Premature Ovarian Insufficiency (POI)

Healthcare professional toolkit

based on the ESHRE Guideline on Premature Ovarian Insufficiency

asrm American Society for Reproductive Medicine

CREWHiRL Centre for Research Excellence in Women's Health in Reproductive Life

International IMS Menopause Society Promoting education and research on midlife women's health

eshre

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www.eshre.eu/guidelines

Introduction

This resource is for healthcare professionals involved in the care of people with premature ovarian insufficiency (POI):

This resource is for intended healthcare professionals (HCPs) including primary care, endocrinologists and gynaecologists. It may also be helpful for other HCPs such as psychologists, nurse practitioners and physical therapists. Greater details regarding POI can be found in the full guideline available at the ESHRE website.

This resource aims to:

- increase awareness of premature ovarian insufficiency
- facilitate recognition and prompt diagnosis of POI
- encourage shared decision making between those with POI and their HCP
- provide HCPs with tools to provide evidence-based best practice care of people with POI and reduce care variation

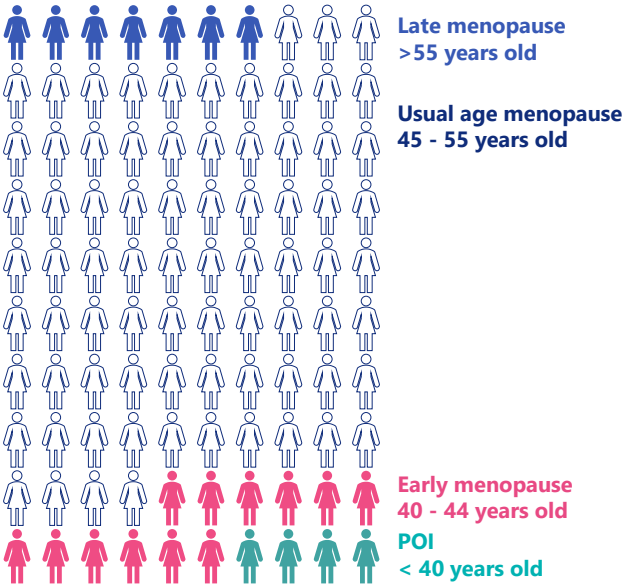
Content:

This resource and the information presented are based on the 2024 updated ESHRE Guideline on the management of women with Premature Ovarian Insufficiency. This new guideline builds on, updates and expands the previous 2016 ESHRE Premature Ovarian Insufficiency guideline and was developed by a partnership between European Society for Human Embryology and Reproduction (ESHRE), American Society for Reproductive Medicine (ASRM), Monash University Centre for Research Excellence- Women's Health in Reproductive Life (CREWHiRL), and the International Menopause Society (IMS). The final POI guideline contains 40 key questions with 145 recommendations. All the information and recommendations in the guideline are based on the best available evidence from research. When there is insufficient evidence from research, a group of experts formulated recommendations based on their clinical expertise (see Development of the recommendations).

The information in the resource can be used with the co-designed consumer summaries of topics and the Ask Early menopause App. More information is available in the Resources for Information and support.

PART A: Introduction to POI

- Premature ovarian insufficiency (POI) is a clinical condition characterised by loss of ovarian function in women before age 40 years
- Menstrual disturbance (amenorrhoea or oligomenorrhoea) and biochemical confirmation of ovarian insufficiency (elevated FSH concentration) are needed for the diagnosis
- POI may be iatrogenic or non-iatrogenic.
- POI differs from usual-age menopause, as women with POI have unique needs and management options.
- POI is more common than was previously thought (Figure)



The usual age of menopause is between 45-55 years but may vary between countries. This diagram shows a group of 100 women and the prevalence of POI (3.7%), early (12.2%) or late menopause and usual age menopause.

- **Risk factors:**
  - positive family history
  - having a known genetic cause of POI (eg. Fragile X premutation or Turner syndrome)
  - smoking
  - low body mass index (BMI)
  - autoimmune diseases (eg. rheumatoid arthritis, polyglandular autoimmune disease, inflammatory bowel disease)
  - medical treatments (chemotherapy, pelvic/ whole body irradiation or ovarian/ pelvic surgery)
  - ethnicity (lower prevalence in women of Asian background)
  - The risk of POI may also vary according to: reproductive factors (earlier menarche or short menstrual cycle length), early life and social factors (lower education or socioeconomic status, living in a developing country), and exposure to environmental toxins; but it is less clear whether there is a direct association with POI.

- It is unknown whether lifestyle modifications can prevent future POI. Since smoking is a stand-alone risk factor for POI, women without other POI risk factors who smoke should be counselled about smoking cessation.
- Fertility preservation strategies such as oocyte cryopreservation should be discussed for women at risk for POI when appropriate.

The guideline group recommends that women with risk factors for POI are identified and counselled regarding POI risk and fertility preservation.	**GPP**

- Except for those undergoing bilateral oophorectomy, at present we cannot reliably predict who will develop POI or when.

The guideline group recommends that HCPs do not routinely perform AMH testing to predict POI due to insufficient evidence of accuracy	**GPP**

- Women may not only suffer from symptoms associated with estrogen deficiency, but can also experience other issues, with a significant impact on their quality of life and longterm health (Table)

Table: Longterm consequences

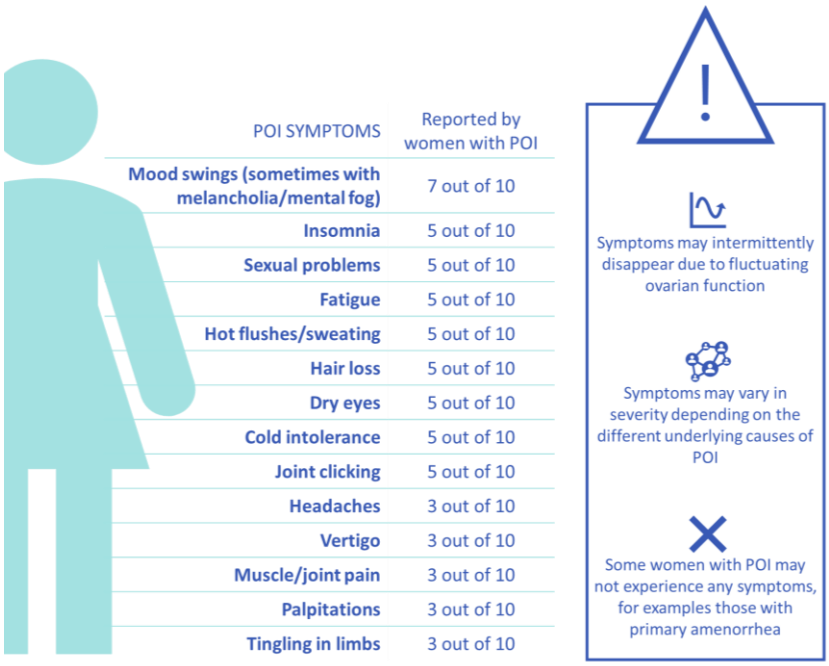
	Increased risk of:	
	**Cardiac**	• Hypertension • Coronary artery disease, heart failure, • Atrial fibrillation • Stroke
	**Metabolic**	• Diabetes mellitus • Dyslipidemia • Metabolic syndrome
	**Musculoskeletal**	• Decreased bone density and osteoporosis • Decreased muscle mass and strength
	**Psychological**	• Anxiety • Depression • Poor self-esteem, body image • Decreased quality of life
	**Brain**	• Cognitive impairment • Dementia • Parkinsonism
	**Infertility**	
	**Life expectancy**	• Reduced life expectancy with untreated POI mainly due to cardiac disease

PART B: Diagnosis of POI

1. Clinical Presentation

- Variable
- Menstrual disturbance is a characteristic feature.
    - secondary amenorrhoea/ oligoamenorrhoea is most common
    - primary amenorrhoea occurs in a minority and is usually associated with a genetic cause of POI.
- Estrogen deficiency symptoms may or may not be present
    - usually absent in those with primary amenorrhoea.
- Symptoms and signs related to the cause of POI eg Turner syndrome, autoimmune disease or cancer
- Symptoms and signs of coexisting co-morbidities.
- Primary or secondary infertility.
- Psychological distress
- Symptoms may be more severe in those with iatrogenic POI.

