ADVANCED CASE DISCUSSION:
COMPLEX GYNECOLOGICAL ISSUES FACING YOUNG WOMEN
WITH HEMATOPOIETIC STEM CELL TRANSPLANT

Kate Debiec, MD and Nicole Todd, MD FRCSC
Disclosures

- Drs. Debiec and Todd have no disclosures
Learning Objectives

At the end of the presentation, through three illustrative cases, participants will be able to describe

1. Gynecologic concerns for women undergoing hematopoietic stem cell transplant
2. Pre-transplant gynecologic evaluation and counseling
3. Post-transplant gynecologic care and management
Illustrative cases

- 1. Menstrual suppression
- 2. Vulvovaginal graft versus host disease
- 3. Hormone replacement therapy for post transplant ovarian failure
Background

- **Hematopoietic stem cell transplantation** (HSCT) is the transplantation of multipotent hematopoietic stem cells, derived from bone marrow, peripheral blood, or umbilical cord blood.

- Transplant may be **autologous** (the patient's own stem cells are used) or **allogeneic** (the stem cells come from a donor).

- ~50,000 HSCT are performed each year for greater than 30 chronic and acute, malignant and non-malignant conditions.

- Of the 500,000 HSCT survivors in the US by the year 2030, 14% will be **survivors of childhood HSCT (HSCT <18 years of age)**

Auto vs allo

- **Autologous** transplant: Involves extraction of stem cells from the patient, followed by treatment with chemotherapy with or without radiation, followed by transfusion of the patient's own stem cells. Autologous transplants usually have
  - lower risk of infection during the immune-compromised portion of the treatment
  - lower risk of graft versus host disease

- **Allogeneic** transplant: Involves transfusion from a related (usually a closely HLA matched sibling), syngeneic ('identical' twin of the patient), unrelated donor (donor who is not related and found to have very close degree of HLA matching) or using umbilical cord blood. Allogeneic transplants usually have
  - higher risk of infection during the immune-compromised portion of the treatment
  - higher risk of graft versus host disease, necessitating immunosuppressive medications after transplantation
Allogeneic HSCT- Peripheral blood HSCT versus bone marrow transplant (BMT)

- Granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood stem cell transplant has become the preferred source for allogeneic HSCT

- Peripheral blood stem cell transplant is associated with
  - Faster engraftment
  - Earlier hematopoietic recovery
  - Potentially improved antileukemic effects
  - Increased chronic GVHD

Stratton, et al. 2007
Typical transplant timeline

- Urgency of transplant depends on indication
- Donor identification time can be variable
- Once a donor is identified, the recipient undergoes a preparative (also known as conditioning) regimen (1-2 weeks)
- Receives the graft infusion (1 day)
- Initial signs of engraftment occur in 10-28 days
- Repopulation of the bone marrow takes 60-90 days
### Conditions treated with hematopoietic stem cell transplants

<table>
<thead>
<tr>
<th>Allogeneic stem cell transplants</th>
<th>Autologous stem cell transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic malignancies</strong></td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Diffuse large B cell lymphoma</td>
</tr>
<tr>
<td>Peripheral T cell lymphoma</td>
<td>Peripheral T cell lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Diffuse large B cell lymphoma</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>Multiple myeloma* (in clinical trials)</td>
<td>Waldenström macroglobulinemia</td>
</tr>
<tr>
<td><strong>Nonhematologic malignancies</strong></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Immunoglobulin light chain amyloidosis</td>
</tr>
<tr>
<td>Allogeneic stem cell transplants</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td><em>Nonmalignant inherited or acquired marrow disorders</em></td>
<td></td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td></td>
</tr>
<tr>
<td>Beta cell thalassemia major</td>
<td></td>
</tr>
<tr>
<td>Refractory Diamond-Blackfan anemia</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>Idiopathic severe aplastic anemia</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td></td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td></td>
</tr>
<tr>
<td>Dyskeratosis Congenita</td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td></td>
</tr>
<tr>
<td>Congenital thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td><em>Autoimmune disease, inborn errors in metabolism, or congenital immune deficiencies</em></td>
<td></td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td></td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
<td></td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td></td>
</tr>
<tr>
<td>Krabbe disease</td>
<td></td>
</tr>
<tr>
<td>NKT cell deficiency syndromes</td>
<td></td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td></td>
</tr>
<tr>
<td>GATA2 haploinsufficiency</td>
<td></td>
</tr>
<tr>
<td>DOCK-8 deficiency</td>
<td></td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td></td>
</tr>
</tbody>
</table>
Case 1.

