regimen for HCT [8]. Premature primary ovarian insufficiency (POI), defined as amenorrhea for at least 3 months with elevated serum follicle-stimulating hormone (FSH) levels a month apart, often occurs following exposure to cytotoxic drugs and total body irradiation [9,10]. POI leads to deficient ovarian hormone production and infertility [11]. For those who experience POI, menopause management may include hormone therapy, which, in turn, may offer long-term health benefits [12]. Genital chronic graft-versus-host disease (GVHD) may produce severe symptoms that can affect intimacy and contribute to sexual dysfunction [1]. Women post-HCT may have immune dysfunction or may be using topical or systemic immunosuppressive therapy that, in turn, may confer an increased risk of cervical and lower genital tract intraepithelial neoplasia and cancer [11]. Throughout this article, we suggest junctures to consult with a gynecology provider with expertise and experience in caring for women throughout transplant and beyond.

Financial disclosure: See Acknowledgments on page e340.

* Correspondence and reprint requests: Jeanne Murphy, PhD, CNM, George Washington University School of Nursing, 1919 Pennsylvania Avenue NW, Washington, DC 20006.
E-mail address: jeannemurphy@email.gwu.edu (J. Murphy).

https://doi.org/10.1016/j.bbmt.2019.07.038
1083-8791/

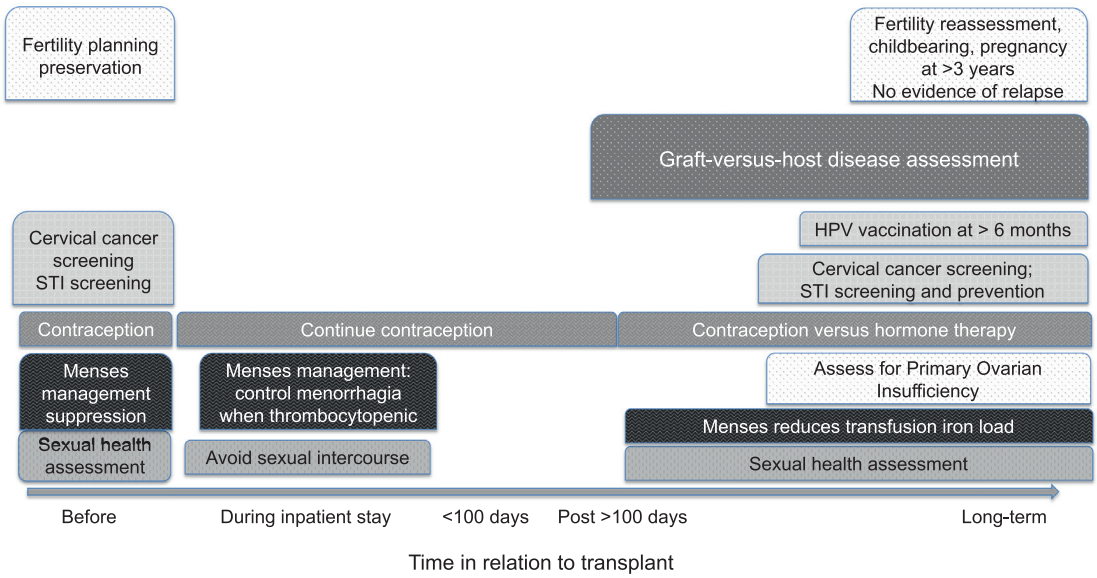

Figure 1. Gynecologic considerations throughout HCT.

GYNECOLOGIC ISSUES

General Principles

Before and throughout transplant, gynecologic and reproductive endocrinology referrals allow for evaluation of each female patient's current gynecologic and sexual health and planning for transplant-relevant gynecologic and fertility care (Table 1). Gynecologic advice can be greatly enhanced when transplant specialists convey any special considerations for individual HCT patients with their referral. Any postpubertal female may benefit from gynecologic evaluation to evaluate undiagnosed abnormal genital or vaginal bleeding or for menstrual irregularities. In addition, it is important to assess for ovarian function, fertility preservation, sexuality, contraception needs, sexually transmitted infections, and breast and cervical cancer screening. Adolescents are seen for menses suppression and fertility preservation. Children and young adolescents are seen only if there are pubertal concerns or for fertility preservation [9]. After transplant, females are assessed for genital GVHD.

HCT Impact on Ovarian Function in Women

Depending on the age of the patient and intensity of the conditioning regimen, including type and dose of agents used, HCT in women usually leads to disruption of the hypothalamic-pituitary-ovarian axis, direct damage to the ovaries with chemotherapy or total body radiation (TBI), and damage to the uterus with TBI [9,10,13] (Table 2). Physiologically, the rapid and profound decrease in ovarian follicle numbers (known as follicular atresia) and decay in oocyte quality ultimately result in decreased estradiol levels, infertility, and early onset of menopause [11]. Such effects may be reversible with use of reduced-intensity conditioning in younger patients [14-16].

Two elevated FSH levels a month apart, low estradiol, and no menstrual cycle for several months are suggestive of POI in women not on hormonal therapy. Antral follicle count, the sum of immature ovarian follicles in both ovaries counted using transvaginal ultrasound, may predict fertility and the ovary's ability to produce oocytes when stimulated by gonadotropins. Low antral follicle count (3 to 6 follicles) suggests low ovarian reserve [17].

Serial measurement of anti-Mullerian hormone (AMH) may be helpful in assessment of ovarian reserve [18]. AMH, a member of the transforming growth factor β superfamily, is a hormone secreted by the ovarian granulosa cells surrounding follicles and is a menstrual cycle-independent laboratory marker of ovarian reserve. AMH levels less than 1.5 ng/mL suggest low ovarian reserve and a high risk of menopause, although not necessarily low fertility in the general population [19,20]. Low AMH has been observed before treatment for hematologic malignancies and may recover after treatment, especially with the use of nonalkylating chemotherapy and no radiation, returning to normal in some [14-16]. In Fanconi anemia and other inherited bone marrow failures or genetic conditions frequently requiring transplant, low AMH levels potentially associated with POI are reported [21,22]. Thus, AMH levels are best considered as part of serial ovarian assessment over time, rather than as a single parameter predicting a woman's ability to conceive after transplant.

PRETRANSPLANT ASSESSMENT OF GYNECOLOGIC ISSUES AFFECTING FEMALE HCT PATIENTS

General Principles

In the pretransplant assessment, a gynecologic referral would allow for evaluation of a woman's current gynecologic and sexual health and begin planning for relevant peri- and post-HCT care (Table 1). Gynecologic care is greatly improved by conveying any special or time-sensitive considerations for individual HCT patients. It is essential to assess women for pretransplant conditions predisposing them to gynecologic complications. One such example is extensive human papillomavirus (HPV) disease predating transplant among some patients with primary immunodeficiencies such as GATA2 [23]. Similarly, the DNA repair defect persisting in the somatic cells after HCT of patients with Fanconi anemia predisposes them to HPV-independent genital squamous cancer, among other types of cancer. Both groups of patients will continue to need close follow-up even if their overall immunodeficiency improves after transplant. A potentially overlooked aspect of pretransplant care is counseling reproductive-aged women about POI symptoms and signs arising from decreased

Table 1
When to Refer to Gynecology and Sub-Specialty Care

Pretransplant|
- To reproductive endocrine team for discussion of fertility preservation
  - For children: First, assess for puberty and menarche; if postpubertal, consider oocyte cryopreservation as the preferred option.
  - For adults: "Do you plan to have children?"
  - Consider referral for any female up to age 45.
- To general gynecology (any postpubertal female)
  - Assess known abnormal cervical cytology or known HPV disease.
  - Assess STI (eg, discharge or other symptoms).
  - Screen for HPV, cervical cytology, and STI—if no assessment in the past 2 years.
  - Initiate or manage failure of menses suppression.
  - Discuss and initiate contraceptive options.
  - Remove copper IUD.
  - Discuss problems with sexual health.

Early post-transplant
- To general gynecology
  - Assess any lower genital symptom or complaint—with caveat, vaginal examination generally not done if low counts.
  - Manage failure of menses suppression.