Symptoms reported by women with POI



The guideline group recommends that HCPs enquire about symptoms of estrogen deficiency in women presenting with irregular menstrual cycles or amenorrhea.	**GPP**

The guideline group recommends HCPs consider and exclude the diagnosis of POI in women aged less than 40 years who have amenorrhea/ irregular menstrual cycles or estrogen-deficiency symptoms.	**GPP**

2. Diagnosis of POI

- POI is characterised by oligo/amenorrhoea, raised gonadotropins and low estradiol.
- FSH concentration >25 IU/l represents a value greater than the physiological peak observed in premenopausal women and will encompass women with POI due to autoimmune causes.
- Fluctuating ovarian activity may occur resulting in variable FSH concentrations, including into the normal range.

HCPs should diagnose POI based on the presence of spontaneous amenorrhea or irregular menstrual cycles and biochemical confirmation.	**STRONG** ⊕⊕◯◯

Algorithm for Diagnosis of POI

Step 1: Clinical Presentation

Women aged <40 years with

- **Bilateral oophorectomy = diagnosis of POI, no further testing needed**
- **Menstrual disturbance (amenorrhoea or oligomenorrhoea) for at least 4 months**
  - Use of hormonal therapy (including oral, injectable, or long-acting contraceptives) may conceal or cause amenorrhoea or irregular menstrual cycles
- **(Symptoms of estrogen deficiency may or MAY NOT be present)**
- **Signs and symptoms of potential cause of POI such as Turner syndrome or autoimmune disease**

Step 2: Investigations

- **Pregnancy test**
- **Measure follicle stimulating hormone concentration (FSH)**
  - FSH testing for the diagnosis of POI does not have to be timed to a specific day of the menstrual cycle
  - Some hormonal therapy can potentially lower FSH concentrations and may need to be ceased before a diagnosis of POI can be confirmed. (eg cease combined oral contraceptive for at least two to six weeks before measuring FSH but consider need for non-hormonal contraception)
- **FSH > 25IU/L + oligo/amenorrhoea for at least 4 months = DIAGNOSIS**
- Diagnosis of POI is not based on estradiol concentrations. However, a low estradiol concentration indicates hypoestrogenism, and in combination with an elevated FSH concentration provides additional confirmation of the POI diagnosis.
- Ultrasound may show small ovarian volume and/or a low antral follicle count (the number of follicles measuring 2–10 mm) but is not required to make the diagnosis of POI.

Step 3. If POI is not confirmed on the first FSH test

- Repeat FSH in 4-6 weeks if diagnosis uncertain
- Consider measuring Anti-mullerian hormone (AMH)
    - AMH testing may be useful to confirm POI diagnosis where FSH results are inconclusive, but AMH results need to be interpreted within the clinical context. Consider need for fertility preservation if detectable AMH.

AMH should not be used as the primary diagnostic test for POI. **STRONG** ⊕◯◯◯

3. Identifying the cause of POI

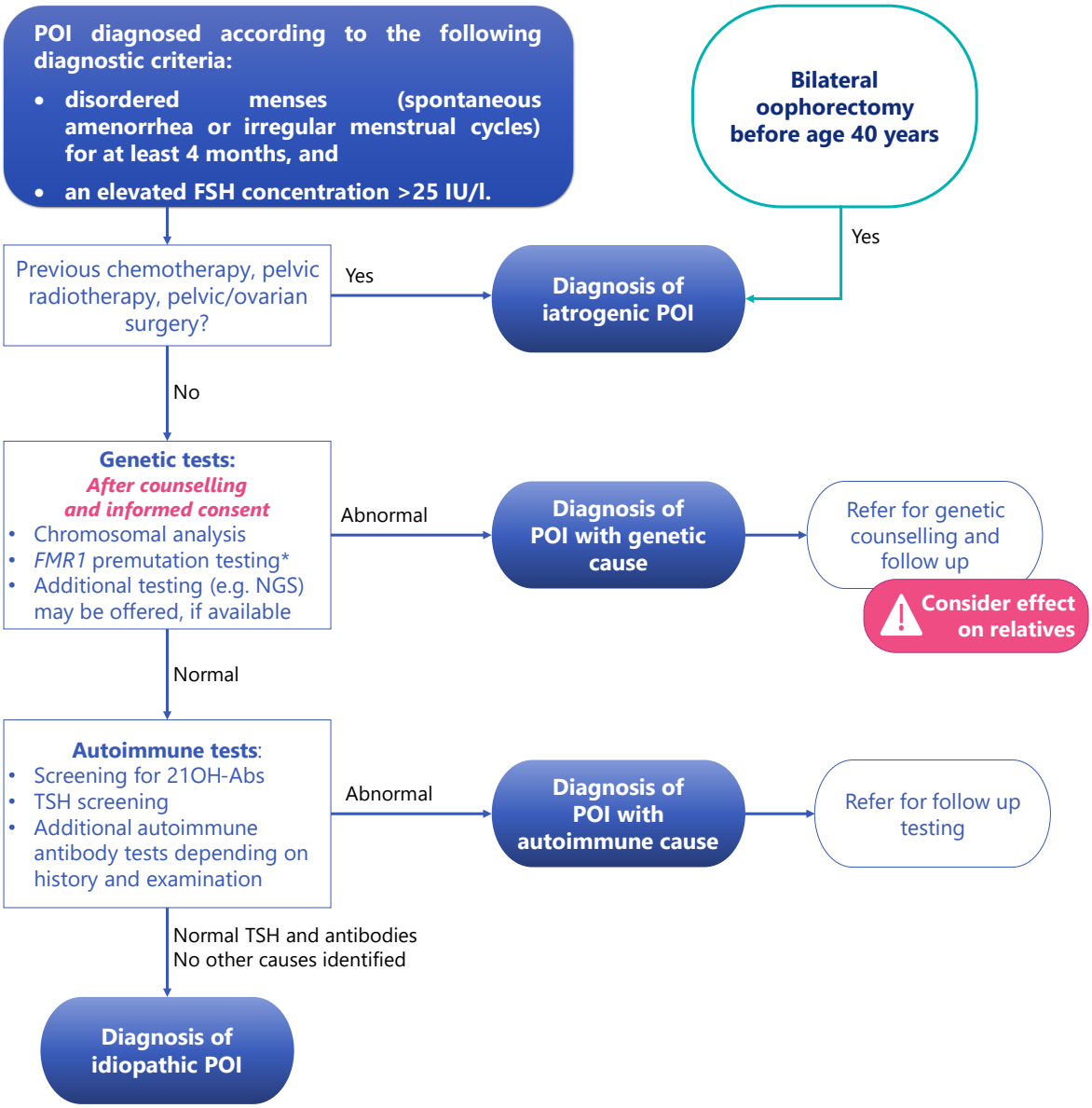
- May be iatrogenic (e.g. bilateral oophorectomy or chemotherapy-induced) or non-iatrogenic (see table).
- For most women, no cause is able to be identified, and the term "idiopathic POI" is applied.
- Genetic causes encompass chromosomal annomalies or specific gene variants, with over 100 genes implicated. However, specific gene testing (eg next generation sequencing) is not available in all countries. Informed consent is needed and any genetic test should only be performed after informing the patient of the nature of the tests, the implications, and possible associated comorbidities including cancer risk.
- Autoimmune disorders are more frequent in women with POI than in the general population, the most important being Addison's disease and autoimmune polyglandular syndrome; non-iatrogenic POI is more frequent in women with certain autoimmune disorders. 21-hydroxylase antibodies are associated with the highest diagnostic accuracy for autoimmune POI.
- The risk of iatrogenic POI varies according to age, chemotherapy type and dose and radiation dose.