- JMR is a 17 year old with a history of relapsed AML, who presents prior to planned hematopoietic stem cell transplant. She was told this gynecology visit was a requirement prior to her transplant. She is not sure what that means.
  - Past Medical History: AML
  - Past Surgical History: None
  - Gynecologic History: Menarche age 12. Menses were regular, once a month, lasting 5 days, requiring 3 pads per day with minimal cramping prior to her diagnosis. Just prior to her diagnosis, she had very heavy bleeding, prompting a CBC, which led to her diagnosis. During her initial chemotherapy, she was placed on oral medroxyprogesterone for menstrual suppression. She has had some breakthrough bleeding on this method.
  - Sexual History: She has not yet been sexually active. Preferred partners would be male.
  - Vaccine History: She received all three HPV vaccines around age 15-16.
Gynecologic evaluation prior to HSCT

- **Address menstrual suppression if clinically needed**
- Sexuality counseling and education including safe sexual practices
- Fertility counseling and education (consider baseline FSH, estradiol, AMH on day 2-4 of menstrual cycle if possible)
- Gynecological examination including breast examination if indicated
- Collect Papanicolau smear if clinically indicated/insurance mandated
- Breast cancer screening if clinically indicated
  - *(Per NCCN guidelines if patient had prior thoracic Radiation Therapy (RT) between ages 10-30 years old and is 8-10 years after RT therapy or age > 40 years, then annual breasts MRI are recommended)*
- Other evaluation or testing as clinically indicated (i.e., transvaginal ultrasound, colposcopy, treatment of vaginal infection if present)
- Introductory counseling on post transplant complications
Indication for menstrual suppression/therapeutic amenorrhea

- Cytopenia during transplantation includes thrombocytopenia which can be problematic during menses
- **Moderate to severe bleeding can affect 40% of transplant** patients not receiving therapeutic menses suppression
- The choice of agent depends on time to transplant, contraceptive needs, desire for future fertility, need to manage acute uterine bleeding
- Amenorrhea is generally desired until engraftment, which generally occurs within 90 days of transplantation

Chang, et al. 2015
Options for inducing therapeutic amenorrhea

- Gonadotropin releasing hormone agonist
- Depot medroxyprogesterone acetate
- Levonorgestrel IUD
- Etonogestrel implant
- Progestin only pills
- Combined hormonal contraceptives?
GnRH Analogue

- Completely binds pituitary GnRH receptor
- Initially, stimulates pituitary to produce gonadotropins (LH/FSH) which stimulate gonads
- Chronically, LH/FSH production reduced due to down regulation of GnRH receptor and pituitary desensitization
- Results in low levels of circulating estrogen and progesterone
GnRH agonists (GnRH-a)

- Associated with high rates of amenorrhea (~80%)
- No prothrombotic effects
- After GnRH-a is given, there may be an initial flare of gonadotropins, followed by down regulation of the hypothalamic pituitary ovarian axis
  - May have withdrawal bleeding within the first 2 weeks after initial injections
  - Bleeding is more likely if injection during follicular phase
  - Bleeding most likely to be suppressed if initiated mid luteal, 1 week before next menses
- Can overlap with another short acting method if switching methods
- Because engraftment generally occurs within 90 days, dose is 11.25 mg depot leuprolide acetate IM (can be given again at 3 months if necessary, but generally limited to 3-6 months total)
  - Add back should be given if longer use of GnRH-a

Chang, et al. 2015
GnRH agonist vs depot medroxyprogesterone acetate (DMPA)

- Meirow, et al. 2006
  - Retrospective chart review of young female oncology patients with regular menstrual cycles undergoing myelosuppressive treatments.
  - Only patients who later developed severe thrombocytopenia (<25,000 platelets per μL) were included in the study. Daily blood counts, menorrhagia, nonvaginal bleeding episodes, and the need for blood products, gynecologic consultations, and other medical interventions recorded.
  - 101 women met the inclusion criteria
    - 42 patients received DMPA, 39 patients received GnRH-a, 20 patients untreated
    - General bleeding from nongynecologic sites was similar for all groups
    - Severe or moderate menorrhagia was documented in none of the 39 women who received GnRH-a, in 9 patients (21.4%) who received DMPA, and in 9 untreated patients (40%; P = .02).
    - Fewer calls for urgent gynecologic consultations were documented in the GnRH-a group compared with the untreated group (P < .0001).
Theoretical Basis GnRH-a Adjunctive Tx for ovarian protection

- Born out of observation that ovarian function less affected when chemo given before puberty
- Proposed mechanism of action:
  - Suppression of HPO axis
  - Decreased ovarian perfusion
  - Direct gonadal effect (preventing cellular apoptosis)
What does data show about GnRH-a for ovarian protection?

