Management of Patients With Premature Ovarian Insufficiency

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Premature Ovarian Insufficiency (POI)

- Premature ovarian insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40.

- POI is characterised by:
  - Menstrual disturbance (amenorrhea or oligomenorrhea)
  - Raised gonadotropins
  - Low estradiol
Premature Ovarian Insufficiency (POI): Definitions

- The terms "Premature menopause" and "Premature ovarian failure" were used in the past for POI, but both inaccurate.
  - Because ovarian function is intermittent or unpredictable in many cases (46 XX, 50-75%)
  - In 5-10 percent of cases, women conceive and have a normal pregnancy
- "Premature ovarian insufficiency" is the preferred term to describe this condition.

Practice Committee of ACOG 2016
Guideline of the ESHRE 2015
POI – Prevalence

- The prevalence of POI approximately 1%

- Age specific incidence:

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1/10,000</td>
</tr>
<tr>
<td>&lt;30</td>
<td>1/1,000</td>
</tr>
<tr>
<td>&lt;35</td>
<td>1/250</td>
</tr>
<tr>
<td>&lt;40</td>
<td>1/100</td>
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</table>
Diagnosis of POI

- The diagnosis of POI is based on the presence of menstrual disturbance and biochemical confirmation

- <40 years

- ≥4 months, oligomenorrhea or amenorrhea

- Two serial measurements of elevated FSH
  >25 IU/L taken 4 weeks apart

Nelson, NEJM 2009
POI – Clinical Features

POI is characterised by

- Menstrual disturbance
- Raised gonadotropins
- Low estradiol
- Estrogen deficiency symptoms and consequences
- Serum AMH levels, direct markers of ovarian reserve
POI – Importance of Early Diagnosis

• Early diagnosis of POI is important for osteoporosis prevention (and possibly prevention of later coronary heart disease)

• Many women experience a significant delay in diagnosis after the onset of a disordered menstrual pattern

• As long as a five year delay in 25 percent of women

• Over 50 percent of young women with spontaneous POI have reported seeing three or more clinicians before the diagnosis

• Loss of menstrual regularity may be a sign of ovarian insufficiency and the associated estrogen deficiency

Alzubaldi, Obstet Gynecol 2002
Fritz MA, Speroff, Clinical Gynecologic Endocrinology and Infertility 2011
POI – Etiology

- Follicle depletion
- Follicle dysfunction

It is often caused by:
- Chromosomal abnormalities and genetic defects
- Damage from prior ovarian surgery, chemotherapy or radiation therapy
- Autoimmune ovarian damage
- Idiopathic
- A family history of POI, approximately 10 percent of cases are familial
POI – Etiology

● Chromosomal and genetic defects

● 10-13% women diagnosed with POI have chromosomal abnormalities
  X chromosomal abnormalities (X structural abnormalities or X aneuploidy, 94%)

● Turner syndrome (45X)

● Fragile X (FMR1) premutation, testing is indicated in POI women
  • 6 percent of cases of POI are associated with premutations in the FMR1 gene

Kumar, Ind J Med Res 2012
POI – Etiology

Caused by autoimmune ovarian damage

- Autoimmune disorders are more frequent in POI than in the general population.
- POI is more frequent in women with certain autoimmune disorders.
- The most clinically association is with autoimmune Addison’s disease, in the autoimmune polyendocrine syndrome (APS).
- Addison’s disease and APS type 2 are known to predispose to POI (is found 3-4% in POI cases).

La Marca, Curr Opin Obstet Gynecol 2010
POI – Etiology

Thyroid autoimmunity

- POI is associated most commonly with thyroid autoimmunity
- Young women with spontaneous POI are also at increased risk of autoimmune hypothyroidism and should be screened for this condition.
POI – Additional Evaluation

POI may also be associated:

- Thyroid diseases
- Hypoparathyroidism
- Type 1 diabetes mellitus

with localised or systemic non-adrenal disorders

- Systemic lupus erythematousus (SLE)
- Sjögren’s syndrome
- Rheumatoid arthritis
- Immune thrombocytopenic purpura (ITP)
- Autoimmune haemolytic anemia
- Pernicious anemia
- Vitiligo
- Multiple sclerosis
- Coeliac disease
- Myastenia gravis
Additional Evaluation – POI

Genetic / Chromosomal

- Chromosomal analysis should be performed in all women with non-iatrogenic POI (among younger women with secondary amenorrhea 13% have an abnormal karyotype)

- Gonadectomy should be recommended for all women with detectable Y chromosomal material

- Fragile-X premutation testing is indicated in POI women (approximately 6% of cases of POI are associated with premutations in the FMR1 gene)

Guideline of the ESHRE 2015
Additional Evaluation – POI
Autoimmune Evaluation

Test for adrenal antibodies

- Screening for 21OH-Ab (or alternatively adrenocortical antibodies - ACA) should be considered in women with POI of unknown cause or if an immune disorder is suspected

(approximately 3-4% of women with spontaneous POI found asymptomatic autoimmune adrenal insufficiency)

- Refer POI patients with a positive 21OH-Ab – ACA test to an endocrinologist for testing adrenal function and to rule out Addison’s disease

Guideline of the ESHRE 2015
Additional Evaluation – POI

Autoimmune Evaluation

- Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI

- In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year

- If 21OH-Ab / ACA and TPO-Ab are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of these endocrine disease develop
# POI – Summary of diagnostic workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive test</th>
<th>Negative test</th>
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</thead>
<tbody>
<tr>
<td>Genetic/Chromosomal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotyping (for diagnosis of Turner syndrome)</td>
<td>Refer to endocrinologist, cardiologist and geneticist</td>
<td>A second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)</td>
</tr>
<tr>
<td>Test for Y-chromosomal material</td>
<td>Discuss gonadectomy with the patient</td>
<td></td>
</tr>
<tr>
<td>Fra-X</td>
<td>Refer to geneticist</td>
<td></td>
</tr>
<tr>
<td>Autosomal genetic testing&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA/21OH antibodies</td>
<td>Refer to endocrinologist</td>
<td>Re-test in case of clinical signs or symptoms</td>
</tr>
<tr>
<td>TPO-Ab</td>
<td>Test TSH every year</td>
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<sup>1</sup> not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).