Table: Causes of POI

Genetic	• Chromosomal eg Turner syndrome • Specific Gene Variant
Autoimmune	• Thyroid, adrenal, systemic lupus erythematosus, rheumatoid arthritis, immune thrombocytopenic purpura, autoimmune haemolytic anaemia, pernicious anaemia, vitiligo, alopecia areata, inflammatory bowel diseases, primary biliary cirrhosis, multiple sclerosis, and myasthenia gravis
Metabolic	• Galactosemia (associated with GALT gene mutation)
Infectious	• Mumps oophoritis, HIV
Toxins	
Iatrogenic	• Bilateral oophorectomy, chemotherapy, pelvic field radiotherapy, ovarian or pelvic surgery,

The guideline group recommends that HCPs should inform women with POI of the different causes of POI, the limitations of current knowledge and testing for causes of POI and that an exact cause may not be identified	**GPP**
Screening for anti-ovarian autoantibodies should not be used to diagnose autoimmune POI.	STRONG ⊕◯◯◯
The guideline group recommends that HCPs do not routinely perform thyroid peroxidase (TPO) antibody screening as part of testing for autoimmune causes of POI due to the high prevalence of positive TPO antibodies in the general community.	**GPP**

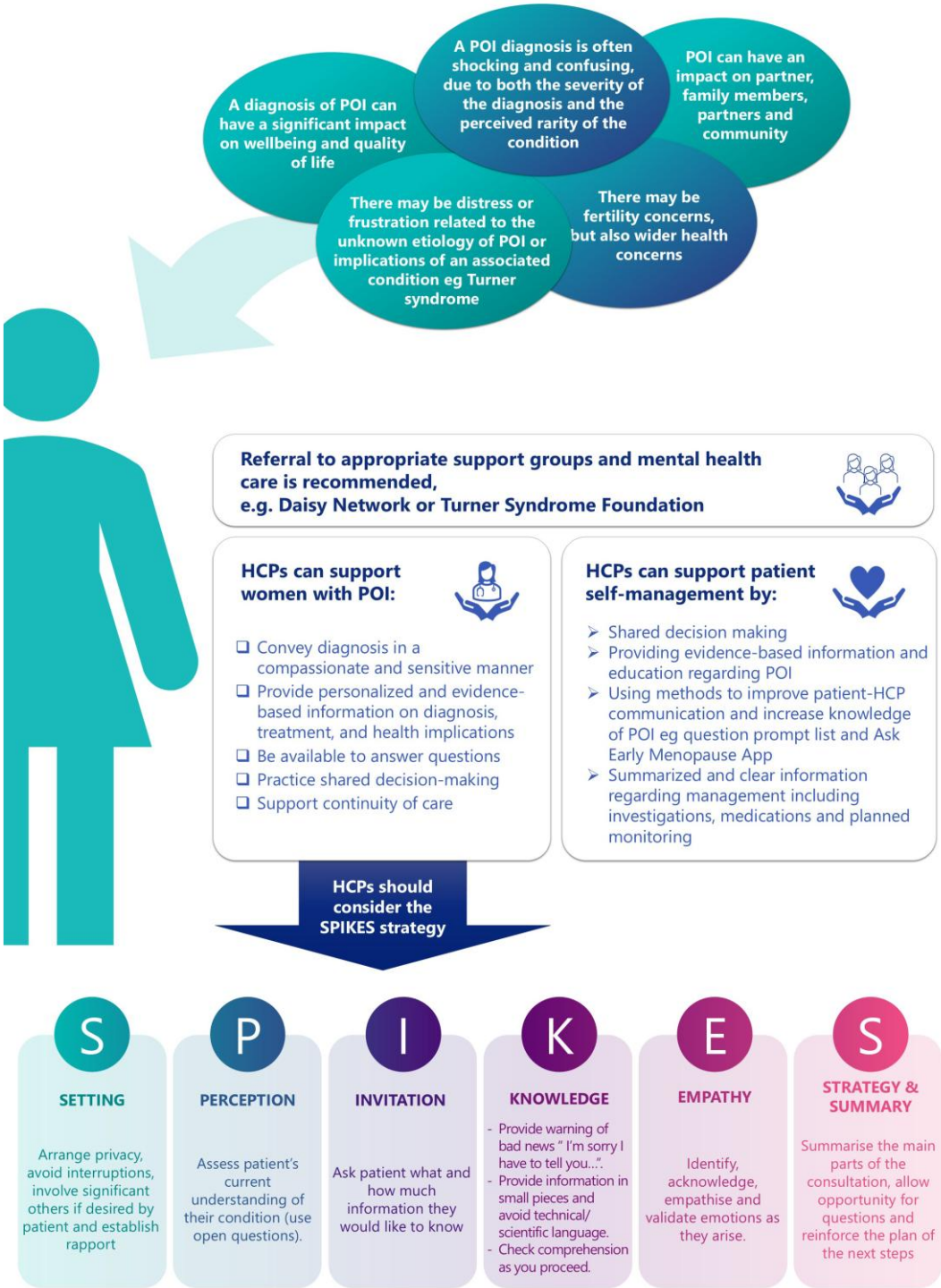
Algorithm for Identifying the Cause of POI



**Fragile X premutation testing is indicated in all women diagnosed with POI. This needs to be performed as a specific test as multigene panels and NGS are not useful in detecting FMR1 premutation. Abbreviations: FSH, follicle stimulating hormone; NGS, next generation sequencing;*