>**100 days**
- In transplant practice, general gynecology or primary care: HPV vaccination ages 9 to 45*
- To general gynecology
  - Assess any genital discharge or other symptoms.
  - Screen and treat genital GVHD and HPV.
  - Assess ovarian function.
  - Treat POI symptoms.
  - Discuss and initiate contraceptive versus hormone therapy options.
  - To lessen transfusion iron overload, consider hormonal methods resulting in menses.
  - Screen and treat STI.
  - Discuss sexual health.
  - Conduct breast cancer screening.
- To adolescent gynecology/endocrinology/pediatric endocrinology
  - For children: concerns about puberty and menarche

Long-term survivor
- To reproductive endocrine team
  - Assess and manage fertility.
- To adolescent gynecology/endocrinology/pediatric endocrinology
  - For children: concerns about puberty and menarche
- To general gynecology
  - Periodic well-woman screening for STI, HPV, cytology testing, ovarian function, hormone therapy, genital GVHD, breast cancer screening, and sexual health as described in list above
  - Manage genital GVHD

* ACOG practice advisory [85].

Table 2
Chemotherapy and Radiation Exposure and Known Risk for Ovarian Dysfunction and Premature Ovarian Insufficiency

Chemotherapeutic Agents and Class*	Radiation Amount and Age at Exposure†
Alkylating agent	20.3 Gy at birth
Nitrogen mustard	18.4 Gy at age 10 years
Chlorambucil	16.5 Gy at age 20 years
Cyclophosphamide	14.3 Gy at age 30 years
Carmustine	6.0 Gy at age 40 or more years
Busulfan	
Ifosfamide	
Mechlorethamine	
Melphalan	
Lomustine	
Thiotepa	
Temozolomide	
Dacarbazine	
Anthracycline	
Doxorubicin	
Substituted hydrazine	
Procarbazine	
Heavy metals	
Cisplatin	
Carboplatin	

Adapted from ACOG Committee Opinion No. 747 [9] and Torrealday et al. [10].

* Other common chemotherapeutic agents including fludarabine, Campath, and Anti-thymocyte globulin have insufficient evidence to assess ovarian toxicity. This list is not comprehensive. Other chemotherapeutic agents may have adverse ovarian effects.

† Radiation doses refer to permanent amenorrhea; doses resulting in POI are lower.

ovarian hormonal production and assessing and managing them [24].

General Considerations for Pregnancy Planning

A woman who does not yet have children at the time of HCT or who desires to have more children in the future benefits from discussing treatments for future fertility before transplant, including fertility preservation options (Table 3) [25,26]. Conditioning regimens, especially TBI, result in up to 90% risk of ovarian failure and pregnancies are rare, with an incidence below 3% [27-31]. Patients generally are advised to avoid pregnancy from the time of pretransplant evaluation through at least 2 years post-HCT and often longer because of risk of relapse and continued use of potentially teratogenic, transplant-related medications, although this recommendation is tailored for individual patients. Additionally, during any period of pancytopenia, women are counseled to abstain completely from sexual intercourse or vaginal examinations because of risk of infection, pregnancy, and bleeding. It is essential that pregnancy avoidance is emphasized; that contraceptive methods are discussed, prescribed, and their use reviewed; and that pregnancy testing is performed at regular intervals [4,25].

Fertility Preservation

The current standard of care for the pretransplant evaluation includes counseling regarding subsequent fertility after treatment and fertility preservation options and, if the patient chooses and is medically able, undergoing a pretransplant procedure like oocyte harvesting before starting the conditioning regimen [4,7,32,33] (Table 3). Fertility preservation has become an important aspect of cancer treatment, requiring planning around programmatic requirements (Table 4) [25,26]. At some centers, fertility preservation programs led by reproductive endocrinologists foster interdisciplinary interaction with the transplant team to facilitate expeditious completion of the necessary care [25]. As concerns exist about the impact of undergoing fertility preservation on treatment initiation and long-term survival, 1 center's experience has shown that women with lymphoma and other cancers who underwent fertility preservation procedures were delayed slightly in initiating treatment but experienced no significant impact on recurrence or mortality compared with those who did not pursue fertility preservation [34,35].

With recent advances in cryopreservation, oocyte harvesting takes as little as 2 weeks and will not significantly delay HCT, especially with the use of menstrual cycle independent, random-start controlled ovarian stimulation [36]. In particular, centers in which weekly oncofertility clinics are offered report an average of 2 days to see a fertility specialist referral. In addition, providing patients with navigators to coordinate

Table 3
Discussion Topics between Female Patient and Provider on Fertility Preservation at the Time of HSCT

Topic	Counseling
Likelihood of infertility	Indication and type of transplantation vary in their likelihood of causing infertility. Individual factors such as disease, age, treatment before HSCT, and type of conditioning should be considered in counseling patients about the likelihood of infertility.
Timing of fertility preservation	Patients who are interested in fertility preservation should be informed of and consider their options as soon as possible to maximize the likelihood of success. However, even if the patient has received cancer or other treatment before being referred to the transplant center, fertility preservation methods should be discussed. Although some fertility treatment options can be initiated at any time during the menstrual cycle, some fertility treatments can only be initiated at specific times during the menstrual cycle.
Methods of fertility preservation	Embryo freezing remains the most successful option for fertility preservation for women with a partner. Oocyte freezing and ovarian tissue cryopreservation are increasingly associated with promising results and may be an option for young women or for women without a partner.
Disease progression or recurrence	Data are very limited, but in highly selected patients, there appears to be no detectable increased risk of disease recurrence associated with delays in treatment due to fertility preservation or undergoing fertility preservation before treatment. Patients needing urgent chemotherapy (eg, patients with leukemia) may not be candidates for fertility preservation.
Pregnancy	Pregnancy (conceived naturally or by assisted reproductive technology) is associated with increased risks for spontaneous abortion, preterm labor and delivery, and babies with low birth weight, but not an increased risk of malformation of the offspring.
Distress caused by infertility	Treatment-related infertility may be associated with psychosocial distress for the patient and her partner, and early referral for counseling may be beneficial in moderately distressed people or before fertility preservation in young women.
Costs	In locations where the insurance or health care service does not cover the costs of fertility preservation, costs should be addressed; in this case, the patient and her partner should be informed that they will be charged for all costs.
Legal issues	When oocytes, tissues, or embryos are cryopreserved, the patient or couple should make decisions in advance on the fate of these reproductive products in case they have not been used for any reason, including the death of the patient.

Adapted from Tichelli et al. [7].

oncofertility scheduling and return to transplant care improves integrating fertility preservation into cancer and transplant care [37].

The fertility specialist works closely with the transplant team to determine the timing and whether the patient is medically fit to undergo fertility preservation, taking a patient-centered approach to counseling about options [38]. Age and prior therapy already resulting in POI may preclude successful ovulation induction. Low platelet counts and neutropenia may increase the risk of bleeding and infection. As high levels of reproductive hormones occurring during ovarian stimulation are associated with increased thrombotic risk, it is essential to evaluate this risk and plan possible management of thromboses on an as-needed basis [4].

The steps required to complete cryopreservation are similar for either embryos or mature oocytes, providing the patient has sufficient ovarian reserve to undergo stimulation. Previously, embryo cryopreservation offered a better success rate but required having a partner or sperm donor. Mature oocyte cryopreservation has become more widely available, conferring a nearly equivalent efficacy compared with embryo cryopreservation, with a live birth probability of about 30% with 2 or more oocytes thawed [39]. Oocyte cryopreservation may offer greater reproductive flexibility to the woman [40,41]. In postpubertal girls, oocyte collection and cryopreservation after hormonal hyperstimulation is an option [32] and preferred over embryo cryopreservation as these young patients are generally without lifetime partners. In pre- and postpubertal girls, ovarian tissue cryopreservation can be offered, as it provides the potential for future hormone production to counteract transplant-related POI and may offer possibilities for later fertility, although malignant relapse has been shown in ovarian tissue transplantation from patients with acute lymphoblastic leukemia into mouse models [42–45]. However, it is not yet standard of care and considered

Table 4
Proposed Requirements for a Fertility Preservation Program

Requirements	Components
Rapid access	• Able to accommodate patients rapidly and be available year-round
Interdisciplinary medical team	• Oncologist • Reproductive endocrinologist and urologist • Reproductive surgeons with training in fertility preservation techniques
Laboratory	• Provides full complement of fertility preservation ○ Including embryo and oocyte cryopreservation • Analogous infrastructure for cryopreservation of testicular tissue and sperm

Counseling	• Provide access to a variety of counselors, including:
	  ○ Mental health professionals
	  ○ Genetic counselors
	  ○ Financial counselors

Access for prepubertal patients	• Have ability to counsel prepubertal patients on their fertility preservation options • Provide access to procedures (under institutional review board-approved protocols) such as ovarian and testicular tissue cryopreservation, both of which are still considered experimental

Summarized from ASRM Practice Committee Opinion [25].

experimental; to date, a small number pregnancies have been reported after prepubertal and reproductive-age ovarian tissue harvesting before chemotherapy and orthotopic ovarian cortex grafting after treatment [44,46], but no reported pregnancies yet in vitro maturation of ovarian tissue in HCT patients.

