If you work with young female cancer survivors, come attend this comprehensive session on premature ovarian failure (POF). You’ll identify the causes of POF, learn about assessing at-risk patients, and hear how treatment strategies can minimize its impact. You’ll also discuss its impact on physical, emotional, reproductive, and sexual health, and what you can do to promote quality of life under these challenging conditions.

Content Area: Clinical Practice

Content Level: Intermediate

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Full Disclosure:
Intends to discuss unapproved/investigational use of a commercial product/device during this educational activity

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Full Disclosure:
Nothing to Disclose

Objectives:
At the end of this session, participants will be able to:
1. Identify female cancer survivors who are at risk for premature ovarian failure.
2. Generate a treatment plan for premature ovarian failure, whether for at-risk patients or for cancer survivors who have developed it.

Content Outline:
I. Premature ovarian failure (POF)
   A. Definition
   B. Etiology in cancer survivors
   C. Manifestation
      1. Infertility
      2. Premature menopause
   D. Impact on physical, reproductive, sexual, and psychosocial health
II. Pretreatment strategies to prevent or minimize the risk and impact of POF
   A. Treatment planning
   B. Fertility preservation
III. Post-treatment assessment for POF
   A. Identifying patients at risk
   B. Assessment parameters
      1. Biologic markers
      2. Menopausal symptoms
      3. Bone health
      4. Cardiac health
   C. Referrals for additional assessment
IV. Post-treatment strategies to manage POF and its impact on physical, reproductive, sexual, and psychosocial health
   A. Education
   B. Medical treatment
   C. Behavioral strategies
   D. Supportive strategies

Bibliography:
Ovarian Function

**Folliculogenesis**
- Development of mature oocytes

**Hormone secretion**
- Support ovulation, fertilization, and implantation

Premature Ovarian Failure

**Definition**
- Premature ovarian dysfunction
- Premature menopause
- Hypergonadotropic hypogonadism
- Ovarian dysgenesis

**PRIMARY OVARIAN INSUFFICIENCY**

Premature Ovarian Failure

**Etiology**

- Follicle Depletion or Follicle Dysfunction
  - Idiopathic
  - Chromosomal abnormalities/genetic defects
  - Autoimmune disease
  - Infection
  - Environmental
  - Iatrogenic

**Spectrum of Clinical Findings**

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>FSH</th>
<th>Fertility</th>
<th>Menses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Regular</td>
</tr>
<tr>
<td>Occult</td>
<td>Normal</td>
<td>Reduced</td>
<td>Regular</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Elevated</td>
<td>Reduced</td>
<td>Regular</td>
</tr>
<tr>
<td>Overt</td>
<td>Elevated</td>
<td>Reduced</td>
<td>Irregular or absent</td>
</tr>
</tbody>
</table>

Adapted from Welt 2007

Premature Ovarian Failure

**Etiology**

- Chemotherapy (alkylating agents)
- Pelvic RT (ovarian exposure)
- Pelvic surgery (oophorectomy or damage to ovarian blood vessels)
Premature Ovarian Failure
Health Implications

Goal is to prevent delay in diagnosis and treatment to minimize subsequent health problems

- Identify patients who are at risk
- Monitor regularly at follow up visits
- Inform patients of risk and need to contact you for signs or symptoms of POF

Systemic Symptoms

- Vasomotor symptoms
  - Hot flushes/flashes
  - Night sweats
- Sleep disturbances
- Mood disturbances
- Cognitive changes
  - Memory loss
  - ↓ Cognitive function

Assessment

- Presence of symptoms of estrogen deficiency
- Presence and regularity of menses
- Biologic markers
  - FSH (Follicle Stimulating Hormone)
  - LH (Luteinizing Hormone)
  - Estradiol

Ovarian function cannot be reliably assessed if on hormone therapy

Management

- Nonhormonal therapies – some evidence
  - SSRIs – venlafaxine, paroxetine
  - Gabapentin
  - Clonidine
- Natural supplements – no evidence
  - Vitamin E, phytoestrogens, black cohosh
- Behavioral interventions
  - Maintaining a cool environment
  - Dressing in light cotton clothing
  - Complementary therapies

Hormone Replacement Principles

- Unless there is an absolute contraindication, prescribe estrogen therapy, not just to treat systemic symptoms, but to prevent other health effects of estrogen deficiency
- Stress need to consider this as just one part of an overall strategy to address POF
  - Lifestyle behaviors regarding diet, exercise, smoking avoidance, and alcohol consumption are equally important

References

Goodman et al. 2011; Maclaran & Panay 2011; Metzger et al. 2013

Ovarian function cannot be reliably assessed if on hormone therapy

Maclaran & Panay 2011; Rosenberg & Partridge 2013
**Hormone Replacement Principles**

- Anticipate potential resistance because of reported breast cancer and cardiovascular risks in post-menopausal women
- Explain that there is no evidence that these results are relevant for young women replacing hormones that should be present naturally to maintain health

**Hormone Replacement Principles**

- Select a regimen that mimics normal physiology as much as possible – continue until the average age of menopause
- No solid evidence regarding optimal regimen
  - Estrogen ± Progestin
  - Combined oral contraceptives

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**Hormone Replacement Estrogen**

- 17-beta estradiol is the principal estrogen produced by the ovary
  - Transdermal (100 mcg/day) patch
  - Oral (2 mg/day)
- Benefits of transdermal route
  - Avoids first pass hepatic metabolism
  - Delivers dose by steady absorption
  - ↓ Risk of VTE and gall bladder disease

**Hormone Replacement Progestin**

- For women with an intact uterus, to reduce the risk of endometrial hyperplasia and carcinoma
  - Medroxyprogesterone acetate (10 mg daily or for at least 12 days/month)