4. Care for women with POI at diagnosis

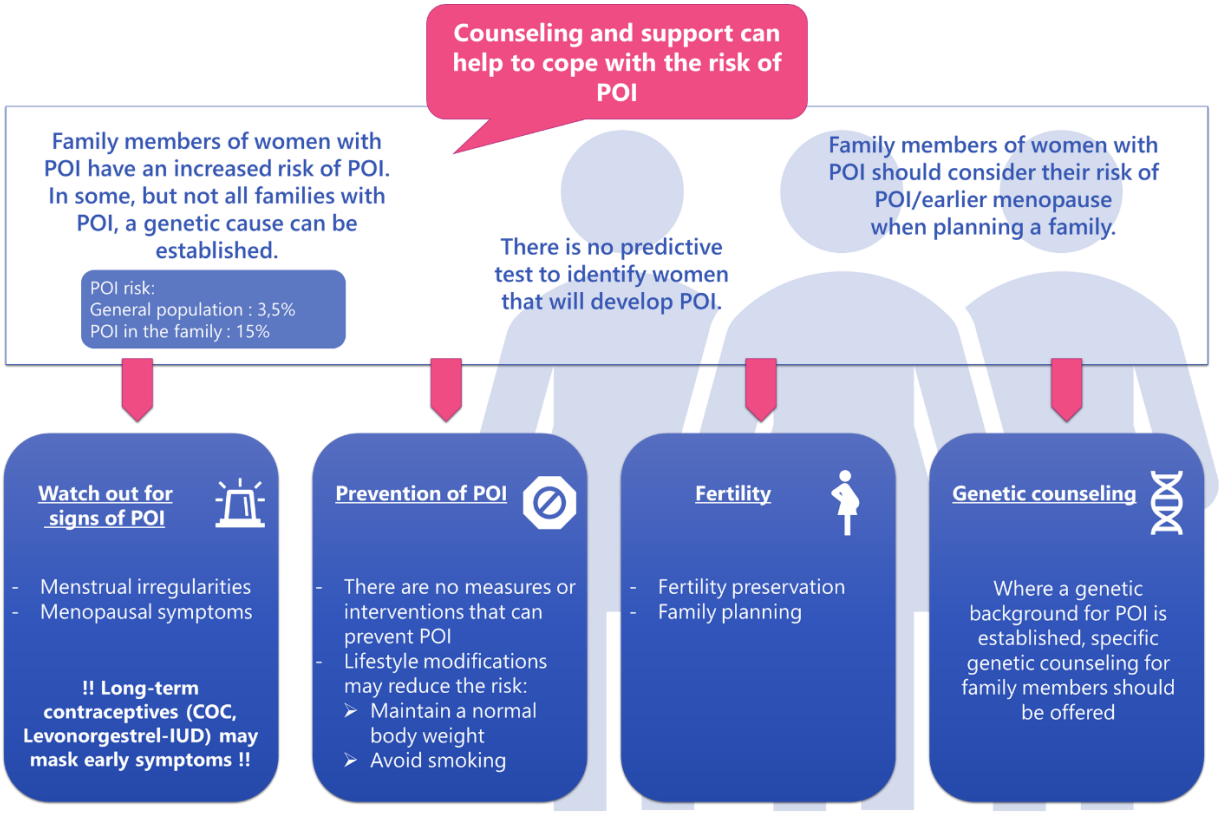
- A diagnosis of POI can be very distressing and women may experience a range of emotions.
- Impact of diagnosis on family members must also be considered.
- Prioritise a prompt diagnosis, sensitive delivery of the diagnosis, provision of information and follow-up and support.



5. Implications for relatives of women with POI

- Risk is increased 3 -18 x in female relatives of women with POI depending on the degree of association (highest risk for twin sister).
- If a genetic cause of POI is identified, offer genetic testing to female and male relatives

Information for family members of women with POI



COC- combined oral contraceptive

PART C: Management of POI

1. Comprehensive Evaluation:

Once diagnosis is made, comprehensive evaluation is required to screen for and address:

(i) symptoms including genitourinary symptoms;

(ii) psychological health;

(iii) sexual function;

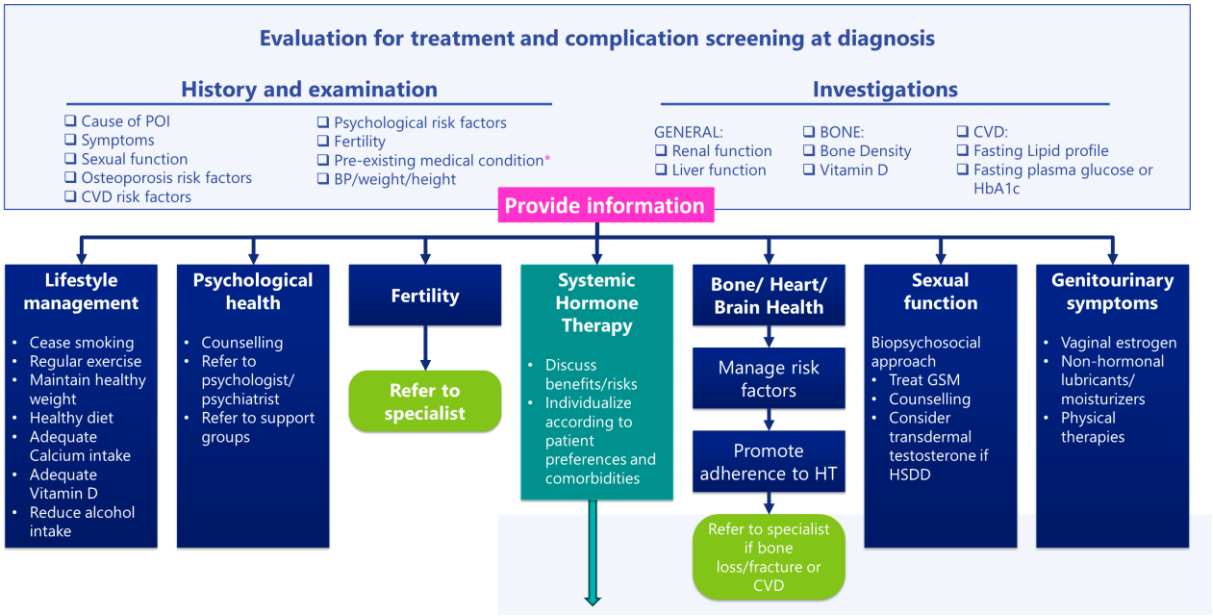
(iv) risks of longterm consequences;

(v) choice of hormone therapy;

(vi) fertility concerns;

(vii) issues related to cause of POI eg Turner syndrome, autoimmune disease or cancer.

Management Summary



Abbreviations: BP, blood pressure; CVD, cardiovascular disease; GSM, genitourinary syndrome of menopause; HRT, Hormone Replacement Therapy; HSDD, Hypoactive sexual desire disorder; HT, Hormone therapy (HRT+ combined oral contraceptive pill).

2. Hormone Therapy

Indications for hormone therapy

Vasomotor symptoms	**YES**	HT is indicated for the treatment of vasomotor symptoms in women with POI.
Genitourinary symptoms	**YES**	Offer vaginal estrogen therapy to improve genital, sexual and urinary symptoms. Women with POI may be offered vaginal estrogen therapy if genitourinary symptoms are not fully relieved by systemic HT.
Life expectancy	**YES**	Women with POI should be offered HT at least until the usual age of menopause as primary prevention to reduce risk of overall morbidity and mortality
Skeletal health	**YES**	HT is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.
Muscle health	**Uncertain**	The effect of HRT on muscle parameters in women with POI is uncertain but may be of benefit.
Cardiovascular health	**YES**	Estrogen therapy has beneficial cardiometabolic effects which can influence cardiovascular disease risk. Non-use of HT is associated with an increased risk of cardiovascular events and mortality. HT is therefore recommended until the usual age of menopause.
Quality of life	**Uncertain**	HT has a positive impact on quality of life in women at usual age of menopause. There are minimal data regarding women with POI, but HT may be of benefit
Sexual function	**YES**	Where HT has been prescribed for other indications to women with POI, it may ameliorate sexual function, acknowledging the effect is generally small.
Neurological function	**YES**	HT may be recommended in women with POI to protect neurological function even in the absence of menopausal symptoms.
Fertility treatment	**YES**	HRT in higher doses creates a favourable hormonal environment for fertility intervention such as replacement of embryos in oocyte donation IVF.
Puberty Induction	**YES**	HRT is indicated for normal pubertal development and skeletal maturation

