Premature Ovarian Insufficiency
Premature Ovarian Insufficiency (POI)

- POI is a clinical syndrome defined by loss of ovarian activity before the age of 40 *(ESHRE 2015)*.
- Characterised by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol.
- Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease.
- Modifiable factors may include:
  - *gynaecological surgical practice*
  - *lifestyle: smoking*
  - *modified treatment regimens for malignant and chronic diseases*

*Distribution of age at menopause*
Epidemiology

World

• Incidence of POI before 40 yrs ~1%
• Incidence of POI before 30 yrs - 0.1%
• ~10% to 28% experience primary amenorrhea
• ~4% to 18% exhibit secondary amenorrhea
• Prevalence of menopause varies according to age:
  – 1 : 10,000 at the age of 18-25 years
  – 1 : 1000 in women aged 25-30 years
  – 1 : 100 in the age range 35-40 years

India

• According to the Indian National Family Health Survey (NFHS-3) 2005-2006, about 18% married women in the age group of 30-49 yr reached menopause
• 3.1% of women in 30-34 yr and 8% in 35-39 yr were in menopause (NFHS-2)
Etiology

• Chromosomal and genetic defects – X chromosomal abnormalities or aneuploidy, Y chromosome abnormalities, fragile-X syndrome, autosomal gene defects, gonadal dysgenesis with or without Turner syndrome
• Autoimmune disorders
• Infections
• Iatrogenic cause – surgery, radiotherapy, or chemotherapy
• Environmental factors
• Idiopathic – cause remains elusive
Inflammatory aging refers to a chronic and low-degree proinflammatory state which occurs with increasing age and is closely associated with multiple diseases, as excessive inflammation can induce the inflammatory lesions in certain organs of the body. In recent years, studies have shown that inflammatory aging plays a significant role in the pathogenesis of POI.
POI or Diminished Ovarian Reserve?

- POI is distinct from low ovarian reserve
- ‘Ovarian Reserve’ encompasses both quantity and quality of primordial follicles. Low ovarian reserve is a condition in which ovary loses its normal reproductive potential. Low ovarian reserve is characterized as regular menses and alterations of ovarian reserve tests, and can be caused by conditions affecting the ovaries, but in most cases is a consequence of age.

Decay of ovarian reserve with age

Diagnosis

• POI is characterised by menstrual disturbance, raised gonadotropins, and low estradiol.

• **ESHRE 2015** recommends the following diagnostic criteria:
  - oligo/amenorrhea for a period of 4 to 6 months
  - an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart

• **ACOG 2014** recommends:
  - Menstrual irregularity for atleast 3 consecutive months
  - FSH & E2 levels (2 random tests atleast 1 month apart)
  - Prolactin and thyroid function test

<table>
<thead>
<tr>
<th>Different terminologies for POI</th>
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<tr>
<td>Primary Ovarian Insufficiency</td>
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<td>Premature Ovarian Failure</td>
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<td>Gonadal dysgenesis</td>
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<td>Premature menopause</td>
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**Primary Ovarian Insufficiency**

**Premature Ovarian Failure**

**Gonadal dysgenesis**

**Premature menopause**

**Early menopause**

**Hypergonadotropic hypogonadism**

**Premature Ovarian Insufficiency**

**Ovarian dysgenesis**

**Primary ovarian failure**

**Hypergonadotropic amenorrhea**

**Climacterium praecox**

**Menopause praecox**
Clinical States Included in the Spectrum of POI

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Serum FSH Level</th>
<th>Fertility</th>
<th>Menses</th>
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<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>
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Follicle stimulating hormone (FSH)

- FSH levels are used as the gold standard in establishing a diagnosis of POI.
- Most literature uses FSH > 40 IU/l as criteria for POI diagnosis.
- Since patients with autoimmune POI should be included in the diagnosis, ESHRE 2015 use a cut off level of FSH > 25 IU/l. This is above the physiological range for FSH even at the pre-ovulatory peak.

https://rep.bioscientifica.com/view/journals/rep/140/5/633.xml
anti-Müllerian hormone (AMH)

- More direct marker of ovarian reserve and low AMH is more prevalent in POI patients.
- Serum AMH levels follow the reduction in follicular number over time in healthy women and fall to very low levels prior to menopause.
- However, low AMH may also be found in women with regular cycles and low ovarian reserve.
- Women attending fertility clinics with low AMH but regular menstrual cycles should not be diagnosed with POI.

Anti-Müllerian hormone (AMH) is not sufficiently discriminative for a diagnosis of POI.
Other Investigations in POI

- Chromosomal analysis/ karyotyping
- Fragile-X (FMR1) premutation testing
- 21OH-Ab or adrenocortical antibodies (ACA)
- 21-hydroxylase (CYP21)
- Thyroid (TPO-Ab) antibodies
- Thyroid stimulating hormone (TSH)
- Adrenocorticotropic hormone (ACTH)
- Plasma renin activity
- ACTH stimulation test
- Vitamin B12
- Ferritin
- Folate

Autosomal genetic testing is not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).
Karyotyping (For Diagnosis of Turner Syndrome)

- Chromosomal analysis should be performed in all women with non-iatrogenic Premature Ovarian Insufficiency.
- For chromosomal analysis for Turner Syndrome, karyotyping is the gold standard; although microarray-based comparative genomic hybridisation (array CGH) and other new technologies exist.
- If negative, a second analysis of the karyotype from the gonads (in case of high clinical suspicion).
Test for Y-chromosomal Material

• Every women with a Y chromosome, whether or not she has a SRY gene mutation, should be counselled about the risk of development of a gonadal tumour.