Costs regarding ovulation induction with cryopreservation, long-term banking, and, when pregnancy is desired, the in vitro fertilization process are often significant obstacles for patients. Encouraging patients to check with their insurance companies may help them determine coverage for these anticipated costs [43]. Thus far, 5 states have enacted fertility preservation laws for iatrogenic (medically induced) fertility [47]. Sixteen others have passed laws requiring that insurers cover infertility diagnosis and treatment, but this has not yet consistently translated into access to fertility preservation for women undergoing transplantation in these states [47]. While oncofertility is of recognized importance in Canada, the geographic distances between cancer care and fertility specialists have meant that fertility preservation occurs rarely [48]. In contrast, creation of fertility preservation consortiums across Europe has resulted in an increase in the use of fertility preservation procedures among cancer survivors [49].

The potential safety and possibility of future pregnancy after HCT consider factors like the proposed treatment and indication for transplant, including type of cancer. Discussing other reproductive options is especially important to a female patient who is too ill to undergo ovulation induction and oocyte retrieval or if future pregnancy would be relatively contraindicated [26,50]. For example, alternatives to preserving a woman's own eggs includes the use of donor gametes and embryos [29]. Additionally, gestational surrogacy may be considered by those who undergo pelvic irradiation because of their increased risk of pregnancy complications, including preterm birth and low birth weight infants [51,52]. Adoption is also an important option for family building in these women.

Menses Suppression: Assessment and Management

HCT conditioning regimens usually result in pancytopenia. In reproductive-aged women, thrombocytopenia during menses can lead to profound uterine bleeding. To limit the need for transfusion to manage transplant-related menorrhagia, use of hormonal agents for menses suppression is considered and individualized during the pretransplant evaluation [53].

A menstrual history includes the dates of recent menstrual periods to determine menstrual cycle length and number of days of bleeding, current use of hormones and contraception, and contraindications for hormonal methods [54]. Using this information, the clinician, often in consultation with a gynecologist, can tailor the method for menses suppression specifically to medical needs, with consideration of patient preference and adherence to the regimen. Despite the near-universal loss of fertility associated with myeloablative conditioning regimens, contraceptive use is required to mitigate the very small risk of pregnancy after transplant and during use of potentially teratogenic medications, and thus a menstrual suppression method that is contraceptive can be beneficial [13].

Currently favored hormonal approaches to menses suppression include (1) continuous use of combined estrogen and progestin-containing hormonal contraception (skipping the placebo week to avoid withdrawal bleeding and administered orally or transdermally), (2) progestin-only pills or low-dose progestin ("mini-pills") in those with contraindications for estrogen use, and (3) single-dose intramuscular depot GnRH agonist injections (Table 5) [5,55]. GnRH agonist use, although not contraceptive, offers a simple, one-time injection that, when timed more than 2 weeks before pancytopenia, has few side effects and may confer some benefit for fertility preservation, making it the preference of many transplant physicians.

Women already using long-acting reversible contraception (LARC) such as progestin-only subdermal implants, injections, and progestin intrauterine devices (IUDs) may continue their

Table 5
Hormone and Contraceptive Options at the Time of Transplant

Therapy Options	Dose	Comments
Estrogen*		
Estrogen-progesterone	Ethinyl estradiol <0.05-mg patch twice weekly with Provera 2.5 mg daily or Low-dose oral contraceptive pills (≥ 35 mcg ethinyl estradiol; 35 mcg to 1 mg progestin)	Benefit must outweigh risks with regards to thromboembolism
Intravenous estrogen	25 mg every 6 hours for 24 hours	
Progestin only: Contraindications (hormone-sensitive tumors and pregnancy)**		
Norethindrone acetate	5-15 mg/d	High doses associated with sinusoidal occlusive disease[a] May cause irregular bleeding
Norethindrone	0.35 mg/d	
Norgestrel	0.075 mg/d	
Long-acting reversible contraceptives		
Nexplanon	Subdermal implant	May cause irregular bleeding
Copper IUD	Intrauterine devices***	Do not insert immediately before transplant
Progestin IUD		Consider removal before transplant if menses are heavy
Leuprolide acetate: Contraindications (undiagnosed vaginal bleeding, pregnancy, platelets/mm^3 <10,000)		
Leuprolide acetate	Intramuscular 3.75-7.5 mg monthly or 11.12-22.5 mg every 3 months; s.c. injections 3.75 mg monthly; s.c. i.v. 1 mg/d	May cause irregular bleeding 2 weeks after injection

Adapted from Chang et al. [5].
i.m. indicates intramuscular; s.c., subcutaneous.
* Absolute contraindications: history of thromboembolism or pulmonary embolism, hormone-sensitive tumors, liver disease, pregnancy, and coronary artery disease. Relative contraindications: risk of cardiovascular disease, smoking, and myeloablative conditioning.
** All progestins can result in irregular vaginal bleeding.
*** Do not insert IUDs immediately before transplant. Consider removal before transplant if menses are heavy.
[a] Dalle et al. [96].

use. These methods often suppress menses, making additional treatments unnecessary. Copper IUDs confer no menses suppression and are a foreign body potentially posing infection risk and thus are generally removed (Table 1). Importantly, hormonally based LARCs are not usually initiated just before transplantation due to unpredictable bleeding patterns arising from their progestin-only content. As IUDs are foreign bodies, the placement of a progestin-releasing or copper IUD immediately pretransplant may increase the risk of infection during pancytopenia. With each method, there are potential medical benefits and risks recently described in reviews (Table 5) [5,55].

Patients who began a method of menses suppression pretransplant generally may continue it until engraftment. However, to minimize bone loss, GnRH agonist use is limited to the time of transplant and replaced with hormonal contraceptives or replacement therapy in the early peritransplant period, after engraftment [53]. By contrast, patients taking combined hormonal contraception are using a method that is contraceptive, confers benefit for bone mineral density, and treats menopausal symptoms if ovarian failure develops.

Contraception and Sexually Transmitted Disease Prevention

Although infertility is common after HCT, contraception is advisable if fertility status is unknown and pregnancy not advised. Addressing likelihood of pregnancy and methods to avoid pregnancy are important and often-overlooked components of pre-HCT care. The 2016 US Selected Practice Recommendations for Contraceptive Use addresses complex issues regarding initiation and use of specific contraceptive methods for many conditions, including solid organ transplantation, but makes no recommendations for HCT [56]. Patient counseling often provided by a gynecologist includes discussing how to initiate use of each contraceptive method, what follow-up is needed, and how to address problems that arise during use. Even though combined hormonal methods are relatively contraindicated in cancer care, they may be an option for menses suppression at the time of transplant after ensuring there are no absolute contraindications.

In patients with contraindications to hormone use, such as a history of venous thromboembolism (VTE), condom use may be considered. Although condoms are less effective than long-acting or hormonal contraception, their correct and consistent use is contraceptive and protects against sexually transmitted infections (STI).

Cervical Cytology and HPV Disease Pre-HCT

HPV, a common STI, causes cervical cancer, and in particular, HPV16 and HPV18 cause over 70% of cases [57]. Before transplant, immunocompromised patients are at risk of latent HPV reactivation and new HPV infection [58,59]. The pretransplant evaluation for those who have been sexually active, regardless of age, includes reviewing prior cervical cytology and HPV testing along with treatment history, as well as obtaining a pretransplant cervical cytology and HPV test. If the baseline screening is normal, current recommendations advise screening women annually with cervical cytology and HPV cotesting which is more frequent than the recommended interval of 3 to 5 years in a nonimmunosuppressed population [60]. If the pretransplant cervical cytology and HPV testing are abnormal, evaluation and treatment, per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, may be undertaken depending on whether healing from biopsies and treatment can occur before transplantation [61]. Because a high-grade cervical squamous intraepithelial lesion (SIL) or cancer may progress rapidly during immunodeficiency of transplant or while taking immunosuppressive agents to prevent GVHD, it is important to evaluate and treat cervical lesions pretransplant. If there is insufficient time after cervical biopsy or excision of lesions for healing before transplant, biopsies or treatment may be delayed until 3 to 6 months after transplant to allow sufficient recovery of platelets and WBC count to minimize bleeding and infection risk.