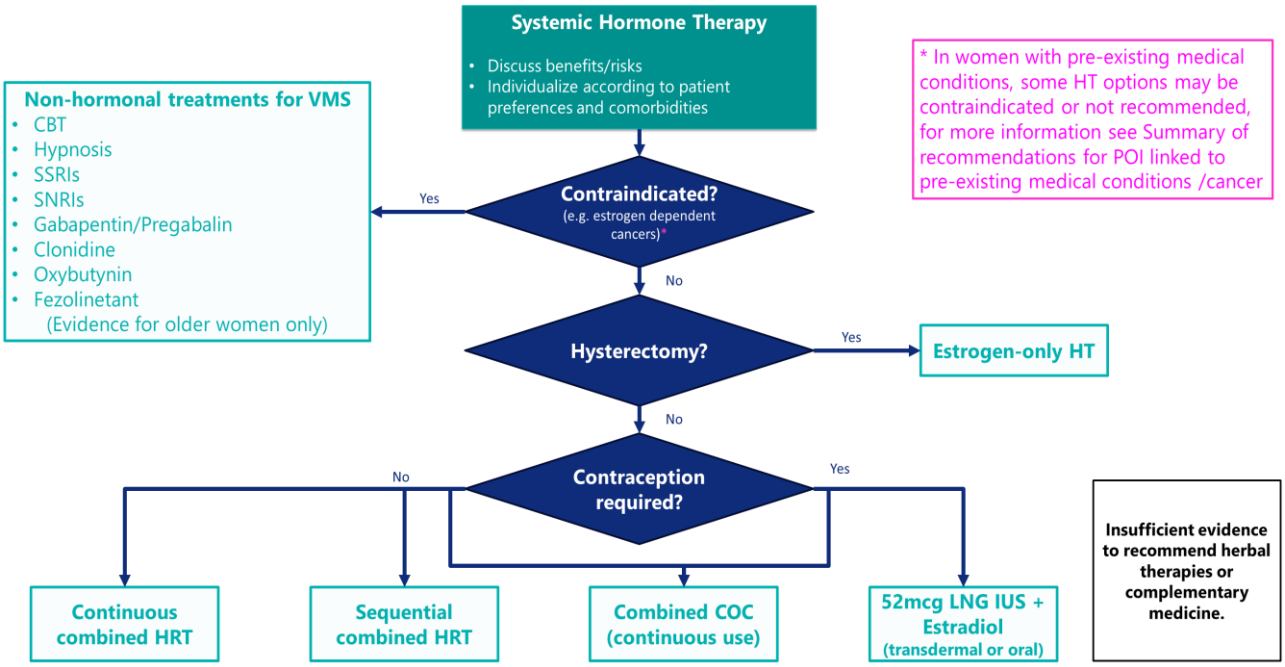
Hormone therapy is recommended for women with POI until the usual age of menopause for primary prevention to reduce the risk of morbidity and mortality, whether there are estrogen deficiency symptoms or not.	**STRONG** ⊕⊕◯◯

The guideline group recommends shared decision making when prescribing each component of hormone therapy with consideration of patient preference, contraceptive needs, and presence of co-morbidities.	**GPP**

If the combined oral contraceptive is used, then a continuous or extended regimen is recommended to provide continuous estrogen therapy and avoid bone loss.	**STRONG** ⊕⊕◯◯
Women with POI can be informed that there is no evidence that hormone therapy use increases their risk of breast cancer compared to women of the same age without POI.	**CONDITIONAL** ⊕⊕◯◯

Algorithm to guide Systemic HT prescribing

- **Hormone therapy** encompasses both **hormone replacement therapy** (also referred to as menopausal hormone therapy when used in older women) and the **combined oral contraceptive** pill.
- Estradiol containing COCs have not been studied specifically in women with POI. Estrogen dose in COCs containing 1.5mg estradiol or 20mcg ethinyl estradiol may be inadequate for bone health. Usual precautions regarding COCs apply.
- Availability of HT preparations may differ between countries.



Abbreviations: CBT, cognitive behaviour therapy; COC, combined oral contraceptive pill; HRT, Hormone Replacement Therapy; HT, Hormone therapy (HRT+COC); LNG IUS, levonorgestrel intrauterine system; SNRIs, serotonin nor-epinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; VMS, vasomotor symptoms

Options for Hormone Replacement Therapy

HRT type	***Sequential combined HRT***		***Continuous combined HRT***	
Per 24 hours or day	*Low/standard doses*	*'POI' doses*	*Low/standard doses*	*'POI' doses*
Estradiol type				
Patch (transdermal, µg/24h	**25–50**	**75–100**	**25–50**	**75–100**
Gel sachet (transdermal, mg)	**0.5–1.0**	**1.5–2.0**	**0.5–1.0**	**1.5–2.0**
Gel pump (1 metered dose = 0.75 mg)	**1–2**	**3–4**	**1–2**	**3–4**
Spray (1.53mg per spray)	**1-2**	**3-4**	**1-2**	**3-4**
Oral (mg)	**1.0–2.0**	**2.0–4.0**	**1.0–2.0**	**2.0–4.0**
Progestogen				
Micronized progesterone (oral/per vagina, mg)	**100–200**	**≥ 200 (e.g. 300–400)**	**100**	**≥ 200**
Dydrogesterone (oral, mg)	**10**	**20**	**5.0**	**10**
Medroxyprogesterone acetate (oral, mg)	**5.0**	**10**	**2.5**	**5.0**
Norethisterone acetate (oral, mg)	**2.5–5.0**	**2.5–10**	**1.25–2.5***	**2.5-5.0**
Levonorgestrel intrauterine system (LNG IUS)	**20 µg/day sufficient for low/standard and POI doses (52mg LNG IUS)**			
17 beta-estradiol (E2)/progestogen fixed dose combined preparations				
E2/micronized progesterone (oral, mg)	**1.0–2.0/100–200**	**≥ 2.0/≥ 200**	**1.0–2.0/100–200**	**3.0–4.0/300–400**
E2/norethisterone acetate (transdermal) (µg)	**25–50/85–170**	**75–100/255–340**	**25–50/85–170**	**75–100/255–340**
E2/dydrogesterone (oral, mg)	**1.0–2.0/10**	**2.0/10**	**0.5–1.0/2.5–5.0**	**3.0–4.0/7.5–10**
E2/norethisterone acetate (oral, mg)	**1.0–2.0/1.0**	**3.0–4.0/2.0–4.0**	**0.1–2.0/0.5–1.0**	**3.0–4.0/1.5–2.0**

Hormone therapy options linked to certain co-morbidities

- The presence of certain co-morbidities may influence the decision to use hormone therapy or the type of hormone therapy.
- Shared decision making and personalised hormone therapy is essential.
- Caution is required in the presence of cardiovascular disease and a lower dose of transdermal estrogen may be required. Discuss with the treating cardiologist and consider referral to a menopause specialist.
- In many other settings, hormone therapy can be used but often transdermal estrogen is preferred.

