Evidence-based guideline: premature ovarian insufficiency

Human Reproduction, 2024

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Why should endocrinologists care?

POI is not simply "early menopause“. The guideline emphasizes POI as a multisystem endocrine condition, not merely a reproductive disorder.

It affects:

- ✓ fertility
- ✓ bone health
- ✓ cardiovascular health
- ✓ sexual health
- ✓ psychological health
- ✓ neurological/cognitive health
- ✓ autoimmune and genetic disease recognition
- ✓ long-term mortality

Menopause	POI
Expected biological transition	Pathological/abnormal loss of ovarian function
Usually irreversible	Intermittent ovarian activity may persist
Pregnancy essentially impossible	Spontaneous conception remains possible
Occurs around 50 years	<40 years
HT usually symptom/risk based	HT generally replacement therapy

How common is POI?

Non-iatrogenic POI

Prevalence varies from 1% in older studies to 3.5% in recent publications.

Non-iatrogenic POI

Population characteristics such as ethnicity may affect the prevalence.

Great Question:

How many women with POI are currently being missed in endocrine practice?

How should POI be defined?

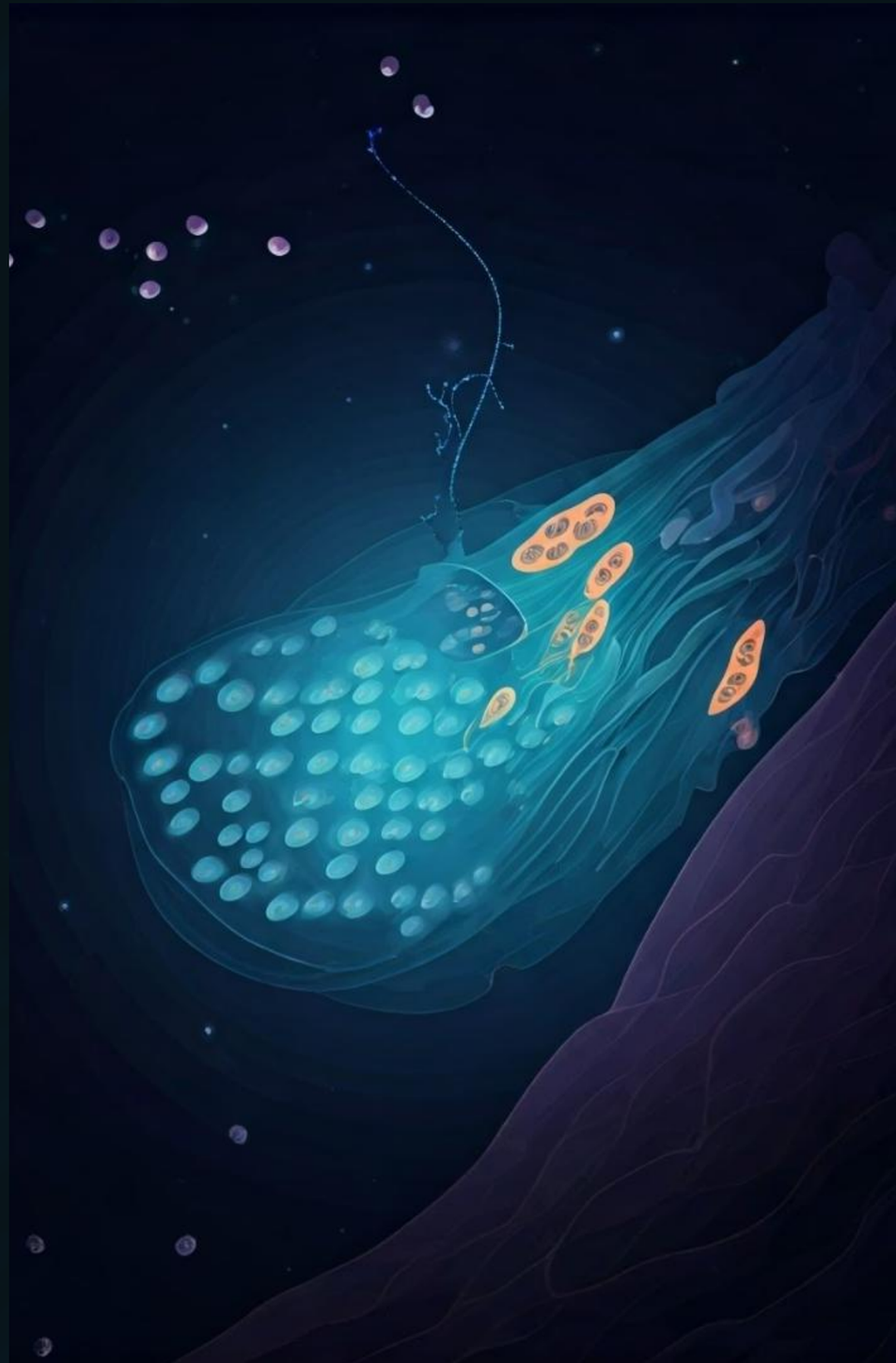
Definition:

POI is a condition defined by loss of ovarian activity before the age of 40years.

POI is characterized by amenorrhea or irregular menstrual cycles with elevated gonadotropins & low estradiol.

early menopause:

cessation of ovarian function in women aged from 40 -45 years.