STI Screening and Prevention

STI screening and treatment are considered pre-HCT if women are sexually active, independent of their fertility status, especially for those with STI symptoms or to minimize infectious complications later when the transplant recipient becomes immunocompromised [60]. Because the early post-transplant phase is a time of low counts and immunosuppression to prevent graft rejection, viral reactivation and bacterial infections are common and may occur in the genital tract. Women may be advised to avoid intimate contact altogether to decrease the risk of infection or bleeding or, if they are sexually active, advised to use male latex or synthetic condoms in addition to their contraceptive methods. Topical spermicide, microbicides, diaphragms, and female condoms are not as effective in preventing STI transmission as male condoms [62]. Antiviral medications to prevent herpes simplex virus reactivation are often prescribed. A woman with genital tract symptoms like discharge, vulvar dryness, vulvar pain, masses, or bleeding warrant assessment by a gynecology provider. Intravaginal treatments and intercourse are usually avoided before engraftment [63].

Sexual Health

Sexual function, an important aspect of quality of life, merits assessment and counseling before transplant to allow for discussion and treatment of changes later [64]. Often in the context of illness leading to transplant, women choose not to have intercourse and relationships become less intimate; other women beginning transplant do not have a sexual partner. Sexual function pretransplant and at 1 year have been shown to be indicators of sexual functioning in female long-term survivors [65,66]. Sexual dysfunction occurs for many, often concurrent, reasons [3]. For example, women may experience discomfort during intercourse because of vaginal atrophy, lack of lubrication, or genital GVHD (Table 6). Additionally, they may consider themselves undesirable and experience decreased libido [3]. Early recognition and management of sexual dysfunction can improve intimacy and quality of life.

Many patients are interested in discussing sexual concerns with their providers, although patients usually expect their providers to initiate these conversations [67,68]. Having a member of the transplant team—a physician, nurse, nurse practitioner, physician assistant, social worker, or therapist—designated to perform this assessment can be useful, and conversations that begin with the treating team can continue in referral to a gynecology provider. Using a standardized assessment tool can facilitate clinical communication. One example, validated in transplant populations, is available in both brief and long forms, with the long form tabulating subscales including interest, desire, arousal, orgasm, satisfaction, masturbation, relationship, activity, and problems [66,69].

POST-TRANSPLANT UNTIL ENGRAFTMENT

Menstrual Management and Hormone Use

If menorrhagia related to thrombocytopenia occurs during inpatient treatment while using methods that had previously controlled menstrual bleeding, a brief course of high-dose

Table 6
Sexual Function Diagnosis and Associated Transplant Issues

Diagnosis	Description	Associated Transplant Issues
Hypoactive sexual desire disorder	Persistent lack of receptivity and desire for sexual activity plus lack of sexual thinking and fantasizing	• Gonadal failure • Psychological distress from HCT • Medications and drug interactions
Dyspareunia	Painful intercourse	• Gonadal failure • GVHD • Medications and drug interactions
Noncoital pain disorder	Genital pain with sexual stimulation or arousal without intercourse	
Vaginismus	Pain and difficulty with penile vaginal entry associated with sense of tightness of perivaginal muscles and no other physical findings	• GVHD • Psychological distress
Female sexual arousal disorder	Poor arousal and no orgasm	• Medications and drug interactions • Psychological distress

Adapted from Li et al. [3].

estrogen or transexamic acid may be considered in those without contraindications [70]. Balloon tamponade has also been used in women who have a history of thrombotic events [71].

Absorption of oral hormonal methods is often hampered in those with chemotherapy or medication-induced mucositis, acute gastrointestinal GVHD, or gastrointestinal infection. Oral hormones merit discontinuation in those with elevated liver transaminases. In these patients, transdermal combined hormonal methods with either a contraceptive or menopausal dose avoid the hepatic first-pass effect and are effectively absorbed, although they may not be an option for those who have extensive skin GVHD [5].

POST-TRANSPLANT GYNECOLOGIC ASSESSMENT AND ISSUES

General Principles

Many gynecology providers working closely with transplant teams recommend that women undergo a routine gynecology assessment between 3 and 6 months post-transplant. At that visit, women are assessed for genital GVHD, especially those with other sites of GVHD or who have genital symptoms. General gynecologic and reproductive health issues are considered in the context of their overall health and the success of transplant. Topics include assessing contraception, the menstrual cycle, and sexual function; planning for breast cancer screening; considering whether hormone replacement is indicated and, if so, whether to use hormone therapy versus hormonal contraception; timing of STI; cytology and HPV testing; and assessment/treatment of any genital lesions. If counts are normal, menses suppression is discontinued. Fertility issues are deferred immediately post-transplant because women are advised to avoid pregnancy during this time.

Genital GVHD

Genital chronic graft-versus-host disease (cGVHD) manifests on the genital mucosal surfaces of the vulva and vagina. Usually women with genital cGVHD have cGVHD elsewhere in the body. Vulvar cGVHD occurs in about a quarter to half of women undergoing transplant at a median of 9 months post-transplant but can occur much later [2]. Female children can present with genital cGVHD, although the prevalence is not known [72]. Vaginal cGVHD comprises scarring and often occurs from weeks to months after vulvar cGVHD, although it is not prevented by treating vulvar cGVHD. Because having vulvar cGVHD often precludes assessment for concurrent vaginal cGVHD due to pain, some delay this assessment until vulvar cGVHD is treated. Strategies to prevent vaginal cGVHD include vaginal self-examinations, attempting to have regular vaginal intercourse, or use of vaginal dilators [2]. Symptoms of genital cGVHD include vulvovaginal dryness, pruritus, burning, pain, dysuria, dyspareunia, and bleeding; many of these symptoms also suggest POI, and presence of any of them warrants referral for gynecologic evaluation. Asking women whether they have pain at rest, pain with urination, or pain with sex will also help identify those who warrant assessment for genital cGVHD. A targeted gynecology examination is the only definitive way to identify genital cGVHD (Figure 2) [2,73]. An external, vulvar assessment can be performed by the transplant clinician or a gynecology provider, with referrals to gynecology for any patients meriting biopsy.

Women with genital cGVHD benefit from using only warm water to cleanse the vulva and avoiding chemical irritants such as soaps or feminine wash products. Emollients like petroleum jelly may be applied to the external genitalia to provide relief from irritation or itching when infection is not present [53,73]. Treatment of genital cGVHD generally involves applying topical high-potency corticosteroids like clobetasol (0.05%) or triamcinolone ointments to affected mucosal areas daily [2]. When a favorable response is achieved, treatment is tapered to prevent mucosal atrophy or superinfection with *Candida*. Women with vaginal cGVHD are provided with individualized treatment depending on the degree and location of sclerotic changes [2]. Periodic assessment by a gynecology provider can aid in tailoring and assessing treatment response. Topical estrogens can increase epithelial thickness of thin, treated mucosa [2]. Genital cGVHD and its treatment may be associated with HPV reactivation [58,59]. Assessment of HPV lesions and cervical cancer screening are included in the lower genital tract examination.

Breast and Cervical Cancer Prevention Post-HCT

HCT patients are at increased risk for breast cancer, especially those women exposed to TBI conditioning (hazard ratio of 4.0) [74]. Those women with prior radiation therapy or TBI should have a mammogram and breast magnetic resonance imaging by age 25 or 8 years after radiation exposure (and no later than age 40 years) [75]. For all others, breast cancer screening recommendations vary, and generally, clinicians engage in shared decision making with women regarding recommended breast cancer screening procedures [76].

After transplant, immunocompromised patients are at risk of new HPV infection and latent HPV reactivation, and they may experience more rapid progression to premalignant and malignant neoplastic lesions than the general population

Name:_____ **Date of birth:**_____ **Assessment date:**_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT **(female)**	☐ No signs	☐ Mild signs and females may have symptoms* WITH discomfort on exam	☐ Moderate signs and may have symptoms* with discomfort on exam	☐ Severe Signs with or without symptoms *

Currently sexually active:
☐ Yes ☐ No

Check all signs that applies:

☐ Lichen planus-like features

☐ Lichen sclerosis-like features

☐ Vaginal scarring (female)

☐ Clitoral/labial agglutination (female)

☐ Labial resorption (female)

☐ Erosions

☐ Fissures

☐ Ulcers

☐ *Abnormality present but NOT thought to represent GVHD (specify cause):*_____

☐ *Abnormality thought to represent GVHD PLUS other causes(specify cause):*_____

**Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection.*

If a gynecologist is unavailable, external examination may be performed. Determine "discomfort on exam" as follows:

a) Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a cotton-tipped applicator. Vulvar pain elicited by the gentle touch of a cotton-tipped applicator is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.

b) If the woman is sexually active, determine whether cotton-tipped applicator palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:

1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis

2) Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds

3) Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechiae, dense sclerotic changes, and complete vaginal stenosis

Biopsy obtained: ☐ **Yes** ☐ **No** **Site biopsied:**_____ **GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

Change from previous evaluation: ☐ **No prior or current GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by (spell out name):_____ **Date form completed:** _____

Adapted from Jagasia et al 2015[73]

Figure 2. Form for assessment of genital GVHD.