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**Hormone Replacement Combined Oral Contraceptives**

- Provide higher dose than needed for physiologic replacement
- May be more acceptable by young women
- Also provides contraception
  - 5-10% spontaneous pregnancies despite POF

**Hormone Replacement Contraindications**

- Hormone-sensitive tumor (e.g., breast, uterus)
- History of thromboembolic disorder (DVT/VTE)
- History of cerebrovascular/cardiovascular disease
- Impaired liver function
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
### Bone Health

- ↓ Bone density from accelerated bone loss
- ↑ Risk osteopenia and osteoporosis
  - Severity related to duration of estrogen deficiency
- ↑ Risk of fractures


#### Bone Health Assessment

- Additional risk factors
  - Maternal or personal history of hip fracture
  - Tall or thin in stature
  - Medication that can cause bone loss
    - Examples - steroids, Dilantin
    - Type I diabetes
    - Hyperthyroidism, hyperparathyroidism

#### Bone Health Assessment

- Laboratory tests
  - Calcium
  - 25(OH) Vitamin D
- DXA Scan (Bone mineral density)
  - Interpretation of T-Score
    | Score          | Status   |
    |----------------|----------|
    | -1 and above   | Normal   |
    | Between -1 and -2.5 | Osteopenia |
    | -2.5 and below | Osteoporosis |

Holick et al. 2011; Ross et al. 2011; NOF

### Cardiovascular Health

- ↑ Morbidity and mortality from CV disease
- Impaired function of vascular endothelium
- Altered lipid profile


#### Cardiovascular Health Assessment

- Blood pressure
- BMI (body mass index)
- Insulin
- Lipoproteins
- Fasting glucose
Cardiovascular Health Management

- Lifestyle behaviors
  - Avoid smoking
  - Nutrition - heart healthy diet
  - Weight management
  - Exercise
- Medication
  - Hypertension
  - Hyperlipidemia

Sexual Health

### Urogenital Symptoms

**Vaginal**
- Dryness
- Itching
- ↓ Elasticity
- Stenosis
- Dyspareunia

**Urinary**
- Frequency
- Stress incontinence
- Recurrent cystitis

### Sexual Health Assessment

**Normalizing Statement**
"Many men/women who have undergone POF have questions or concerns about how this will affect their sexuality."

**Open-Ended Question**
"Do you have any questions or concerns related to sex that you would like to talk about?"

**Directed Questions**
- "Have you had vaginal dryness or pain w/ intercourse?"
- "Has this been bothersome to you?"
- "Has this affected your relationship with your partner?"

### Sexual Health Management

- Hormone replacement (systemic, topical)
- Moisturizers
- Lubricants
- Vaginal dilators
- Pelvic floor exercises
- Vibrators or clitoral stimulators

### Reproductive Health

- Infertility
- 5-10% chance of spontaneous pregnancy in women with POF

### Pre-Treatment Fertility Preservation

- Cryopreservation of Gametes or Gonadal Tissue
  - Oocyte
  - Embryo
  - Ovarian tissue
- Reduction of Gonadal Toxicity
  - Ovarian transposition
  - Ovarian suppression
  - Alternative treatment
Reproductive Health Management

- Inform patients of their risk of infertility
- Explain that menses ≠ fertility
- Suggest patients start family building early

Reproductive Health Management

- Consider referral to reproductive endocrinologist

<table>
<thead>
<tr>
<th>Regular menses</th>
<th>Normal FSH</th>
<th>Refer to RE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular menses</td>
<td>↑FSH</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>Normal FSH</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>↑FSH</td>
<td>Educate and counsel re alternative family building options</td>
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</tbody>
</table>

Reproductive Health Management

Family Building Options

<table>
<thead>
<tr>
<th>Biologic Child</th>
<th>Alternative Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural conception</td>
<td>Donor egg</td>
</tr>
<tr>
<td>IVF → embryo transfer</td>
<td>Donor embryo</td>
</tr>
<tr>
<td>Thawed eggs/embryos → embryo transfer</td>
<td>Adoption/foster parenting</td>
</tr>
<tr>
<td>Surrogacy/gestational carrier</td>
<td>Child-free living</td>
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</tbody>
</table>

Factors Influencing Decision-Making

- Ovarian reserve
- Ability to carry a pregnancy
- Acceptance of assisted reproductive technology
- Comfort with having a non-biologic child
- Religious, cultural, ethical beliefs
- Financial resources

Emotional Well-Being

- Loss of fertility can threaten one’s meaning and purpose in life
- Anxiety, depression, grief
- ↓ Self-esteem and life satisfaction

Emotional Well-Being Management

- Inform patients of their risk
- Provide clear, direct, honest information
- Acknowledge and validate the grief many women will express in response to the diagnosis

“Many women with POF say that they have a difficult time emotionally when they learn of the diagnosis and that it takes time to accept”

Groff et al 2005; Rosenberg & Partridge 2013; Singer et al 2011; Sterling & Nelson 2011
### Emotional Well-Being Management

- **Develop a plan**
  - Teach strategies for addressing specific health effects
  - Introduce options for family building

- **Refer as indicated**
  - Reproductive specialists
  - Mental health specialists

Groff et al 2005; Rosenberg & Partridge 2013; Singer et al 2011; Sterling & Nelson 2011

### Emotional Well-Being Management

- **Provide resources for information and support**
  - Children’s Oncology Group: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers – Female Health Issues (survivorshipguidelines.org/pdf/FemaleHealthIssues.pdf)
  - International Premature Ovarian Failure Association (www.ipofa.org)
  - National Osteoporosis Foundation (http://nof.org)
  - The North American Menopause Society (www.menopause.org)
  - Women’s Health.gov (www.womenshealth.gov/menopause)