Comorbidity	HT	Type of risk	Probability	Proposed HT
Breast cancer survivor	Contra-indicated	Recurrence	High	n/a
BRCA1/2 mutations after RRSO, without a personal history of breast cancer	Can be considered	Developing BC	Low	TE/MP/DYD [1]
Migraine	Can be considered	Ischaemic stroke	Unclear	Dose/regimen/administration can be adapted in line with migraine symptoms
Migraine with Aura	Can be considered	Ischaemic stroke	Unclear	Transdermal estrogen (COC contraindicated[2])
Hypertension	Can be considered	CVD/VTE	Low	TE/MP/DYD [1]
Diabetes mellitus	Can be considered	CVD/VTE	Low	TE/MP/DYD [1]
Obesity	Can be considered	CVD/VTE	Low	TE/MP/DYD [1]
Endometriosis	Can be considered	Disease reactivation / malignancy	Low	combined estrogen-progestogen
Prior VTE	Can be considered after haematologist review.	VTE/PE	High	TE/MP/DYD [1] (COC contraindicated[2])
Malabsorption	Recommended	Inadequate absorption of oral therapy	Unclear	Non-oral HT
Known CVD	Relatively Contra-indicated	CVD	Unclear	TE/MP/DYD [1]
Abnormal liver function	Can be considered	Worsening of liver function	Unclear	Transdermal estrogen

- [1] TE/MP/DYD: Transdermal estrogen, Micronized progesterone, Dydrogesterone
- [2] See https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html

Hormone therapy options in the setting of particular causes of iatrogenic POI

Cancer/previous diagnosis		HT	Risk of recurrence with HT use	Other considerations
Squamous cell carcinoma	✓	Recommended	Not increased	
Cervical adenocarcinoma	💬	Consider after risk assessment	Low risk	
Early-stage low-risk endometrioid adenocarcinoma	💬	Consider after risk assessment	Low risk	
Epithelial ovarian cancer	💬	Consider after risk assessment	Low to moderate risk	
Non-epithelial ovarian cancer	💬	Consider after risk assessment	Moderate risk	Tumour hormone receptor status.
Hormone dependent ovarian or uterine tumours **(uterine sarcoma, endometrioid carcinoma, ovarian clear cell carcinoma, ovarian granulosa cell tumour, sex cord-stromal tumours)**	⊘	Contra-indicated	High risk	
Breast cancer survivors.	⊘	Contra-indicated	High risk	
BRCA1/2 mutation carrier after RRBO, without a personal history of breast cancer	💬	Can be considered	NA	Estrogen-only HRT has lower risk compared to combined estrogen/progestogen
POI following hematopoietic stem cell transplantation	✓	Recommended	Not increased	Individualised HT / pubertal induction

3. Pubertal Induction

Step 1: Assess need for pubertal induction

- No spontaneous start to puberty or progression of breast development at age 11 years
- Primary amenorrhoea (menarche has not occurred by age 15 years or within three years of breast development (thelarche)

Step 2: Commence appropriate estrogen therapy

Age	Age-specific suggestions	Preparation/dose/comments
11 - 12 years	**If no spontaneous development and FSH elevated, start low dose estrogens**	Estradiol (E2) Transdermal: 6.25 µg/day[1] E2 via patch Oral micronized E2: 5 µg/kg/day or 0.25 mg/day
11.5 – 13.5 years	**Gradually increase E2 dose at 6-12 months interval over 2 - 3 years[2] to adult dose**	Transdermal E2: 12.5, 25, 37.5, 50, 75, 100µg/day (*Adult dose: 100-200 µg/day*) Oral E2: 5, 7.5, 10, 15 µg/kg/day. *(Adult dose: 2-4 mg/day)*
13 – 15 years	**Begin cyclic progestogen after 2 years of estrogen or when breakthrough bleeding occurs or use an IUD**	Oral micronized progesterone 100-200 mg/day or dydrogesterone 5-10 mg/day during 12 – 14 days of the month. Levonorgestrel is used in IUD's.

[1] *the lowest dose commercially available E2 transdermal patches deliver 25 or 50 µg/day; it is not established whether various means of dose fractionation (e.g., administering 1/8, 1/6, 1/4 patch overnight or daily or administering whole patches for 7-10 days per month) are equivalent.*

[2] *with concomitant GH therapy in Turner Syndrome, to achieve an optimal adult height the increase in E2 dose might be relatively slow; while in cases of late diagnosis and for those girls in whom growth is not a consideration, E2 may be started at somewhat higher doses and escalated more rapidly.*

- Do not use the combined oral contraceptive for pubertal induction
- Transdermal estradiol results in more physiological estrogen concentrations

Step 3. Monitor response

- Breast and pubic hair development (Tanner stage)
- Uterine development (pelvic ultrasound can help guide timing of addition of progestogen)
- Bone density
- Biochemical monitoring of estradiol (transdermal estrogen) and gonadotropins

4. Non-hormonal and Complementary therapies

A. Non-hormonal therapies

- There is a lack of evidence specific to women with POI regarding the use of non-hormonal agents.

HCPs could consider non-hormonal pharmacologic and non-pharmacologic therapies for women with POI that are effective in peri-/postmenopausal women, although evidence specific to POI is lacking.

CONDITIONAL ⊕◯◯◯

Nonhormonal options for management of vasomotor symptoms (Adapted from (North American Menopause Society., 2023) with permission).

Agent	Dose	Comments
Pharmacological		
SNRIs		
Venlafaxine	37.5-150 mg/day	Commence with lowest dose then titrate upwards
Desvenlafaxine	100-150 mg/day	Commence with 50mg/day and titrate upwards
SSRIs		
Paroxetine	7.5 mg/day[1]	Do not use paroxetine concurrently with tamoxifen. Single dose, no titration needed
	10-25 mg/day	Commence with 5-10mg dose then titrate upwards
Escitalopram	10-20 mg/day	
Citalopram	10-20 mg/day	
Other		
Gabapentin	900-2400 mg/day in three divided doses.	Commence with 100-300 mg nighttime dose.
Fezolinetant	45 mg/day[1]	Single dose, no titration needed
Oxybutynin	2.5-5 mg twice daily	Commence with lowest dose then titrate upwards
Clonidine[2]	50-150 µg/day in twice daily dosing[1]	Commence with 25 µg twice daily and titrate upwards.
This does not represent the entire list as published in (North American Menopause Society., 2023).		
Non-Pharmacological		
Cognitive behavioural therapy		
Hypnosis		

[1]Government approved in some countries for use for vasomotor symptoms

[2] Clonidine was not included in the original NAMS publication

B. Complementary therapies

- Evidence for benefit for Chinese herbal medicine and acupuncture is limited.
- There is insufficient evidence for other complementary therapies.
- Complementary therapies should not replace HT.

5. Genitourinary Symptoms

- Hypoestrogenism plays a crucial role in the clinical manifestation of genitourinary symptoms with a significant impact on QoL and sexual health.
- HCPs should be proactive in discussing genitourinary health because genitourinary symptoms are highly prevalent and undertreated, as women may not volunteer such symptoms.
- Genitourinary symptoms in POI are under-researched and most evidence regarding management is extrapolated from older postmenopausal women.

Step 1: Sensitively ask about genitourinary symptoms

- Women may not volunteer symptoms

Step 2: Assess symptoms, distress, contributory factors

- Symptoms include: vaginal dryness, irritation, itching, urinary symptoms and dyspareunia
- Distress and impact on quality of life
- Pelvic examination
- Assess potential contributing/ exacerbating factors
    - Comorbidities eg. cancer treatment, Diabetes mellitus
    - Medications eg. aromatase inhibitors

Step 3. Personalised treatment

- **Adequate systemic estrogen therapy**
- Offer **local vaginal estrogen** if symptoms not contolled on systemic estrogen
    - Caution in those with estrogen sensitive cancer especially breast cancer
- **Non-hormonal vaginal moisturisers and lubricants** can be used for treatment of vaginal discomfort and dyspareunia in women with POI and can be combined with other treatments.
    - Hyaluronic acid-based moisturisers have the best evidence base
- **Physical therapy**
- Prasterone (Intravaginal DHEA) and oral ospemefine are other options, although not investigated in women with POI and may not be available in all countries

The guideline group currently does not recommend laser or thermal energy as standard care for genitourinary symptoms due to inconclusive evidence of benefit from RCTs. **GPP**

6. Sexual Function

Sexual function problems are common, multifactorial and a source of distress and impaired quality of life.

The diverse presentations of sexual dysfunction are unique for each woman suggesting the need for combined therapy and a mix of pharmacological and non-pharmacological strategies.