[6,59,75,77]. About 40% of females have an abnormal cervical cytology after HCT, with 20% having high-grade cervical or lower genital tract SIL warranting treatment [59]. Thus, both cervical and vulvar precancerous lesions are potentially more common in those with cGVHD and pose an increased genital squamous cell cancer (cervical or vulvar) risk compared with the general population [1,6,77].

If the pretransplant cervical cytology and HPV testing were abnormal but not evaluated or treated, this evaluation and treatment may be undertaken after sufficient recovery of platelets and WBC count to minimize bleeding and infection risk, usually by 3 to 6 months after transplant [61]. If lesions are detected that warrant treatment, the standard approach involves an excisional procedure followed by screening the patient every 6 to 12 months until there is a normal cervical cytology, negative HPV testing, and no other HPV lesions in the genital tract [78]. Performing an excisional biopsy excludes high-grade SIL or cancer and alleviates concerns of rapid progression during transplant-related immunodeficiency or while taking immunosuppressive or immunomodulating agents. As HPV disease can occur anywhere in the lower genital tract, the examination includes inspection and assessment of the vulva, vagina, and entire anogenital region, in addition to cervical cancer screening [1,59]. Current consensus for post-HCT care recommends annual pelvic examination with cervical cytology and HPV DNA cotesting for all HCT patients annually following transplant [75,78]. ASCCP risk-based algorithms [79] include new recommendations that lengthen intervals for cervical cancer screening for immunocompromised women post-HCT to every 3 years when cytology and HPV screening are negative [80].

Primary prevention of HPV-related disease in women post-HCT includes offering 9-valent HPV vaccine post-transplant. HPV vaccines are highly immunogenic in the general

population [81]. Vaccination with 9-valent HPV vaccine post-transplant may be considered after 6 months post-transplant, whenever other routine post-transplant vaccinations are given [78]. As with other vaccinations post-HCT, the full regimen for vaccination is recommended and includes 3 doses at 0, 2, and 6 months [82]. Preliminary evidence indicates that the immunologic response to vaccination is robust and similar to that of immunocompetent women, but whether it decreases the risk of HPV disease warrants further study [83]. Because HPV incidence is high and HPV disease generally occurs later after HCT, combining vaccinating reproductive-aged women up to age 45 or 50 with periodic cervical cytology/HPV screening may be an effective strategy to reduce HPV-associated intraepithelial neoplasia and malignant disease in this population [82,84,85].

POST-HCT OVARIAN FUNCTION ASSESSMENT AND TREATMENT OF PRIMARY OVARIAN INSUFFICIENCY AND CONTRACEPTION

General Considerations

Women not taking hormones or who received GnRH agonists may experience estrogen deficiency symptoms like hot flashes and night sweats, sleep disturbance, and dyspareunia related to vaginal dryness [86]. Clinicians may recommend hormonal medications to treat these symptoms [12], and thus patients using therapies containing estrogen may not experience estrogen deficiency-related symptoms even if they have POI [5].

Post-HCT assessment of ovarian hormone production (and follicle count) is delayed until about a year post-transplant to assess whether women are estrogen deficient and have POI or that they have evidence of ovarian reserve and may be at risk of unplanned pregnancy. It is important to assess ovarian function at regular time points post-transplant (such as every 3 to 6 months during follow-up) because these women may have significant hormonal fluctuations before entering early menopause [53].

Ovarian function assessment includes testing with FSH and estradiol and may include AMH, luteinizing hormone, and progesterone levels as well as transvaginal ultrasound for antral follicle count. Although cancer survivors may initially start with lower AMH levels and antral follicle counts, the rate of change in these measures of ovarian reserve appears to be similar to similar-aged healthy women [58]. Results are interpreted considering the patient's current hormone use, current menstrual history, and prior chemotherapy, an interpretation within the scope of practice of most gynecology providers.

For those taking hormones for contraception, discontinuing them for 2 to 3 weeks before hormone testing and ultrasound may be necessary to restore hypothalamus-pituitary-ovarian axis signaling. Stopping contraceptive hormones poses a risk of pregnancy for sexually active women, and nonhormonal contraceptive methods are recommended during even brief interruption of hormones [5].

Hormonal Treatment of POI: General Considerations

When hormonal levels and transvaginal ultrasound indicate ovarian insufficiency, offering hormonal treatment (HT) is reasonable, especially to young women under 40 years who do not have contraindications to hormone use. The International Consensus Project on Clinical Practice in Chronic GVHD recommends systemic HT in these younger women regardless of symptoms [53], mirroring the HT recommendations by the American College of Obstetrics and Gynecology regarding all-cause POI [12], as estrogen deficiency can place them at increased risk of osteoporosis and cardiovascular disease over the long term. Starting treatment early after POI may be especially important for women under age 40, because delayed initiation of hormonal methods may increase these long-term risks [86,87]. HT may also be indicated to treat urogenital atrophy.

Whether a woman can use hormones and when to initiate them are dependent on her overall health, risk of venous occlusive disease related to transplant or underlying conditions, sites of GVHD, and other factors. Of note, thromboembolism risk may be less with transdermal estrogen in postmenopausal women [88]. With regards to thromboembolism risk and oral hormonal contraception containing estrogen in reproductive-aged women, the Practice Committee of the American Society of Reproductive Medicine found that tobacco use, age (>35 years), obesity, and the presence of hereditary thrombophilias increase the risk of thrombotic events (VTE) [89]. In a woman whose transplant has successfully treated an underlying cancer or hematologic condition, the VTE risk is unknown. For example, adult patients with sickle cell disease post-HCT likely experience fewer sickle crises but may still have increased VTE risk (P. Stratton, 2019). Although it is difficult to determine to what degree a specific factor increases the risk of VTE, the risks compared with the benefits regarding hormonal therapy are weighed in these particular patients. In those who do not need contraception, some advocate transdermal approaches containing physiologic doses of estradiol to lessen this risk [12,88]. However, if a woman on combined hormonal contraceptives or HT develops VTE, any estrogen-containing hormonal treatment is discontinued.

Hormonal Therapy versus Hormonal Contraception

In those with evidence of primary ovarian insufficiency, an unanswered question is whether to prescribe menopausal or contraceptive hormonal regimens as no comparative studies have been done regarding the optimal approach to replace estrogen. Physiologic estrogen doses of either hormonal contraception or menopausal HT are preferable to no therapy in preventing osteoporosis and other chronic health issues [12]. Regardless of the hormonal regimen initiated, allowing cyclic menstruation post-HCT may supplement other methods used to manage transfusion-related iron overload. Contraception may be preferable in the first 2 years post-transplant to prevent pregnancy. Additionally, many reproductive-age women prefer contraceptives their peers might use, as HT regimens are typically provided to older women [90].

Menopausal HT and contraception differ in formulation, dose, and delivery. Although hormonal contraceptive doses suppress the hypothalamic-pituitary-ovarian axis, menopausal HT with lower doses of estrogen and progestin does not, and thus may not be contraceptive. For women not needing contraception, lower dose and transdermal options exist [12,88].

Combined hormonal contraception contains ethinyl estradiol, a synthetic estrogen, at higher amounts than in menopausal HT, along with various progestins, some of which may carry higher risk for VTE [89]. In hormonal contraception, ethinyl estradiol serves as estrogen replacement but is not measured by estradiol assays. For women who do not want to take a pill every day or have contraindications to oral preparations such as gastrointestinal GVHD, other contraceptive forms of estrogen and progesterone may be offered. For example, a 0.1-mg estradiol transdermal patch combined with a progestin-releasing IUD provides estrogen replacement; the progestin IUD is contraceptive and protects the endometrium from unopposed estrogen stimulation [90].