- **LIMITATIONS** of several published studies:
  - Non-randomized
  - Small in size
  - No controls / historical controls
  - Different length of follow-up for treatment vs. control
  - Short follow-up limiting conclusions on long-term efficacy
  - Treatment regimens differ, for both gonadotoxic treatment and GnRH-a administration protocol
  - Outcome measures differ
  - Outcome measures variably defined

Beck-Fruchter et al. 2008
Bedaiwy, et al. (2011)

- Systematic review/meta analysis of GnRH analog co-treatment for preservation of ovarian function during gonadotoxic chemo
- Six eligible trials (340 women) analyzed
- Incidence of women with spontaneous
  - *menstrual* after chemo (OR 3.46, 95% CI 1.13–10.57), favoring use of GnRH-a
  - *ovulation* after chemo (OR 5.70; 2.29–14.20), favoring use of GnRH-a (only 2 studies)
- No statistical difference between treatment and control groups in incidence of pregnancy
  (OR 0.26; 0.03–2.52) (3 studies)
Chen, et al. (2011) Cochrane Review

Review of adjuvant gonadotropin-releasing hormone analogues for prevention of chemotherapy-induced premature ovarian failure in premenopausal women

- IM/SC GnRH agonists effective in protecting menstruation and ovulation after chemotherapy; pregnancy rates not significantly different

<table>
<thead>
<tr>
<th>Resumed menses</th>
<th>1.90 (1.30 - 2.79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>0.08 (0.01 - 0.58)</td>
</tr>
<tr>
<td>Ovulation</td>
<td>2.70 (1.52 - 4.79)</td>
</tr>
<tr>
<td>Pregnancy rates</td>
<td>0.21 (0.01 - 4.09)</td>
</tr>
</tbody>
</table>

- Intranasal GnRH-a had no protective effect
Elgindy E, et al. (2015)

- Systematic review/meta analysis of RCTs comparing resumption of ovarian function between GnRH analogs + chemotherapy vs. chemotherapy alone

- 10 eligible trials (907 women) analyzed

- GnRH analog co-treatment did not significantly increase ovarian function resumption (320/468 [68.4%] in GnRH arm and 263/439 [59.9%] in chemotherapy alone arm; Risk Ratio 1.12, 95% CI 0.99-1.27)

- Spontaneous pregnancy also comparable (Risk Ratio 1.63; 0.94-2.82)
IUDs-to remove or not to remove?

- Continuation of hormonal intrauterine devices (IUDs) - widely used and highly effective contraceptives that also decrease menstrual flow - is controversial during hematopoietic stem cell transplants (SCTs) due to infectious and vaginal bleeding concerns.

- Formerly, removal of IUDs was routinely recommended.

- In 2017, Brady and colleagues reported a case of a 23-year-old nulligravid female was diagnosed with acute myeloid leukemia. She elected to retain her existing levonorgestrel-containing IUD during chemotherapy and SCT. During and following treatment, she remained amenorrheic without infection, despite severe neutropenia and thrombocytopenia. Eight months later, she remained in remission without IUD-related complications.

- Copper IUD’s do not suppress menses or decrease infection risk and should be removed.

Brady, et al. 2017
Etonogestrel implant

- Can be continued if patient has achieved amenorrhea with the implant
- Like the IUDs, due to unpredictable bleeding post-insertion of IUDs and implants, they should not be initiated as part of pre-transplant care
Short acting methods—should we use combined hormonal contraceptives?