2024 diagnostic criteria:

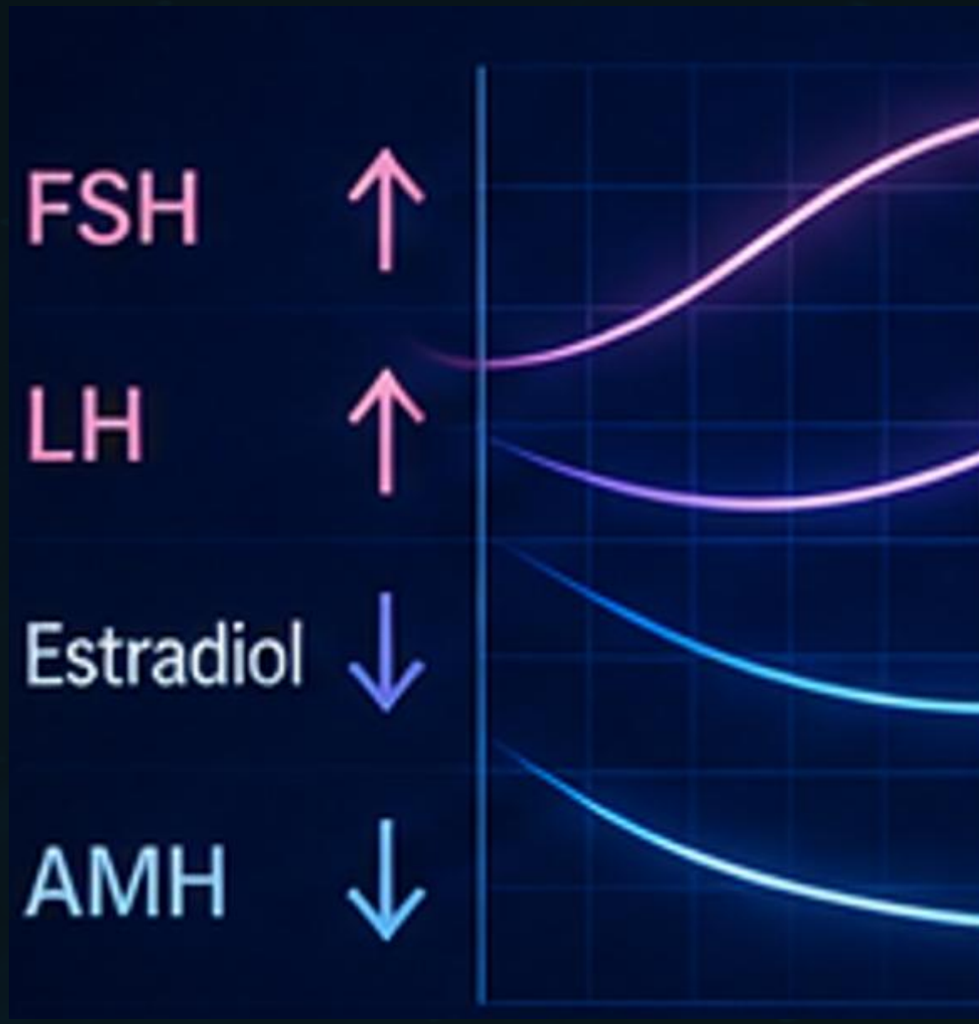
Disordered menstrual cycles ≥4 months + FSH >25 IU/L

If diagnostic uncertainty exists: Repeat FSH after 4–6 weeks

R/O the following:

Pregnancy, Use of hormonal therapy

Women who had BSO before age 40 have a diagnosis of POI, and additional diagnostic testing is unnecessary.



What about estradiol?

1. **The guideline group does not recommend to:**

   diagnose POI based on serum estradiol concentrations.

2. **However:**

   a low estradiol concentration indicates hypoestrogenism

3. **And:**

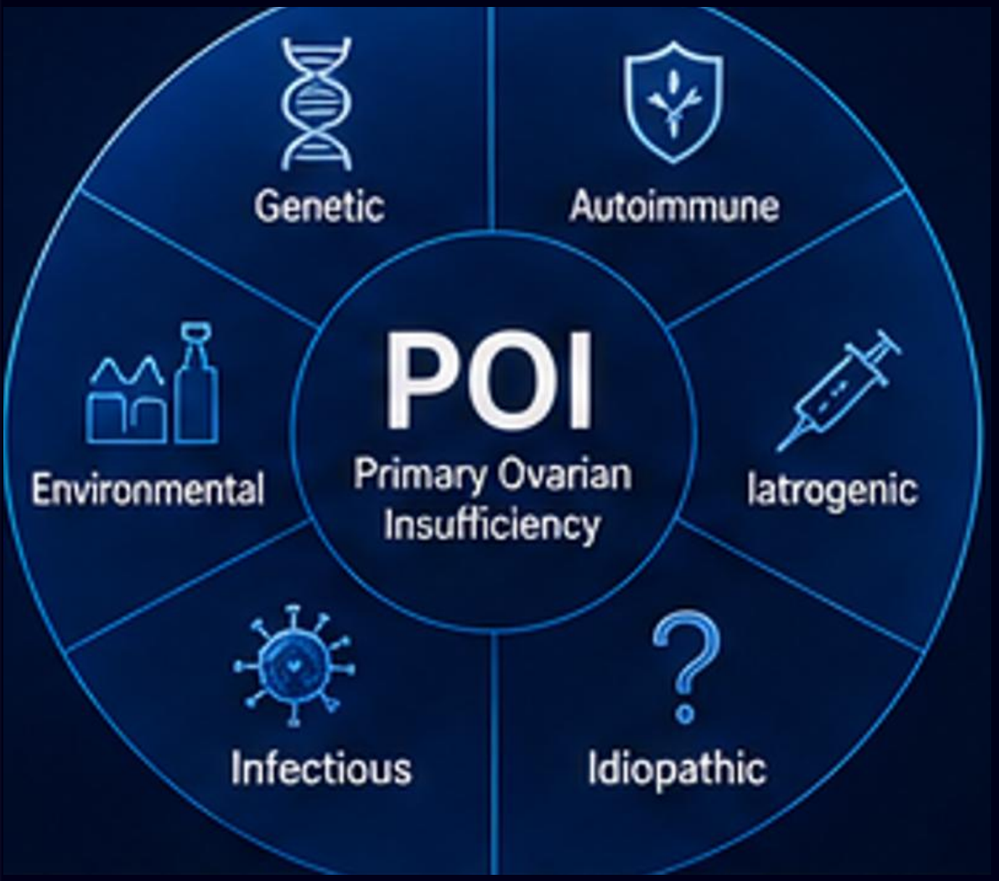
   Low serum estradiol combined with an elevated FSH, provides additional confirmation of the POI diagnosis.