Alternative, acceptable forms for patients needing contraception with VTE risk include a progestin-only pill [56]. One progestin, norethindrone acetate, present in many contraceptive and menopausal preparations, is metabolized into a weak estrogen and at higher doses (5 mg) increases bone mass [91]. As POI contributes to loss of bone density, a progestin-only contraceptive may not be preferred long term unless the progestin has an estrogenic action [13,90,92,93]. Medroxyprogesterone acetate in either oral or depot forms, progestin implants, and the progestin-releasing intrauterine device do not confer estrogen-related benefits. Of particular concern, medroxyprogesterone acetate increases the risk of osteoporosis [94] and sinusoidal occlusive syndrome in women after allogeneic cell transplantation and other populations [13,95,96].

Contraceptive Alternatives Other Than Oral Hormones Post-HCT

As progestin-releasing IUDs do not pose an increased risk of intrauterine infection in the general population [97], its placement after engraftment may be considered. As mentioned above, male condoms protect against STIs and are contraceptive, important options for these immunocompromised patients. For patients at minimal risk of pelvic (upper tract) infection, copper IUD and condom use may be considered after engraftment to combine a LARC with one that offers STI protection.

Sexuality and Fertility Post-HCT

As patients recover from transplant, many patients are interested in resuming a normal sex life and benefit from discussing sexual concerns with their providers [67,68]. During follow-up, the previously designated member of the transplant team can assess for sexual issues and, if desired, refer the patient to a gynecology provider. Sexual dysfunction often includes loss of libido (83%), painful intercourse (73%), and less enjoyment of sex (68%) [98] and may be attributable to several aspects of transplant (Table 5) [3]. The standardized tools described above can facilitate assessment and communication [66,69]. The PLISSIT model for counseling patients about sexuality in chronic illnesses such as cancer may be useful and advocates 4 levels of intervention organized by the acronym PLISSIT (permission, limited information, specific suggestions, and intensive therapy)– although it is not validated in HCT. Using the PLISSIT approach in patients with cancer is associated with an increased report of normalizing sexual changes and increased communication about sex with partners, but not necessarily improvement in depression or quality of life [99].

Historically, HCT with TBI and myeloablative treatment has led to infertility, but now with improved survival, after some types of cell transplant and with use of fertility preservation, women may be seeking pregnancy. Successful spontaneous pregnancies with delivery of healthy children have been reported in female HCT recipients, although the rate is less than 3% [27-30,100]. Patients who have received TBI may have a significantly higher than normal rate of preterm delivery and low birth weight babies [27,52]. These outcomes may result from impaired uterine blood flow, which may reduce uterine volume and affect implantation [51].

Pregnancies using cryopreserved embryos have been successful after HCT. In 1 report, 33 of 72 female patients younger than 42 years were offered fertility preservation and 12 accepted before transplant. Following transplant, 2 of 4 women attempting pregnancy using cryopreserved embryos were successful [101], illustrating the potential acceptance, utilization, and success of fertility preservation methods. Long-term follow-up after cancer treatment in 1 center reported a low return rate for embryo use and more pregnancies achieved by use of gestational carriers [102].

Better pregnancy outcomes, in general, and higher success rates of assisted reproductive technologies, in particular, are associated with a healthy diet and exercise, underscoring the importance of optimizing lifestyle and overall health [103]. If a woman is at least 3 to 5 years post-HCT for hematologic malignancies, is free from cGVHD, and desires pregnancy, assessments to confirm the absence of relapse are undertaken before attempting pregnancy or starting assisted reproductive technologies. Medications related to HCT or other medical conditions are reviewed for potential teratogenic or other pregnancy-related risks, so they can be discontinued or changed to safer alternatives. The woman's overall health, including late effects such as systemic or genital cGVHD and medical conditions such as hypertension and diabetes, is also assessed. Any women with genetic conditions that led to transplant, such as sickle cell anemia or inherited immunodeficiencies, are offered preconception genetic counseling.

Nongynecologic Consequences of Primary Ovarian Insufficiency

Estrogen deficiency from ovarian insufficiency increases the risk for cardiovascular disease, metabolic syndrome, mood disorders like depression and anxiety, and decreased bone mineral density, as well as all-cause mortality [12,24,104]. Although the Women's Health Initiative study initially found an increased risk of cardiovascular events on hormone therapy at a median age of 63 years, early initiation of hormones soon after menopause showed lower rates of all-cause mortality, myocardial infarction, and cancer deaths when compared with those with a later start [87,105]. In this same Women's Health Initiative study, a slight increase in breast cancer incidence in women taking the combined HT regimens was observed. Therefore, increased awareness for breast cancer screening is reasonable for those taking HT or other hormonal regimens, especially given their already elevated risk for breast cancer [78].

Loss of ovarian function at a young age has been associated with a loss of bone density and increased risk of fractures [106]. Estrogen deficiency before attaining peak bone mass at age 30 years results in lower peak bone mass, and hypoestrogenism after this age results in early bone loss [24]. In addition to estrogen deficiency, HCT patients are also predisposed to accelerated bone loss from prolonged immobility, conditioning regimens, vitamin D deficiency from recommendations to avoid sun exposure, endocrine dysfunction like hypoparathyroidism and hypothyroidism, and prolonged, high-dose corticosteroid use for GVHD [107]. In addition to using hormone therapy, patients are advised to take calcium and vitamin D and may benefit from periodic screening with a dual-energy X-ray absorptiometry to assess for bone loss [12]. Weightbearing exercise and intermittent zoledronic acid have been shown to be effective in preserving long-term bone health in adult HCT patients [105].

Long-term survivors after HCT are screened for an increased risk of cardiovascular disease, metabolic syndrome, and liver dysfunction [91]. However, screening guidelines do not consider how risks differ between women using or not using hormone therapy. Estrogen may slow early stages of atherosclerosis and have favorable endothelial effects in recently menopausal women [87,105]. Counseling should include tobacco avoidance and ways to achieve a healthy diet and

exercise. Measuring blood pressure and obtaining lipid profiles and hemoglobin A1C annually are reasonable [78].

DISCUSSION

Gynecologic care and screening vary throughout HCT (Figure 1). Optimizing the knowledge and expertise of the transplant team will improve the timing of referrals and women's health. In the pretransplant period, women are screened for STIs, advised about fertility preservation and future family building, assessed for contraceptive and menses suppression needs, and screened for cervical intraepithelial neoplasia and cancer. Sexual functioning is reviewed and anticipatory guidance provided about potential changes to sexual functioning during and after transplant. During the transplant process, a gynecologist plays a key role in managing complications of menorrhagia and guiding contraceptive and hormonal options. After transplant, regular gynecologic assessments and treatments address POI, hormone therapy, contraception, genital GVHD, STI, cervical cancer screening, and sexual functioning. After a successful transplant and recovery period, fertility can be addressed.

A close working relationship with a gynecology team will ensure that women receive optimal reproductive health care and minimize potential gynecologic and pregnancy-related complications during or after HCT. HCT clinicians who partner with gynecology providers experienced in care of post-HCT patients can provide sensitive, comprehensive care to optimize outcomes throughout the woman's life. Transplant providers could begin to address the complex reproductive health needs of female HCT patients—giving permission for women to discuss reproductive health, limited information about problems they may encounter and plans they should ponder, and then considering gynecology referral to address the Specific Suggestions and Intensive Therapy as suggested in the PLISSIT model. Specific, respectful queries about women's reproductive health and sexuality issues enable referrals to gynecology specialists to manage identified concerns. Gynecologic care of HCT patients is essential for their improved long-term wellness and quality of life.