• Gonadectomy should be recommended for all women with detectable Y chromosomal material.
Fragile X Testing

- Fragile-X syndrome is an X-linked inherited condition caused by a mutation of the fragile-X mental-retardation 1 (FMR1) gene.
- Prevalence of 0.8 to 7.5% in women with sporadic POI (i.e. women without other family members with POI) and up to 13% in women with a positive family history of POI.
- Women who carry the premutation (55-200 repeats) do not have an increased risk of intellectual disability, but have an increased risk of 13 to 26% to develop POI.
- The risk of developing POI is not increased in women with the full mutation or intermediate sized CGG repeats (45 – 54 repeats).
- Family members may be carriers and therefore have a risk of developing POI and a risk of having (grand)children with fragile-X syndrome. In addition, the patient herself may already have daughters, who may be carriers. This requires careful counselling before the test is performed, including permission from the patient to perform the test. An additional reason to counsel about Fra-X testing is the risk of fragile-X-associated tremor/ataxia syndrome (FXTAS), a late onset neurological problem predominantly in male carriers of the Fra-X-mutation.
Antibodies

- Autoimmune disorders are more frequent in POI than in the general population, and POI is more frequent in women with certain autoimmune disorders.
- Addison’s disease and APS type 2 are known to predispose to POI while POI of adrenal autoimmune origin is the most frequent type observed in 60 to 80% of patients with autoimmune POI.
  - Screening for adrenocortical antibodies (ACA) and/or 21-hydroxylase autoantibodies (21OH-Ab) should be considered in every POI patient because of the possibility of subclinical or latent Addison’s disease in POI patients. Positive 21OH-Ab/ACA test should be directed to adrenal function testing to rule out Addison’s disease. In the presence of peripheral 21OH-Ab, SCA on cryostatic sections of ovaries and/or 17α-hydroxylase antibodies (17α-OH-Ab) and/or P450SCC antibodies can be detected on cryostatic sections of ovaries in over 90% of cases.
- POI is associated most commonly with thyroid autoimmunity (14–27%) when adrenal autoimmunity is absent.
  - Screening for thyroid antibodies (TPO-Ab) should be performed in women with POI. In patients with a positive TPO-Ab test, thyroid-stimulating hormone (TSH) should be measured every year. TSH screening could occur at 5-year intervals if negative.
Fertility and Pregnancy

• Oocyte donation is an established option for fertility in women with POI. However, women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as karyotype.

• Women with POI should have their blood pressure, renal function, and thyroid function assessed prior to pregnancy.
Bone Health

• POI is associated with reduced bone mineral density (BMD). Reduced BMD is very likely to indicate that POI is associated with an increased risk of fracture later in life.

• Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially when there are additional risk factors.

• 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. A decrease in BMD should prompt review of estrogen replacement therapy and of other potential factors.
Cardiovascular Health

• Women with POI are at increased risk of cardiovascular disease and should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).

• All women diagnosed with Turner Syndrome should be evaluated by a cardiologist.

• Cardiovascular risk should be assessed in women diagnosed with POI. At least blood pressure, weight and smoking status should be monitored annually with other risk factors being assessed if indicated.

• In women with Turner Syndrome, cardiovascular risk factors should be assessed at diagnosis and annually monitored (at least blood pressure, smoking, weight, lipid profile, fasting plasma glucose, HbA1c).
Genetic Counseling

• Relatives of women with non-iatrogenic POI (fragile-X premutation) who are concerned about their risk for developing POI should be informed that:
  – currently there is no proven predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected
  – there are no established POI preventing measures
  – fertility preservation appears as a promising option, although studies are lacking
  – their potential risk of earlier menopause should be taken into account when planning a family
## Tests Done in SRL

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<tr>
<th>TEST</th>
<th>METHOD</th>
<th>CODE</th>
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<tr>
<td>Fertility Panel, Female, Endocrine (TSH3G UL, Prolactin, Progesterone, Estradiol, LH, FSH)</td>
<td>Chemiluminescence</td>
<td>1578</td>
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<tr>
<td>Inhibin B, LH, FSH &amp; Prolactin</td>
<td>Enzyme Immunoassay/Chemiluminescence</td>
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<tr>
<td>Cytogenetics: Blood Lympho Culture</td>
<td>Cell Culture</td>
<td>5814B</td>
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<tr>
<td>Cytogenetics: Fragile X Chromosome Analysis</td>
<td>Karyotype Cell Culture</td>
<td>5364B</td>
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<tr>
<td>Fragile X (FMR1) Mutation Screen</td>
<td>Triplet Primed PCR Fragment Analysis</td>
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<tr>
<td>Thyroid Antibodies</td>
<td>Chemiluminescence</td>
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Premature Ovarian Failure

Thank You