AMH: biomarker or diagnostic test?

1. AMH should not be used as the primary diagnostic test for POI.
2. 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.
3. AMH should not routinely be used to predict POI.

   due to insufficient evidence of accuracy

How should we investigate the known causes of non-iatrogenic POI?



1

Genetic:
Turner syndrome, X chromosome abnormalities, FMR1 premutation, other genetic causes

2

Autoimmune:

adrenal autoimmunity, thyroid disease

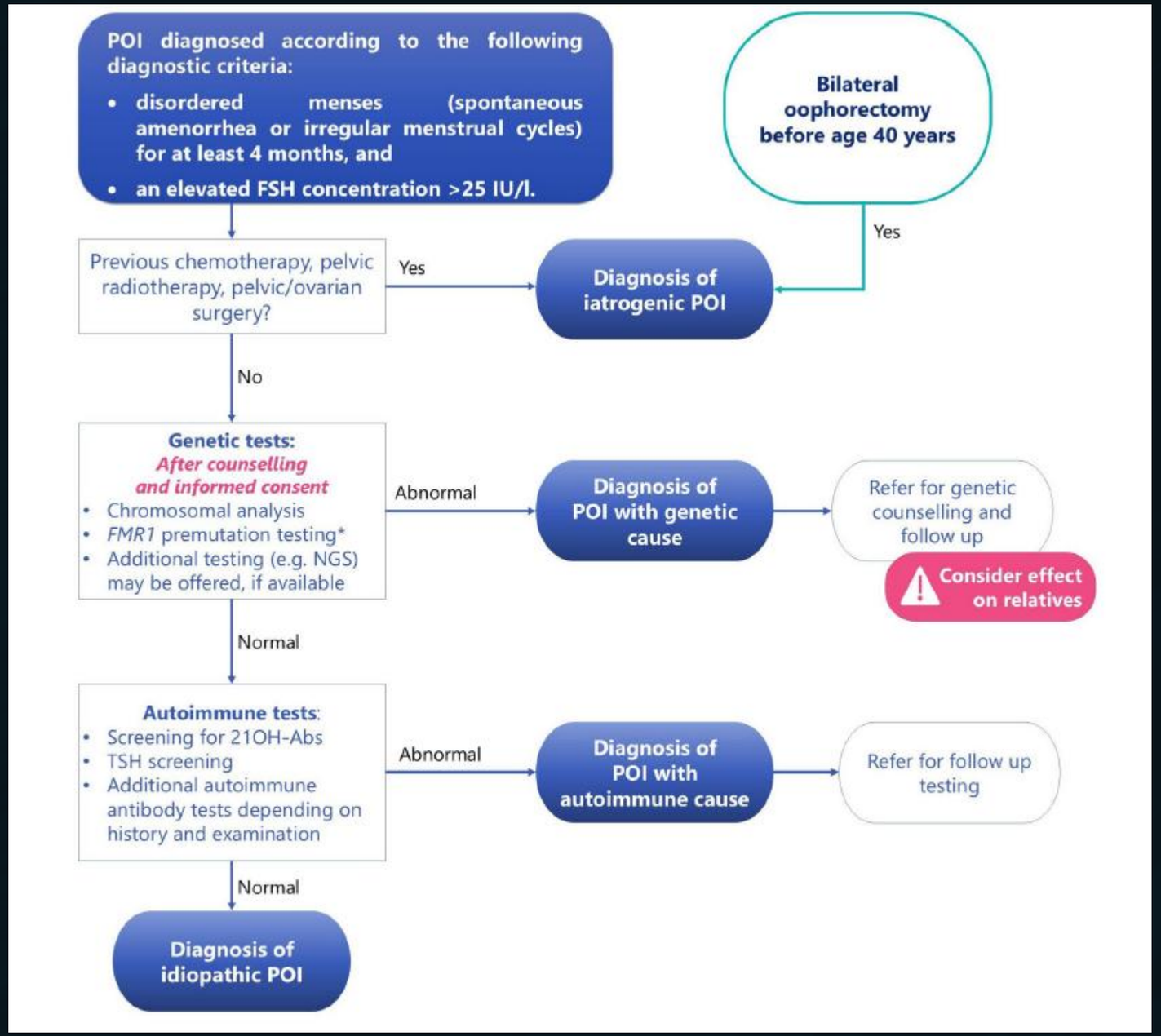
3

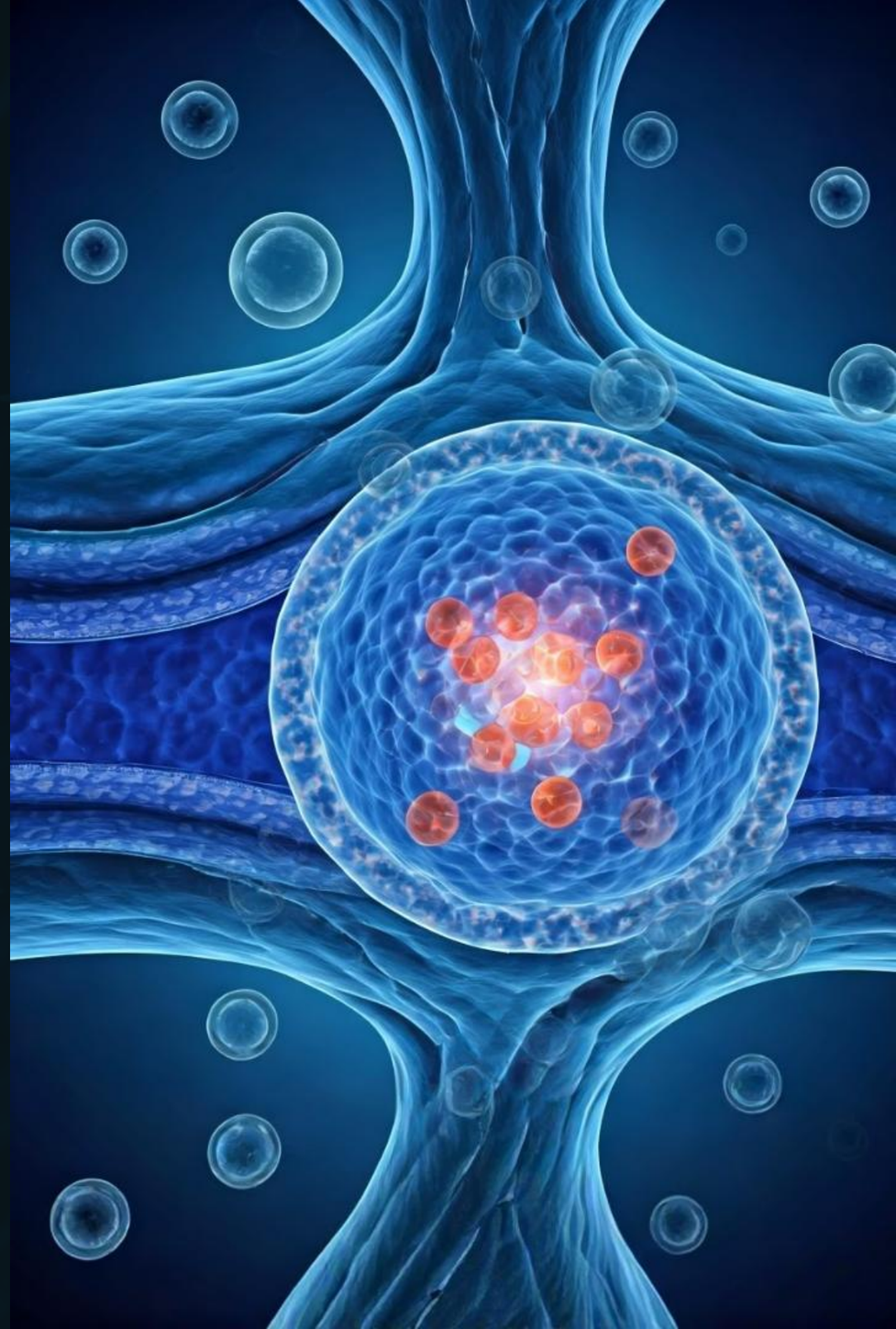
Iatrogenic:

Chemotherapy, radiotherapy, ovarian surgery

4

Idiopathic


POI diagnosed according to the following diagnostic criteria:
• disordered menses (spontaneous amenorrhea or irregular menstrual cycles) for at least 4 months, and
• an elevated FSH concentration >25 IU/l.
Bilateral oophorectomy before age 40 years
Yes
Previous chemotherapy, pelvic radiotherapy, pelvic/ovarian surgery?
Yes
Diagnosis of iatrogenic POI
No
Genetic tests:
After counselling and informed consent
• Chromosomal analysis
• FMR1 premutation testing*
• Additional testing (e.g. NGS) may be offered, if available
Abnormal
Diagnosis of POI with genetic cause
Refer for genetic counselling and follow up
Consider effect on relatives
Normal
Autoimmune tests:
• Screening for 21OH-Abs
• TSH screening
• Additional autoimmune antibody tests depending on history and examination
Abnormal
Diagnosis of POI with autoimmune cause
Refer for follow up testing
Normal
Diagnosis of idiopathic POI



Genetic testing: a major 2024 update

We should discuss the implications of genetic testing before the test is performed

Chromosomal analysis testing and FMR1 premutation is recommended for all women with non-iatrogenic POI.

additional genetic testing (NGS):

Where available and after comprehensive genetic counselling, additional genetic testing (e.g. NGS) can be offered to all women with non-iatrogenic POI to identify other potential genes that may cause POI

the age of a woman with POI should not be used to restrict access to genetic testing.