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. Shanis D, Merideth M, Pulanic TK, Savani BN, Battiwalla M, Stratton P. Female long-term survivors after allogeneic hematopoietic stem cell transplantation: evaluation and management. *Semin Hematol*. 2012;49:83–93.
2. Hamilton BK, Goje O, Savani BN, Majhail NS, Stratton P. Clinical management of genital chronic GvHD. *Bone Marrow Transplant*. 2017;52:803–810.
3. Li Z, Mewawalla P, Stratton P, et al. Sexual health in hematopoietic stem cell transplant recipients. *Cancer*. 2015;121:4124–4131.
4. Joshi S, Savani BN, Chow EJ, et al. Clinical guide to fertility preservation in hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2014;49:477–484.
5. Chang K, Merideth MA, Stratton P. Hormone use for therapeutic amenorrhea and contraception during hematopoietic cell transplantation. *Obstet Gynecol*. 2015;126:779–784.
6. Chang HA, Armenian SH, Dellinger TH. Secondary neoplasms of the female lower genital tract after hematopoietic cell transplantation. *J Natl Compr Canc Netw*. 2018;16:211–218.
7. Tichelli A, Rovo A. Fertility issues following hematopoietic stem cell transplantation. *Expert Rev Hematol*. 2013;6:375–388.
8. Marsh JCW, Ball SE, Cavenagh J, et al. Guidelines for the diagnosis and management of aplastic anaemia. *Br J Haematol*. 2009;147:43–70.
9. ACOG Committee Opinion No. 747. Gynecologic issues in children and adolescent cancer patients and survivors. *Obstet Gynecol*. 2018;132:e67–e77.
10. Torrealday S, Kodaman P, Pal L. Premature ovarian insufficiency—an update on recent advances in understanding and management. *F1000Res*. 2017;6:2069.
11. Overbeek A, van den Berg MH, van Leeuwen FE, Kaspers GJ, Lambalk CB, van Dulmen-den Broeder E. Chemotherapy-related late adverse effects on ovarian function in female survivors of childhood and young adult cancer: a systematic review. *Cancer Treat Rev*. 2017;53:10–24.
12. ACOG Committee Opinion No. 698. Hormone therapy in primary ovarian insufficiency. *Obstet Gynecol*. 2017;129:e134–e141.
13. Tauchmanova L, Selleri C, De Rosa G, et al. Estrogen-progestin therapy in women after stem cell transplant: our experience and literature review. *Menopause*. 2007;14:320–330.
14. Lawrenz B, Fehm T, von Wolff M, et al. Reduced pretreatment ovarian reserve in premenopausal female patients with Hodgkin lymphoma or non-Hodgkin-lymphoma—evaluation by using antimullerian hormone and retrieved oocytes. *Fertil Steril*. 2012;98:141–144.
15. Dillon KE, Sammel MD, Prewitt M, et al. Pretreatment antimullerian hormone levels determine rate of posttherapy ovarian reserve recovery: acute changes in ovarian reserve during and after chemotherapy. *Fertil Steril*. 2013;99:477–483.
16. Decanter C, Morschhauser F, Pigny P, Lefebvre C, Gallo C, Dewailly D. Anti-Mullerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results. *Reprod Biomed Online*. 2010;20:280–285.
17. ASRM Practice Committee Opinion. Testing and interpreting measures of ovarian reserve. *Fertil Steril*. 2015;103:e9–e17.
18. Dunlop CE, Anderson RA. Uses of anti-Mullerian hormone (AMH) measurement before and after cancer treatment in women. *Maturitas*. 2015;80:245–250.
19. Dólleman M, Verschuren WMM, Eijkemans MJC, Broekmans FJM, van der Schouw YT. Added value of anti-Müllerian hormone in prediction of menopause: results from a large prospective cohort study. *Hum Reprod*. 2015;30:1974–1981.
20. Santoro N. Using antimullerian hormone to predict fertility. *JAMA*. 2017;318:1333–1334.
21. Sklavos MM, Stratton P, Giri N, Alter BP, Savage SA, Pinto LA. Reduced serum levels of anti-Mullerian hormone in females with inherited bone marrow failure syndromes. *J Clin Endocrinol Metab*. 2015;100:E197–E203.
22. Sklavos MM, Giri N, Stratton P, Alter BP, Pinto LA. Anti-Mullerian hormone deficiency in females with Fanconi anemia. *J Clin Endocrinol Metab*. 2014;99:1608–1614.
23. Leiding JW, Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. *J Allergy Clin Immunol*. 2012;130:1030–1048.
24. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril*. 2016;106:1588–1599.
25. ASRM Practice Committee Opinion. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy. *Fertil Steril*. 2013;100:1214–1223.
26. Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. *BMC Med*. 2016;14:1.
27. Salooja N, Szydlo RM, Socie G, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *Lancet*. 2001;358:271–276.
28. Carter A, Robison LL, Francisco L, et al. Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: report from the Bone Marrow Transplant Survivor Study. *Bone Marrow Transplant*. 2006;37:1023–1029.
29. Loren AW, Chow E, Jacobsohn DA, et al. Pregnancy after hematopoietic cell transplantation: a report from the late effects working committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). *Biol Blood Marrow Transplant*. 2011;17:157–166.
30. Nabhan SK, Bitencourt MA, Duval M, et al. Fertility recovery and pregnancy after allogeneic hematopoietic stem cell transplantation in Fanconi anemia patients. *Haematologica*. 2010;95:1783–1787.
31. Borgmann-Staudt A, Rendtorff R, Reinmuth S, et al. Fertility after allogeneic haematopoietic stem cell transplantation in childhood and adolescence. *Bone Marrow Transplant*. 2012;47:271–276.
32. Balduzzi A, Dalle JH, Jahnukainen K, et al. Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group. *Bone Marrow Transplant*. 2017;52:1406–1415.
33. Dalle JH, Lucchini G, Balduzzi A, et al. State-of-the-art fertility preservation in children and adolescents undergoing haematopoietic stem cell transplantation: a report on the expert meeting of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) in Baden, Austria, 29-30 September 2015. *Bone Marrow Transplant*. 2017;52:1029–1035.