- Combined hormonal therapies may increase risk of thromboembolism
- Incidence of venous thromboembolism in patients undergoing transplant for malignancies is 3.4-4.6%
- Many women undergoing HSCT have increased risks of thromboembolic events
  - preexisting thrombophilias
  - disease related increased risks
  - myeloablative conditioning
- Progestin-only methods such as norethindrone acetate (5 mg po daily starting dose) or medroxyprogesterone acetate (5 mg po daily starting dose) may effectively provide menses suppression
  - High dose progestins may also increase the risk of thromboembolism
- Some concern whether OCPs can be taken or absorbed in setting of mucositis
- Patches may be difficult to tolerate due to skin sensitivity
- Concerns about vaginal rings and infections preclude their use

Chang, et al. 2015
Proposed algorithm for therapeutic amenorrhea

Chang, et al. 2015
Treatment of heavy menstrual bleeding

- If no estrogen contraindications: OCPs can be used and titrated or tapered
- Continuous progestins can also be titrated and tapered as necessary
  - Oral medroxyprogesterone acetate 20 mg three times daily for 1 week, then once daily for three weeks was equally effective and tolerated in treating hemodynamically stable acute uterine bleeding compared to combined oral contraceptive pills
- GnRH-agonist (may not work in acute setting)
- If these fail to resolve issues, consider tranexamic acid, intrauterine tamponade, uterine artery embolization
  - Purisch et al describe the use of balloon tamponade as an adjunct to IV estrogen followed by oral medroxyprogesterone to control heavy bleeding just prior to induction chemotherapy, days after initiation of leuprolide intramuscularly

Case 2.

- CS is an 19 year old who underwent HSCT 2 years ago for relapsed Hodgkin lymphoma.
  - Past Medical History: Hodgkin lymphoma, Post transplant, she has had GVHD of the skin and liver.
  - Past Surgical History: None
  - Gynecologic History: Menarche age 14. Menses were regular, once a month, lasting 7 days, requiring 6 pads per day. During her initial chemotherapy, she was placed on oral medroxyprogesterone for menstrual suppression. She had resumption of menses approximately 6 months after completion of chemo. She had a recurrence and subsequently underwent HSCT after conditioning with xyz. Post transplant, she was amenorrheic and found to have primary ovarian insufficiency.
  - Sexual History: Coitarche was age 15. She has had one male partner. She was sexually active prior to her initial diagnosis. She and her boyfriend have tried to have sex post transplant, but it is too painful and all attempts have had to be stopped.
  - Vaccine History: She received a second round of all three HPV vaccines post transplant.
Graft versus host disease

- Chronic graft versus host disease is a systemic immune disorder and the most common late complication of allo HSCT
  - Typically occurs several months post transplant
  - Skin, mouth, eyes, liver and gut are the most commonly involved organs
  - Chronic GVHD after peripheral blood HSCT tends to be more protracted, less responsive to glucocorticoids and more commonly involves skin, vagina and vulva

Stratton, et al. 2007
Vulvovaginal GVHD

- **Occurrence of vulvar GVHD** after traditional bone marrow transplant (BMT) ~25%
- **Occurrence of vulvar GVHD** after peripheral blood HSCT ~35% at 1 year and 49% at 2 years
- Identification of vulvovaginal GVHD has been noted up to 8 years post transplant (median time 7-10 months)
- **Vulvar GVHD precedes vaginal GVHD**, so early recognition and treatment is important
- Hypoestrogenism from chemotherapy-induced ovarian failure can contribute to the sequelae of chronic GVHD
- Vulvovaginal GVHD may worsen with flaring of other chronic GVHD sites, like during viral illnesses

Vulvovaginal GVHD

- **Symptoms**
  - dryness, burning, itching, pain, pain with urination and dyspareunia
  - Amenorrhea and cyclic pain due to hematocolpos or inability to insert a tampon can be a symptom of severe GVHD

- **Signs**
  - patchy or generalized erythema, tenderness with q-tip test, erosions, fissures, labial resorption, clitoral hood agglutination, vaginal synechiae, dense vaginal stenosis

- Symptoms can mimic genital atrophy, but patients with genital GVHD more likely to have tenderness to tuch, vulvar erythema, fissures, open flat (HSV negative) sores, vaginal scarring

- Vulvodynia and vestibulitis may be indistinguishable from mild vulvar GVHD

Shanis et al. 2012
Scoring of Vulvovaginal GVHD

Severity Scoring for Vulvovaginal Graft-Versus-Host Disease

Grade I (Minimal)
- Generalized erythema and edema of vulvar structures
- Patchy erythema of mucosa and glandular structures of vulvar vestibule
- Erythema around openings of vestibular (Bartholin’s & Skene’s) glands