<sup>2</sup> POI of unknown cause or if an immune disorder is suspected.
What are the implications for relatives of women with POI?

- Relatives of women with the fragile-X premutation should be offered genetic counseling and testing.
- Currently there is no proven predictive test to identify women that will develop POI.
- There are no established POI preventing measures.
- Fertility preservation appears as a promising option, although studies are lacking.
- Potential risk of earlier menopause should be taken into account when planning a family.

Guideline of the ESHRE 2015
POI – Emotional Health

- The diagnosis of POI is emotionally traumatic for most women
- Because it disrupts their
  - Life plans
  - Hopes
  - Dreams with regard to raising family
- Women with POI may develop related
  - Depression
  - Anxiety disorders
- POI benefit from
  - Encouragement
  - Support
- The first step is encourage a woman with POI and her partner
Sequelae of POI

POI – Life Expectancy

- Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease (CVD)

- To reduce cardiovascular risk factors:
  - Stop smoking
  - Taking regular exercise
  - Maintaining healthy weight

Guideline of the ESHRE 2015
POI – Fertility

- Women with POI should be informed that there is a small chance of spontaneous pregnancy (5-10%).
- Should be advised to use contraception if they wish to avoid pregnancy (OCP, Barrier methods, IUD).

Guideline of the ESHRE 2015
POI – Fertility Intervention

- There are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.
- Oocyte donation is an established option for fertility in women with POI.
- In women established POI, the opportunity for fertility preservation is missed.
POI – Bone Health

- POI is associated with reduced bone mineral density (BMD)

- For to optimise bone health maintain a healthy lifestyle:
  - Maintenance of normal body weight
  - Avoidance of smoking
  - Weight-bearing exercise
  - A balanced diet, calcium 1200-1500 mg/d, Vit D 1000 U/d

- Estrogen replacement is recommended to maintain bone health and prevent osteoporosis

- The OCP may be appropriate for some women

Guideline of the ESHRE 2015
POI – Bone Health - Monitoring

- Measurement of BMD at initial diagnosis of POI should be considered for all women.

- If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DEXA scan is low.

- If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years.
POI – Cardiovascular Health

- Women with POI are at increased risk of CVD
- Stop smoking, regular exercise, healthy weight
- All women diagnosed with Turner syndrome should be evaluated by a cardiologist
- HRT with early initiation is strongly recommended in women with POI to control future risk of CVD
- It should be continued at least until the average age of natural menopause

Guideline of the ESHRE 2015
POI – Quality of Life

- A diagnosis of POI has a significant negative impact on psychological wellbeing and quality of life

- Psychological and lifestyle interventions should be accessible to women with POI
POI – Genito-urinary Symptoms

- Local estrogens are effective in treatment of genito-urinary symptoms

- Clinicians should be aware that despite seemingly adequate systemic hormone replacement therapy (HRT), women with POI may experience genito-urinary symptoms. Local estrogens may be given in addition to systemic HRT
POI – Hormone Replacement Therapy (HRT)

- Hormone replacement therapy is indicated for the treatment of symptoms of low estrogen in women with POI.

- Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause.

- Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus.
POI – HRT

1. 17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.

2. Women with POI, using HRT should have a clinical review annually, paying particular attention to compliance.

3. No routine monitoring tests are required but may be prompted by specific symptoms or concerns.

Guideline of the ESHRE 2015
POI – HRT and Special Issues

- **Turner syndrome**: Should be offered HRT throughout the normal reproductive lifespan
- **HRT** is generally contraindicated in **breast cancer** survivors
- **Endometriosis**: Combined estrogen/progestogen therapy can be effective for the treatment of vasomotor symptoms

*Guideline of the ESHRE 2015*
POI – HRT and Special Issues

- **Migraine:** Should not be seen as a contraindication to HRT use by women with POI. Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine sufferers with aura.

- **Hypertension:** Should not be considered a contraindication to HRT. Transdermal estradiol is the preferred method.

*Guideline of the ESHRE 2015*
POI – HRT and Special Issues

- **History of prior venous thromboembolism (VTE):** Should be referred to a haematologist prior to commencing HRT. Transdermal estradiol is the preferred method for women increased risk of VTE.

- **Obesity:** Transdermal estradiol is preferred.

- **Fibroids:** are not a contraindication to HRT use by women with POI.
Summary – Management of POI

- The management of women with POI begins with informing the patient of the diagnosis in a sensitive and caring manner

- Hormone replacement therapy

- Fertility:
  - Women with POI should be informed that there is a small chance of spontaneous pregnancy
  - Oocyte donation, IVA
  - In women with established POI, the opportunity for fertility preservation is missed
Thank you...