34. Moravek MB, Confino R, Smith KN, et al. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. *Fertil Steril*. 2018;109:349–355.
35. Allen PB, Pavone ME, Smith KN, et al. The impact of fertility preservation on treatment delay and progression-free survival in women with lymphoma: a single-centre experience. *Br J Haematol*. 2018;180:901–904.
36. Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. *Fertil Steril*. 2013;100:1673–1680.
37. Hariton E, Bortoletto P, Cardozo ER, Hochberg EP, Sabatini ME. The role of oncofertility clinics in facilitating access to reproductive specialists. *J Patient Exp*. 2016;3:131–136.
38. Inhorn MC, Birenbaum-Carmeli D, Westphal LM, et al. Medical egg freezing: the importance of a patient-centered approach to fertility preservation. *J Assist Reprod Genet*. 2018;35:49–59.
39. Cil AP, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. *Fertil Steril*. 2013;100. 492-499.e493.
40. Cil AP, Seli E. Current trends and progress in clinical applications of oocyte cryopreservation. *Curr Opin Obstet Gynecol*. 2013;25:1–14.
41. Alvarez RM, Ramanathan P. Fertility preservation in female oncology patients: the influence of the type of cancer on ovarian stimulation response. *Hum Reprod*. 2018;33:2051–2059.
42. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36:1994–2001.
43. Campbell JE, Assanasen C, Robinson RD, Knudtson JF. Fertility preservation counseling for pediatric and adolescent cancer patients. *J Adolesc Young Adult Oncol*. 2016;5:58–63.
44. Pacheco F, Oktay K. Current success and efficiency of autologous ovarian transplantation: a meta-analysis. *Reprod Sci*. 2017;24:1111–1120.
45. Dolmans MM, Marinescu C, Saussoy P, Van Langendonckt A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. *Blood*. 2010;116:2908–2914.
46. Fortin A, Azais H, Uzan C, Lefebvre G, Canlorbe G, Poirot C. Laparoscopic ovarian tissue harvesting and orthotopic ovarian cortex grafting for fertility preservation: less is more. *Fertil Steril*. 2019;111:408–410.
47. Cardozo ER, Huber WJ, Stuckey AR, Alvero RJ. Mandating coverage for fertility preservation—a step in the right direction. *N Engl J Med*. 2017;377:1607–1609.
48. Ronn R, Holzer HE. Oncofertility in Canada: an overview of Canadian practice and suggested action plan. *Curr Oncol*. 2013;20:e465–e474.
49. Melan K, Amant F, Veronique-Baudin J, Joachim C, Janky E. Fertility preservation healthcare circuit and networks in cancer patients worldwide: what are the issues? *BMC Cancer*. 2018;18:192.
50. Critchley HOD, Wallace WHB. Impact of cancer treatment on uterine function. *JNCI Monographs*. 2005;2005:64–68.
51. Critchley HOD, Bath LE, Wallace WHB. Radiation damage to the uterus—review of the effects of treatment of childhood cancer. *Hum Fertil*. 2002;5:61–66.
52. van de Loo L, van den Berg MH, Overbeek A, et al. Uterine function, pregnancy complications, and pregnancy outcomes among female childhood cancer survivors. *Fertil Steril*. 2019;111:372–380.
53. Frey Tirri B, Hausermann P, Bertz H, et al. Clinical guidelines for gynecologic care after hematopoietic SCT: report from the international consensus project on clinical practice in chronic GVHD. *Bone Marrow Transplant*. 2015;50:3–9.
54. ACOG Practice Bulletin No. 128. Diagnosis of abnormal uterine bleeding in reproductive-aged women. *Obstet Gynecol*. 2012;120:197–206.
55. Patel A, Schwarz EB. Cancer and contraception. *Contraception*. 2012;86:191–198.
56. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep*. 2016;65:1–66.
57. Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in human papillomavirus-associated cancers—United States, 1999-2015. *Morb Mortal Wkly Rep*. 2018;67:918–924.
58. Cameron K, Sammel MD, Prewitt M, Gracia C. Differential rates of change in measures of ovarian reserve in young cancer survivors across the reproductive lifespan. *J Clin Endocrinol Metab*. 2019;104:1813–1822.
59. Shanis D, Anandi P, Grant C, et al. Risks factors and timing of genital human papillomavirus (HPV) infection in female stem cell transplant survivors: a longitudinal study. *Bone Marrow Transplant*. 2018;53:78–83.
60. Krajewski C, Sucato G. Reproductive health care after transplantation. *Best Pract Res Clin Obstet Gynaecol*. 2014;28:1222–1234.
61. Lees BF, Erickson BK, Huh WK. Cervical cancer screening: evidence behind the guidelines. *Am J Obstet Gynecol*. 2016;214:438–443.
62. Halperin DT, Steiner MJ, Cassell MM, et al. The time has come for common ground on preventing sexual transmission of HIV. *Lancet*. 2004;364:1913–1915.
63. Michaeli J, Weintraub M, Gross E, et al. Fertility preservation in girls. *Obstet Gynecol Int*. 2012;2012: 139193.
64. Mumma GH, Mashberg D, Lesko LM. Long-term psychosexual adjustment of acute leukemia survivors: impact of marrow transplantation versus conventional chemotherapy. *Gen Hosp Psychiatry*. 1992;14:43–55.
65. Syrjala KL, Kurland BF, Abrams JR, Sanders JE, Heiman JR. Sexual function changes during the 5 years after high-dose treatment and hematopoietic cell transplantation for malignancy, with case-matched controls at 5 years. *Blood*. 2008;111:989–996.
66. Yi JC, Syrjala KL. Sexuality after hematopoietic stem cell transplantation. *Cancer J*. 2009;15:57–64.
67. Humphreys CT, Tallman B, Altmaier EM, Barnette V. Sexual functioning in patients undergoing bone marrow transplantation: a longitudinal study. *Bone Marrow Transplant*. 2007;39:491–496.
68. Scanlon M, Blaes A, Geller M, Majhail NS, Lindgren B, Haddad T. Patient satisfaction with physician discussions of treatment impact on fertility, menopause and sexual health among pre-menopausal women with cancer. *J Cancer*. 2012;3:217–225.
69. Corona G, Jannini EA, Maggi M. Inventories for male and female sexual dysfunctions. *Int J Impot Res*. 2006;18:236–250.
70. Committee Opinion No. 606. Options for prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment. *Obstet Gynecol*. 2014;124:397–402.
71. Purisch SE, Shanis D, Zerbe C, Merideth M, Cuellar-Rodriguez J, Stratton P. Management of uterine bleeding during hematopoietic stem cell transplantation. *Obstet Gynecol*. 2013;121:424–427.
72. Ciavattini A, Clemente N. Female genital tract chronic graft-versus-host disease: review of the literature. *Anticancer Res*. 2015;35:13–17.
73. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21. 389-401.e381.
74. Friedman DL, Rovo A, Leisenring W, et al. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. *Blood*. 2008;111:939–944.
75. Inamoto Y, Shah NN, Savani BN, et al. Secondary solid cancer screening following hematopoietic cell transplantation. *Bone Marrow Transplant*. 2015;50:1013–1023.
76. Qaseem A, Lin JS, Mustafa RA, Horwitch CA, Wilt TJ. Clinical Guidelines Committee of the American College of Physicians. Screening for breast cancer in average-risk women: a guidance statement from the American College of Physicians. *Ann Intern Med*. 2019;170:547–560.
77. Curtis RE, Metayer C, Rizzo JD, et al. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. *Blood*. 2005;105:3802–3811.
78. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2012;47:337–341.
79. Demarco M, Lorey TS, Fetterman B, et al. Risks of CIN 2+, CIN 3+, and cancer by cytology and human papillomavirus status: the foundation of risk-based cervical screening guidelines. *J Low Genit Tract Dis*. 2017;21:261–267.
80. Moscicki AB, Flowers L, Huchko MJ, et al. Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. *J Low Genit Tract Dis*. 2019;23:87–101.
81. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev*. 2018;5. CD009069.
82. Tedeschi SK, Savani BN, Jagasia M, et al. Time to consider HPV vaccination after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2010;16:1033–1036.
83. Stratton P, Battiwalla M, Abdelazim S, et al. Immunogenicity of HPV quadrivalent vaccine in women after allogeneic HCT is comparable to healthy volunteers. *Biol Blood Marrow Transplant*. 2018;24:S85–S86.
84. Bosch FX, Robles C, Diaz M, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. *Nat Rev Clin Oncol*. 2016;13:119–132.
85. ACOG Practice Advisory: FDA approval of 9-valent HPV vaccine for use in women and men age 27-45. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/FDA-Approval-of-9-valent-HPV-Vaccine-for-Use-in-Women-and-Men-Age-27-45. Accessed September 5, 2019.
86. Nelson LM. Primary ovarian insufficiency. *N Engl J Med*. 2009;360:606–614.
87. Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;374:1221–1231.
88. ACOG Committee Opinion No. 556. Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. *Obstet Gynecol*. 2013;121:887–890.
89. Pfeifer S, Butts S, Dumesic D, et al. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. *Fertil Steril*. 2017;107:43–51.
90. Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone replacement therapy versus the combined oral contraceptive pill in

premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. *J Clin Endocrinol Metab*. 2016;101:3497–3505.
91. Chwalisz K, Surrey E, Stanczyk FZ. The hormonal profile of norethindrone acetate: rationale for add-back therapy with gonadotropin-releasing hormone agonists in women with endometriosis. *Reprod Sci*. 2012;19:563–571.
92. Sica S, Salutari P, Chiusolo P, et al. Hormonal therapy after stem cell transplantation and risk of veno-occlusive disease. *Blood*. 1999;93:3154.
93. Hagglund H, Remberger M, Klaesson S, Lonnqvist B, Ljungman P, Ringden O. Norethisterone treatment, a major risk-factor for veno-occlusive disease in the liver after allogeneic bone marrow transplantation. *Blood*. 1998;92:4568–4572.
94. Viola AS, Castro S, Bahamondes MV, Fernandes A, Viola CF, Bahamondes L. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. *Contraception*. 2011;84:e31–e37.
95. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women. *Circulation*. 2007; 115:840.
96. Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. *Biol Blood Marrow Transplant*. 2016;22:400–409.
97. Berenson AB, Tan A, Hirth JM. Complications and continuation rates associated with two types of long-acting contraception. *Am J Obstet Gynecol*. 2015;212:761.. e761-e768.
98. Dyer G, Gilroy N, Bradford J, et al. A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia. *Br J Haematol*. 2016;172:592–601.
99. Perz J, Ussher JM. A randomized trial of a minimal intervention for sexual concerns after cancer: a comparison of self-help and professionally delivered modalities. *BMC Cancer*. 2015;15:629.
100. Diesch T, Szinnai G, Rovo A, et al. Pregnancy rates and pregnancy outcomes after hematopoietic stem cell transplantation in childhood: a cross-sectional survey of the EBMT pediatric WP. *Blood*. 2018;132:3418.
101. Babb A, Farah N, Lyons C, et al. Uptake and outcome of assisted reproductive techniques in long-term survivors of SCT. *Bone Marrow Transplant*. 2012;47:568–573.
102. Cardozo ER, Thomson AP, Karmon AE, Dickinson KA, Wright DL, Sabatini ME. Ovarian stimulation and in-vitro fertilization outcomes of cancer patients undergoing fertility preservation compared to age matched controls: a 17-year experience. *J Assist Reprod Genet*. 2015;32: 587–596.
103. Hornstein MD. Lifestyle and IVF outcomes. *Reprod Sci*. 2016;23: 1626–1629.
104. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. *Lancet*. 2010;376:911–921.
105. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353–1368.
106. Gallagher G, Forrest DL. Second solid cancers after allogeneic hematopoietic stem cell transplantation. *Cancer*. 2007;109:84–92.
107. D'Souza AB, Grigg AP, Szer J, Ebeling PR. Zoledronic acid prevents bone loss after allogeneic haemopoietic stem cell transplantation. *Intern Med J*. 2006;36:600–603.