Grade II (Moderate): Grade I findings plus
- Erosions of mucosal surfaces of the vulva
- Fissures in vulvar folds (eg, interlabial sulci; fourchette)

Grade III (Severe): Grade II findings plus
- Agglutination of clitoral hood
- Introital stenosis
- Vaginal synechiae
- Hematocolpos or complete vaginal closure
- Fasciitis or spasticity of levator sling

Stratton, et al. 2007
Clinical Examples

Fig. 1. A. Mild vulvar graft-versus-host disease. Vulvar erythema is indicated by arrow. B. Moderate vulvar graft-versus-host disease. Vulvar fissure is indicated by arrow. C. Severe vulvar graft-versus-host disease. Clitoral agglutination is indicated by black arrow; vulvar erosion indicative of moderate vulvar graft-versus-host disease is indicated by white arrow.

Labial adhesions

FIGURE 2. Complete labial fusion before and after treatment. A, Complete labial fusion is noted on casual inspection of external genitalia. B, Lysed labial adhesion immediately after surgery. C, External genitalia agglutination at 1 month after surgery.

Scrivani 2017
Vulvovaginal scarring

- Vulvar adhesions can be treated topically or with lysis of adhesions (in OR or outpatient)
- Vaginal scarring can appear as filamentous fibrous strands, arcuate or purse-string bands with vaginal narrowing and scarring between anterior and posterior vaginal walls that can obliterate the vaginal canal
  - Filamentous scars can easily be lysed
  - More severe adhesions may need to be treated with lysis of adhesions in the OR
  - In one series, 63% required surgery for vaginal GVHD despite treatment of vulvar GVHD
  - Surgical treatment may be required in women who are menstruating if vaginal adhesions are not treated and hemotocolpos ensues

Treatment of Vulvovaginal GVHD

- Most women in the NIH cohort (33 women treated between 1999-2006) were treated with
  - High dose topical steroid ointments and topical estrogen
    - twice a day to vulva for 6 weeks
    - Once daily for 4-6 weeks
    - 2-3 times weekly for maintenance
  - When improvement permitted, vaginal dilators, topical estrogen and clobetasol were used 2-3 times per week for sexually active patients to lyse vaginal synechiae
  - After adequate vaginal diameter and depth was restored, estradiol vaginal ring was used continuously for 3 months
  - Women with ovarian function or those receiving hormone therapy were noted to heal more rapidly, so hormone replacement was provided as an adjunct
  - *This may also be in combination with systemic treatments for GVHD in other organs

Stratton, et al. 2007
Sexual dysfunction and quality of life may also be impacted by other factors after GVHD

- Nearly half of patients have impaired sexual function after HSCT, contributing to anxiety, depression, decreased self-esteem and stress
- HSCT survivors may have double the prevalence of psychiatric disorders than the general population, with 5% meeting criteria for PTSD
- 77% of cancer patients reported severe problems with at least one sexual health domain (libido, vaginal dryness, dyspareunia, satisfactions) at 1 year follow up
- Women were less likely than men to return to baseline sexual function, even after long-term follow up

Li, 2015
Screen and Manage Sexual Dysfunction

- Screen for sexual dysfunction: use self report, standardized questionnaires
- Screen and treat depression or anxiety
- Sex therapy to treat psychosocial stressors
- Treat GVHD
- Use of hormonal therapy for women with ovarian failure
- Address infertility with a reproductive endocrinologist

Li, 2015
Case 3.

- FJ is an 18 year old with a history of allogeneic HCST for relapsed AML who presents for consultation one year post transplant. Her primary concern is that she has been having ~ 20 hot flashes per day for the past 2 months.
  - Past Medical History: AML, with transplant complications including line associated DVT and gut GVHD
  - Past Surgical History: None
  - Gynecologic History: Menarche age 14. Menses were irregular, once every 4-8 weeks, lasting 3-8 days, some heavier, some lighter prior to her diagnosis. Just prior to her diagnosis, she had very heavy bleeding, prompting a CBC, which led to her diagnosis. She was on oral medroxyprogesterone for menstrual suppression throughout transplant and discontinued approximately 3 months ago.
  - Sexual History: She has not yet been sexually active. Her chosen partners would be female.
  - Vaccine History: She received all three HPV vaccines around age 15-16.
Endocrine consequences of HSCT

- Thyroid function
  - Busulfan conditioning can manifest in a range of thyroid dysfunction

- Bone health
  - Avascular necrosis of bone occurs in more than 10% of BMT survivors