A biopsychosocial approach is required and summarised below:

Step 1: Sensitively ask permission to discuss sexual function

- Screen for sexual concerns

Step 2: Assess current sexual function and genitourinary symptoms

- Sexual response including desire, arousal, orgasm
- Presence of sexual pain
- Genitourinary symptoms such as vaginal dryness
- Other symptoms impacting sexual function eg hot flushes, fatigue
- Sexual and romantic relationships (if applicable)
- Distress and impact on relationship
- Medications (eg aromatase inhibitors, anti-depressants) and co-morbidities (eg. cancer diagnosis, depression) which may impact sexual function

Step 3. Personalised treatment

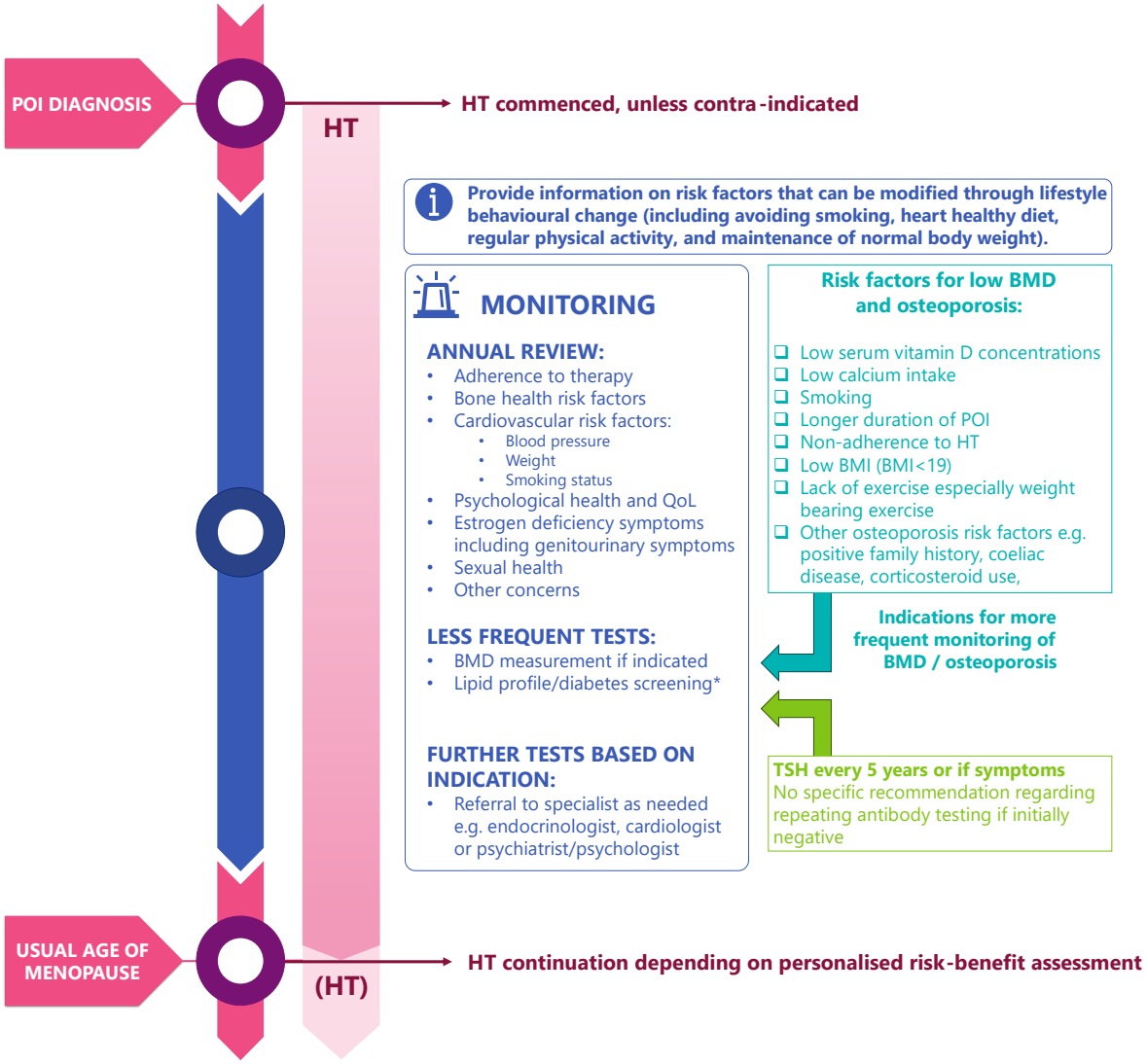
- **Education** regarding sexual function and factors that can affect it.
- Adequate **systemic estrogen** therapy
- Treat **genitourinary symptoms**
- **Topical 4% aqueous lidocaine** applied for 3 minutes before vaginal intercourse may be effective for dyspareunia related to introital pain
- **Transdermal testosterone** therapy can be considered if **hypoactive sexual desire disorder**.
    - Baseline total testosterone concentration should be evaluated before treatment is started and continue to be measured every 3 to 6 months to avoid overdose, particularly with off label use of male gels. Maintain testosterone level in normal female physiological range. Adverse effects and the effect of the treatment should be evaluated and if no improvement of sexual function is seen after a maximum of 6 months, treatment should be discontinued. Long term safety is unknown.
- **Psychosexual counselling**
- **Physical therapy**

7. Psychological Health

Women with POI report lower levels of psychological wellbeing compared to women in the general population. However, it is far from certain whether this constitutes the psychological sequelae of having a chronic condition or is particular to POI per se.

Psychological Domain	Screening protocol/ tools	Intervention
Quality of life	• Lower QoL scores in POI • Consider POI QoL scale • Factors include: ○ diagnosis experience, discontinuous care, negative clinical interactions ○ infertility, feelings of isolation and stigma ○ knowledge gaps, ○ sexual dysfunction ○ lack of social support	• Prompt diagnosis delivered in a sensitive manner • Capture and consider women's perceptions of their symptoms, impact on their QoL, key concerns and priorities for management. • Target treatment to areas of greatest concern to those with POI. • Peer to peer support
Anxiety and depressive symptoms	• Increased prevalence of anxiety and depressive symptoms. • Routine screening for all at diagnosis and subsequently based on clinical judgement, considering risk factors, comorbidities and life events. ○ Suggested screening based on regional guidelines and use regionally validated tools • Factors including infertility, menopausal symptoms, cause of POI, comorbidities, age, age at POI diagnosis may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	• Adequate hormone therapy • Healthy lifestyle • If initial screening is positive then assess risk factors and symptoms using age, culturally and regionally appropriate tools and/or refer to an appropriate professional for further assessment. • If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered to women with POI, informed by regional clinical practice guidelines.
Body image and self esteem	Negative body image and low self esteem has been described in POI and can be screened based on regional guidelines or by a stepped approach.	Psychological therapy should be offered, informed by regaional practice guidlines
Information needs and patient care	• Information, education and resources are a high priority for women with POI. • Patient care experience impacts QoL and treatment adherence	• Information, education and resources should be provided in a respectful and empathic manner. • HCPs should employ shared decision making and support patient agency. • Continuity of care, individualised care, compassionate HCPs

8. Monitoring POI



**frequency of measurement after screening at diagnosis should be based on the presence of hyperlipidaemia, hyperglycaemia and additional risk factors or global cardiovascular risk.*

- Cervical cancer screening and mammography as per national guidelines

Women with POI should be advised that adherence to hormone therapy is important to minimise long term health risks and therefore long term follow up is needed	**STRONG** ⊕⊕◯◯
The guideline group recommends that when women with POI reach the age at which usual menopause occurs, HCPs consider the need for continued hormone therapy based on a personalised risk-benefit assessment and current evidence.	**GPP**

9. Fertility

- Infertility is a significant cause of distress and contributes to impaired quality of life and psychological wellbeing.
- There are currently no known treatments which reliably increase ovarian activity, ovulation rate, and the possibility of conception.
- Rarely, women may have intermittent ovarian activity and natural conception is reported in <5-15%.
- Oocyte donation is the treatment of choice in women wishing to conceive.
- Pregnancy-related risks are associated with the cause of POI and whether the pregnancy is the result of oocyte/embryo donation. Pre-pregnancy evaluation and counselling is essential.
- For some women, pregnancy can be such high risk and life threatening, that donor oocyte pregnancy is inappropriate.