Autoimmune POI: what should we actually test?

1

Screening for 21-hydroxylase autoantibodies:

should be performed in women with POI of unknown cause.

2

Screening for anti-ovarian autoantibodies:

should not be used to diagnose autoimmune POI.

3

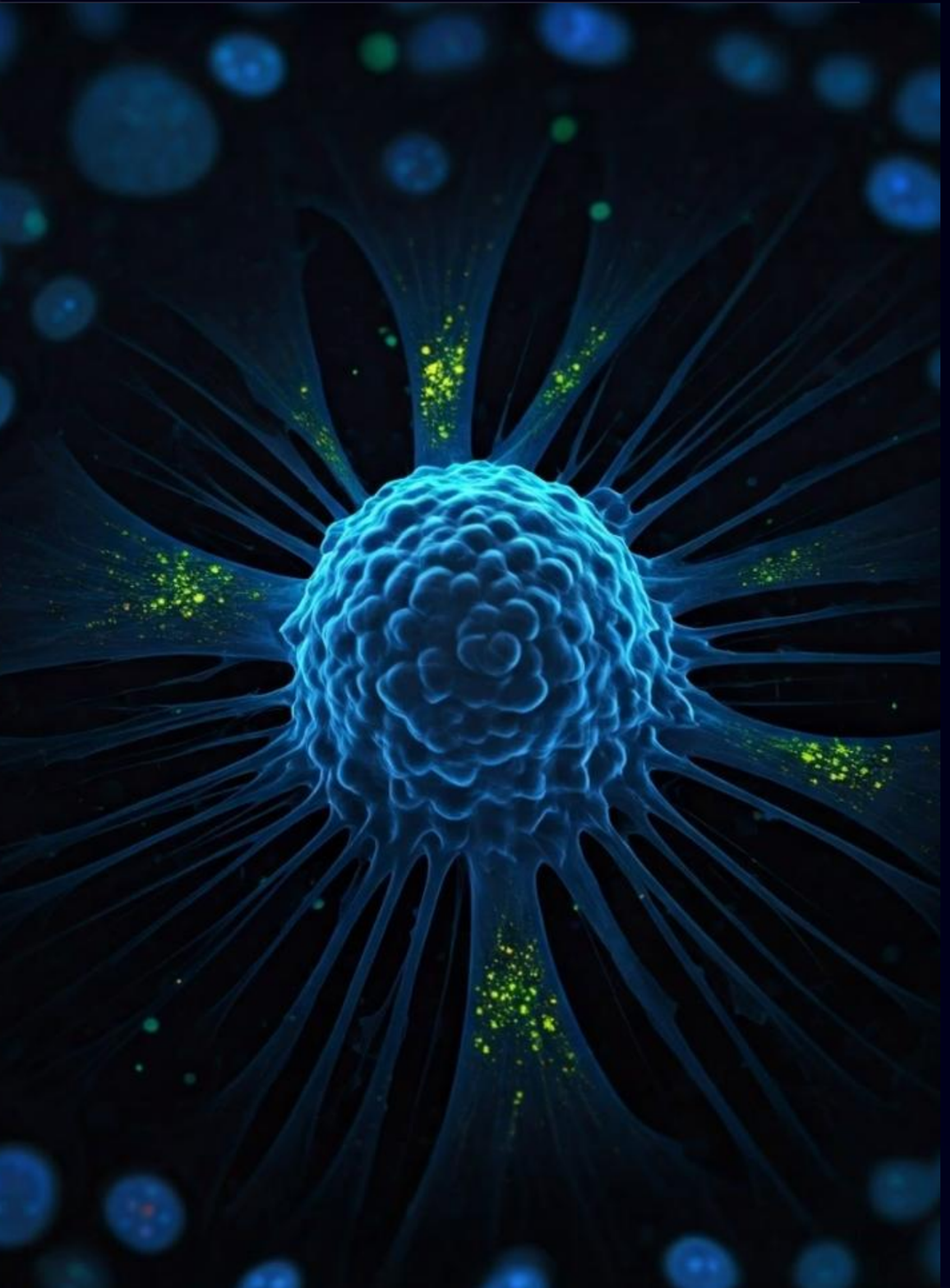
Thyroid function test:

TSH should be measured at POI diagnosis. It should be repeated every 5 years or when symptoms arise.

4

TPO antibody:

It should not routinely perform as part of testing for autoimmune causes of POI: high prevalence of positive test in general community.



POI & adrenal autoimmunity

If 21OH-Ab positive:

evaluate for adrenal insufficiency and arrange longitudinal follow-up

21OH-Ab negative:

there is no indication for re-testing later in life, unless signs or symptoms of adrenal insufficiency develop.

What are we trying to prevent?

bone loss

cardiovascular risk

✓ POI without HT is associated with reduced life expectancy, largely due to cardiovascular disease.

✓ Patients should be encouraged to adopt a healthy lifestyle (avoid smoking, healthy diet and physical activity, and maintaining a healthy weight) to reduce cardiovascular risk.

urogenital symptoms

sexual dysfunction

possible neurological/cognitive consequences

Fertility:
what should endocrinologists tell patients?