- Gonadal function
  - Ovarian failure
  - Diminished ovarian reserve
  - Fertility and hormone implications

Risk of post-transplant ovarian failure

- Conditioning regimen (chemo with or without radiation) can lead to post-transplant ovarian failure in 65-84% of patients
  - Regimens are classified as myeloablative, reduced intensity, and nonmyeloablative
  - In some cases, transplant is performed without conditioning (ie. severe combined immunodeficiency)

- The preparative regimen is the only gonadotoxic aspect, but some women have received gonadotoxic chemo for their underlying diagnosis prior to transplant
Transient ovarian failure

- Menstrual suppression is generally continued for at least 90 days post transplant, so ovarian status difficult to assess initially
- Transient post transplant ovarian dysfunction can be common in the first 2 years after transplant, even for women who resume normal menses
- Ovarian damage may result in premature menopause, even for those who resume menses

Presenting signs and symptoms

- **Symptoms**
  - Menstrual abnormalities, amenorrhea, hot flashes, sleep disturbances, vaginal dryness, dyspareunia, mood disturbances, musculoskeletal pain

- **Signs**
  - Reduced estradiol levels, elevated gonadotropins (FSH >30 u/L), negative pregnancy test
Hormone replacement therapy

- Improves vasomotor and urogenital symptoms
- Increases measures of psychological well being
- Has little effect on sexual desire or dissatisfaction
- There is no clear recommendation for ovarian failure and contraception post allo-HSCT
  - Risks and benefits individualized based on severity of symptoms, underlying disease status, contraindication to hormones (clot/active liver disease)
- For women under age 35 at transplant, hormone therapy can help to acquire bone mass
- There may be a role for stopping therapy every few years to assess HPO axis

Shanis et al. 2012
# Ovarian insufficiency/failure treatment options

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Continuous</th>
<th>Progestogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 mg micronized 17β-estradiol (oral)</td>
<td>2.5–5 mg medroxyprogesterone acetate daily (oral)</td>
<td>10 mg medroxyprogesterone acetate daily (oral) for 12 days each month</td>
</tr>
<tr>
<td>100 micrograms 17β-estradiol (transdermal)</td>
<td>100 mg micronized progesterone daily (oral)</td>
<td>200 mg micronized progesterone daily (oral) for 12 days each month</td>
</tr>
<tr>
<td>0.625–1.25 mg conjugated equine estrogen (oral)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Select one of the estrogen options to be combined with one of the progestogen options.*

ACOG Committee Opinion 698
Combined hormonal contraceptives (CHCs) for primary ovarian insufficiency (POI)

- The dose of estrogen and progestin in CHCs is not replacement dosage; CHCs are significantly more potent than the HT options.
- No randomized trials compare HT with CHCs in women with POI to determine cardiovascular risk, quality-of-life measures, or bone health.
- Doses of estrogen provided in HT are less potent than the estrogen in combined hormonal contraceptives, so HT may have a lower risk of venous thromboembolism.
- Treatment for all women with primary ovarian insufficiency should continue until the average age of natural menopause is reached (age 50–51 years).
Contraception in the setting of ovarian failure

- CHCs prevent ovulation and pregnancy more reliably than HT
- Can consider levonorgestrel intrauterine device with HT estrogen.
- Barrier methods of contraception also may be used.
Fertility and pregnancy concerns

- Reduced-intensity HSCT is more effective at preserving fertility than myeloablative transplant
- In addition to decreased fertility, pregnancies after allo transplant
  - *Increased low birth weight, preterm delivery, c-section*
- After TBI
  - *Patients with decreased uterine volume have increased risk of spontaneous abortion, even with donor oocytes*
  - *Intrauterine growth restriction, abnormal placentation, uterine rupture*

Shanis et al. 2012
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

Shanis et al. 2012
• 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

Shanis et al. 2012
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 dyshpareunia, hypoactive sexual desire, and dysfunction with arousal or orgasm
  - Treat any underlying endocrine or medical conditions
  - Consider vaginal estrogen or lubricants for dyshpareunia from atrophic vaginitis
  - Refer to psychologist for individual or couples therapy

Shanis et al. 2012


Cupit MC, Duncan C, Savani BN, Hashmi SK. Childhood to adult transition and long-term follow-up after blood and marrow transplantation. Bone Marrow Transplantation (2016) 51: 176-181

References