Women with POI should be informed that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.

STRONG ⊕⊕⊕◯

Step 1. Pre-pregnancy screening to assess fitness for pregnancy

	Idiopathic POI	Turner Syndrome	*FMR1* premutation	Autoimmune POI	POI after cancer treatment		POI after surgery
					Chemotherapy only	Chemotherapy + radiotherapy	
Standard antenatal assessment	√	√	√	√	√	√	√
Echocardiogram		√			√[1]	√[2]	
Cardiac MR		√					
Evaluation by cardiologist		√			√[1]	√[2]	
Renal function	√	√	√	√	√	√	√
Thyroid function	√	√	√	√	√	√	√
Adrenal function				√			
Uterine doppler / MRI / Endometrial biopsy						√[3]	

[1] If exposed to anthracyclines or high dose cyclophosphamide.
[2] In case of mediastinal irradiation
[3] If Pelvic Radiotherapy, especially if pre-pubertal

Step 2: Evidence of ovarian activity?	
Yes	**No**

• Usually seen in women with:
  ○ More recent diagnosis of POI
  ○ Lower FSH level
  ○ Detectable AMH level
• Consider fertility preservation
• Natural conception may occur in <5-15%
  ○ HRT does not prevent natural conception
  ○ Contraception should be offered if desired
Cause of POI may have implications for pregnancy and child eg FMR1 premutation or Turner syndrome
	• Donor oocyte/ embyo is the most reliable method of achieving pregnancy
	• Associated with increased obstetric and non-obstetric risks
	Require monitoring via specialised obstetric care team +/- cardiology involvement

Resources for information or support

Healthcare professional

More detailed information on each of the topics in this tool can be found in the health professional's edition of the guideline on the ESHRE website.

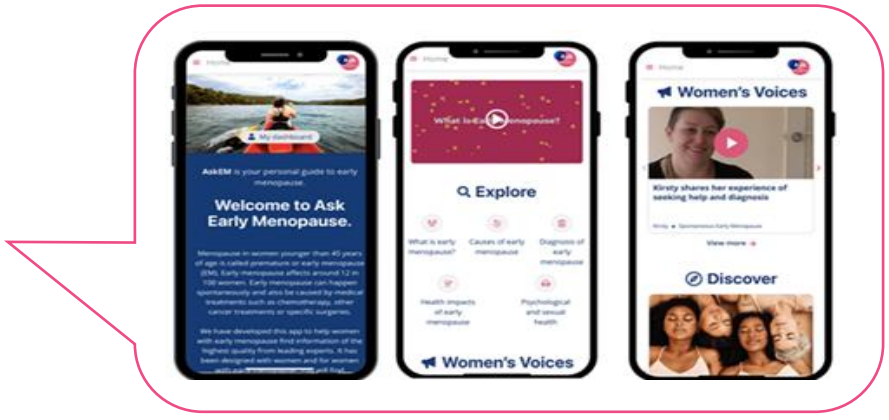
Other useful resources include:

- 2024 Turner syndrome guideline
  - Gravholt, CH et.al., Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2023 Aarhus International Turner Syndrome Meeting, European Journal of Endocrinology, Volume 190, Issue 6, June 2024, Pages G53–G151, doi.org/10.1093/ejendo/lvae050
- North American Menopause Society position statement on non-hormonal therapies for vasomotor symptoms
  - Shufelt, CL. et al., The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause 30(6): p 573-590, June 2023. DOI: 10.1097/GME.0000000000002200
- Sexual wellbeing:
  - Parish SJ, Hahn SR, Goldstein SW, Giraldi A, Kingsberg SA, Larkin L, Minkin MJ, Brown V, Christiansen K, Hartzell-Cushanick R *et al.* The International Society for the Study of Women's Sexual Health Process of Care for the Identification of Sexual Concerns and Problems in Women. *Mayo Clinic proceedings* 2019;94: 842-856. https://doi.org/10.1016/j.mayocp.2019.01.009
- Genitourinary symptoms
  - The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause* 2020;27: 976-992. *DOI:* 10.1097/GME.0000000000001609

Patient

A patient version of the guideline is available on the ESHRE website **here**. Fact sheets on topics related to POI, co-created with women with lived experience are available **here.**

The Ask Early Menopause App is freely available at the Apple or Google stores or at **www.askearlymenopause.org** and has information, women's stories, a dashboard and disucussion forum for women with POI and early menopause.



In some countries, there are patient organisations specifically for women with Premature Ovarian Insufficiency, while in other countries, people could find information and support through national patient organisations for infertility or related to the cause of POI such as Turner Syndrome, Fragile X or cancer support groups.

The Daisy Network is a support group for women suffering with Premature Ovarian Insufficiency (POI). They are a registered charity in the UK but have members from all over the world. Their aim is to provide support, information and a friendly network of people for their members. You can find more information at their website **https://www.daisynetwork.org.uk/**

For contact details of national patient organisations for infertility, you can ask your HCP, or contact **Fertility Europe (www.fertilityeurope.eu)** or **Resolve USA (https://resolve.org/get-help/find-a-support-group/**)

About this resource

This resource aims to assist HCPs and promote shared decision making, evidence-based care, reduce care variation and improve patient experience and outcomes.

How this resource was developed

This resource was written by Associate Professor Amanda Vincent (Co-chair of the Guideline Development Group) and Dr Nathalie Vermeulen (methodological expert) and revised by the Guideline Development Group members and HCP stakeholders. All the information provided is based on the recommendations in the 2024 ESHRE guideline: management of women with Premature Ovarian Insufficiency (POI).

Who developed the ESHRE guideline?

The 2024 ESHRE guideline: management of women with Premature Ovarian Insufficiency (POI) was developed by a multidisciplinary guideline development group including gynaecologists and endocrinologists, but also experts in bone health, cardiology, genetics, psychology, neurology, primary care, a literature methodology expert and patient representatives.

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Definition of the recommendations

The evidence level indicates the quality of the supporting evidence (High ⨁⨁⨁⨁, Moderate ⨁⨁⨁◯, Low ⨁⨁◯◯, Very low ⨁◯◯◯). In line with the GRADE approach, recommendations were labelled as either ''strong'' or ''conditional," with appropriate wording for each option. A strong recommendation implies that most patients should receive the recommended course of action. A conditional recommendation invites health care professionals to apply a shared decision-making approach. Good practice points (GPPs) provide recommendations for good clinical practice on areas where evidence is lacking or provide guidance for implementation of evidence-based recommendations.

Disclaimer

The European Society of Human Reproduction and Embryology (ESHRE) developed the current toolkit for healthcare professionals based on the clinical practice guideline. The aim of clinical practice guidelines is to aid healthcare professionals in everyday clinical decision about appropriate and effective care of their patients.

This resource is in no way intended to replace, dictate or fully define evaluation and treatment by a qualified physician. It is intended solely as an aid for patients seeking general information on issues in reproductive medicine.

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