Does POI mean zero chance of pregnancy?

natural conception

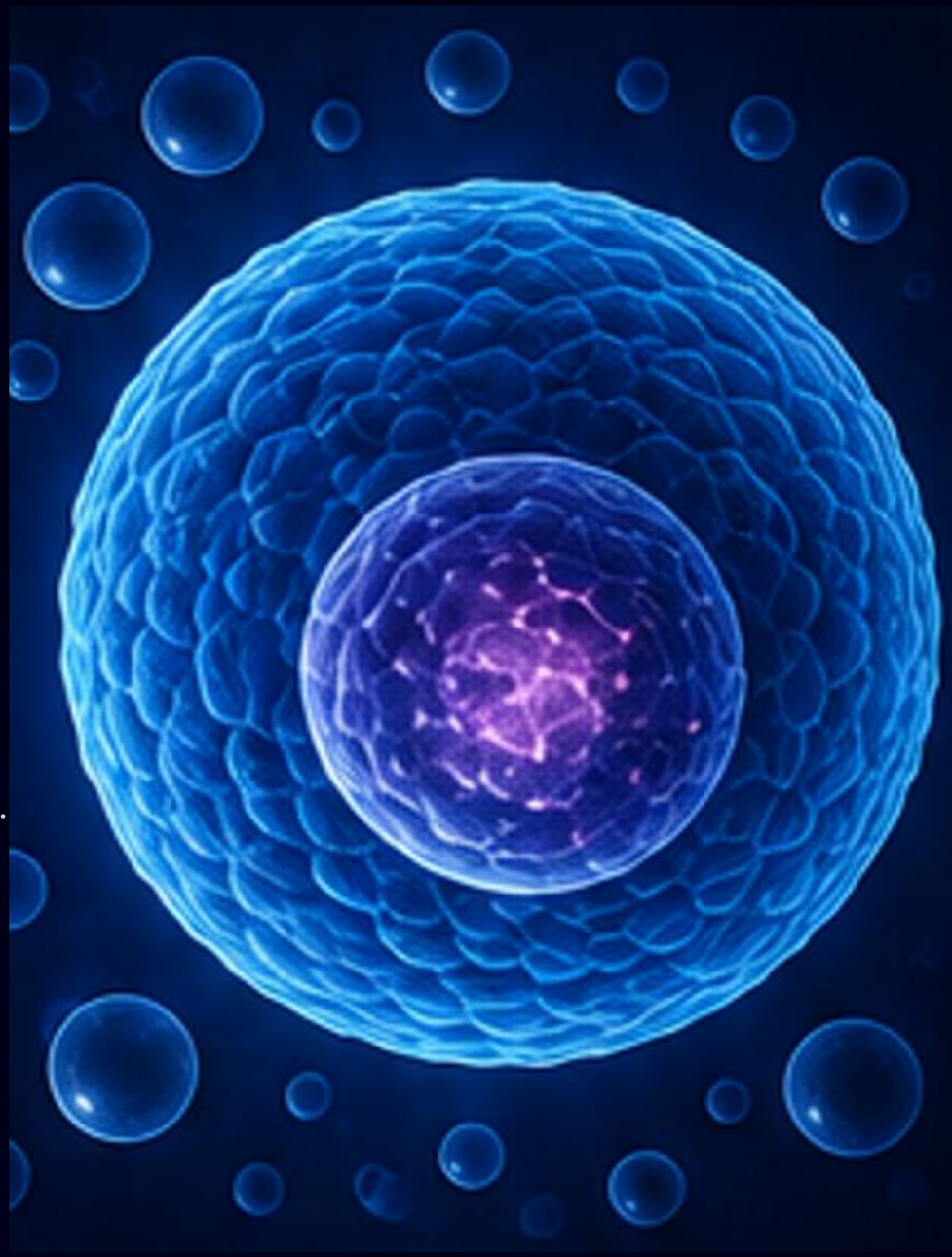
POI substantially reduces the chances of natural conception.

In non-surgical POI:

ovarian activity may occur and there is a chance of natural conception.

Is contraception needed?

Women with non-surgical POI should be advised to use contraception if they wish to avoid pregnancy.



Fertility treatment For established POI:

increasing ovarian activity and natural conception rates:

No proven treatment reliably restores ovarian function.

established option to achieve pregnancy:

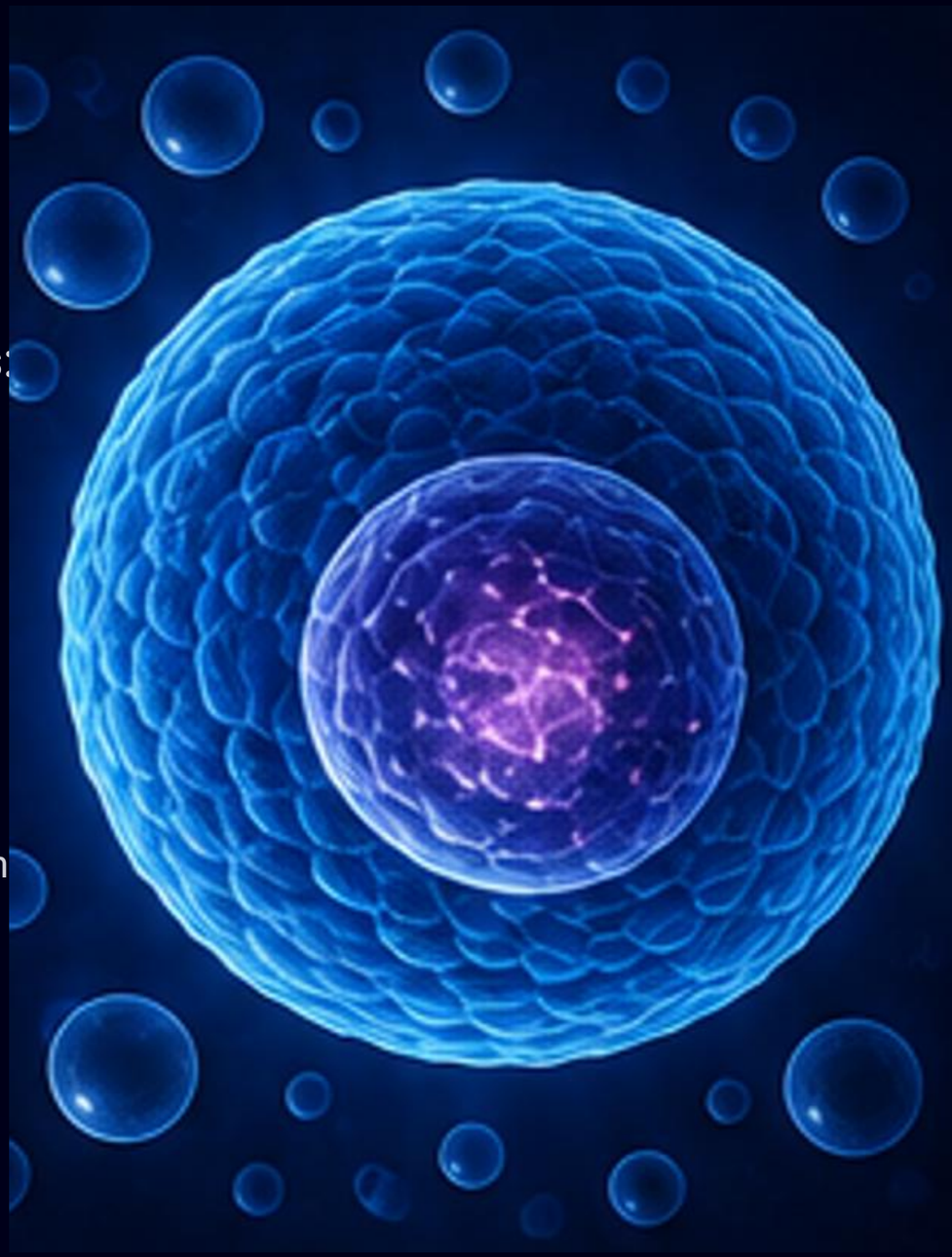
oocyte donation

Genetic risk in oocytes donation

Women with non-iatrogenic POI and considering assisted reproduction Using oocytes donated by their sister should be informed that this includes shared genetic risk and carries a higher risk of ovarian stimulation cycle cancellation.

BUT REMEMBER:

spontaneous pregnancy can occur.

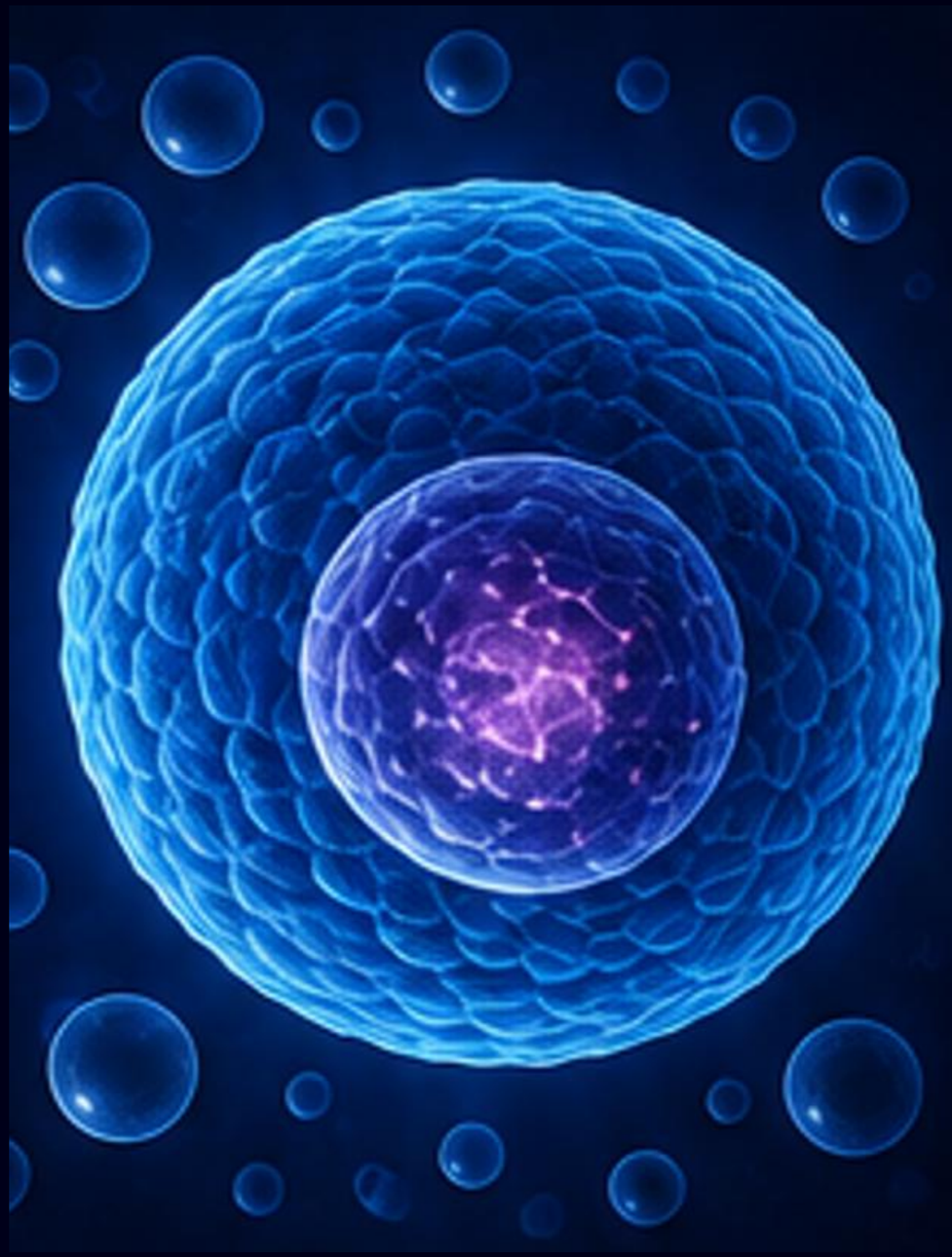


Fertility preservation: don't wait for POI

For iatrogenic causes of POI:

Fertility preservation can be considered prior to treatment

Fertility preservation should be discussed with women at risk of POI. In most women with POI, there is no opportunity for fertility preservation as the follicle pool is depleted.



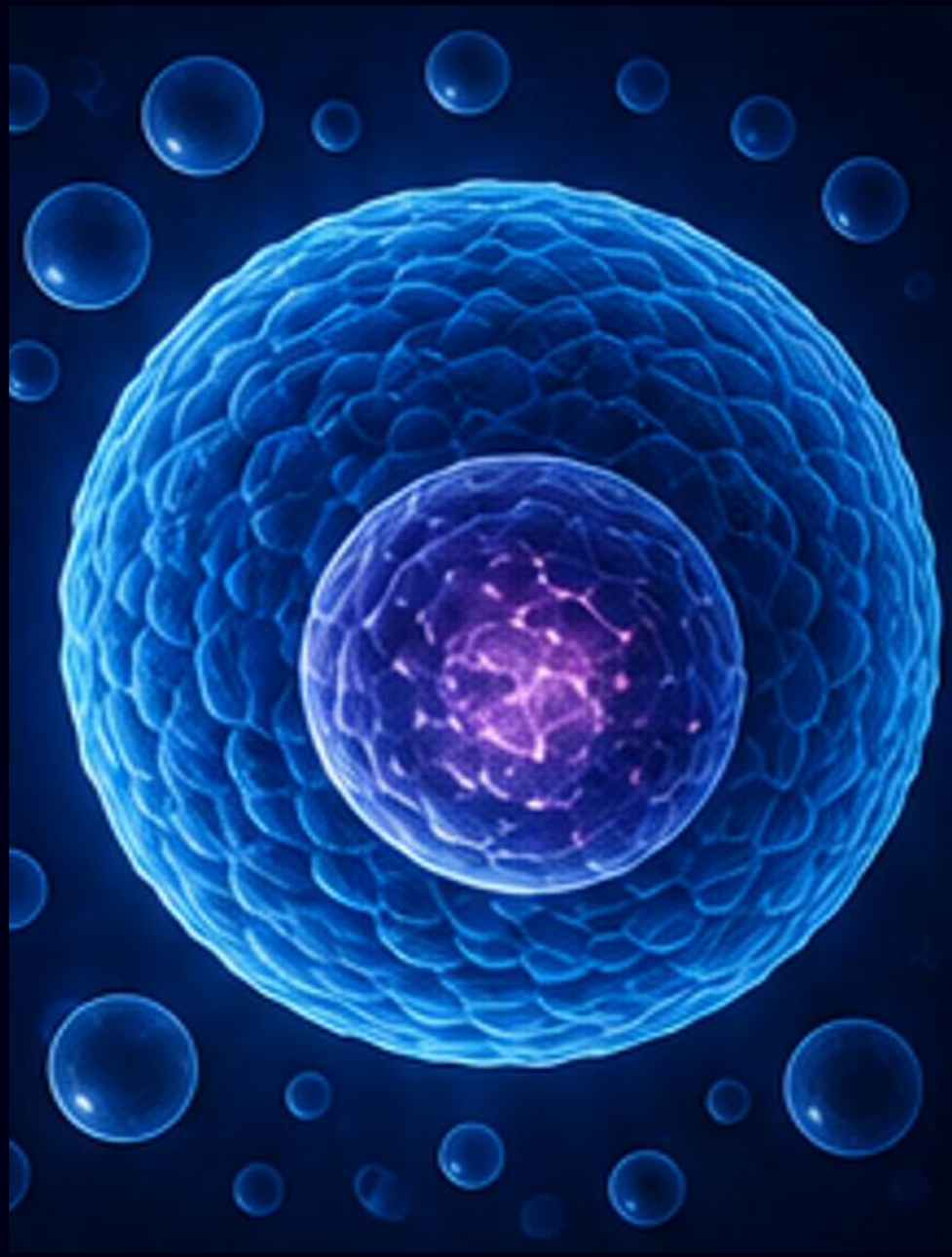
obstetric risks associated with POI

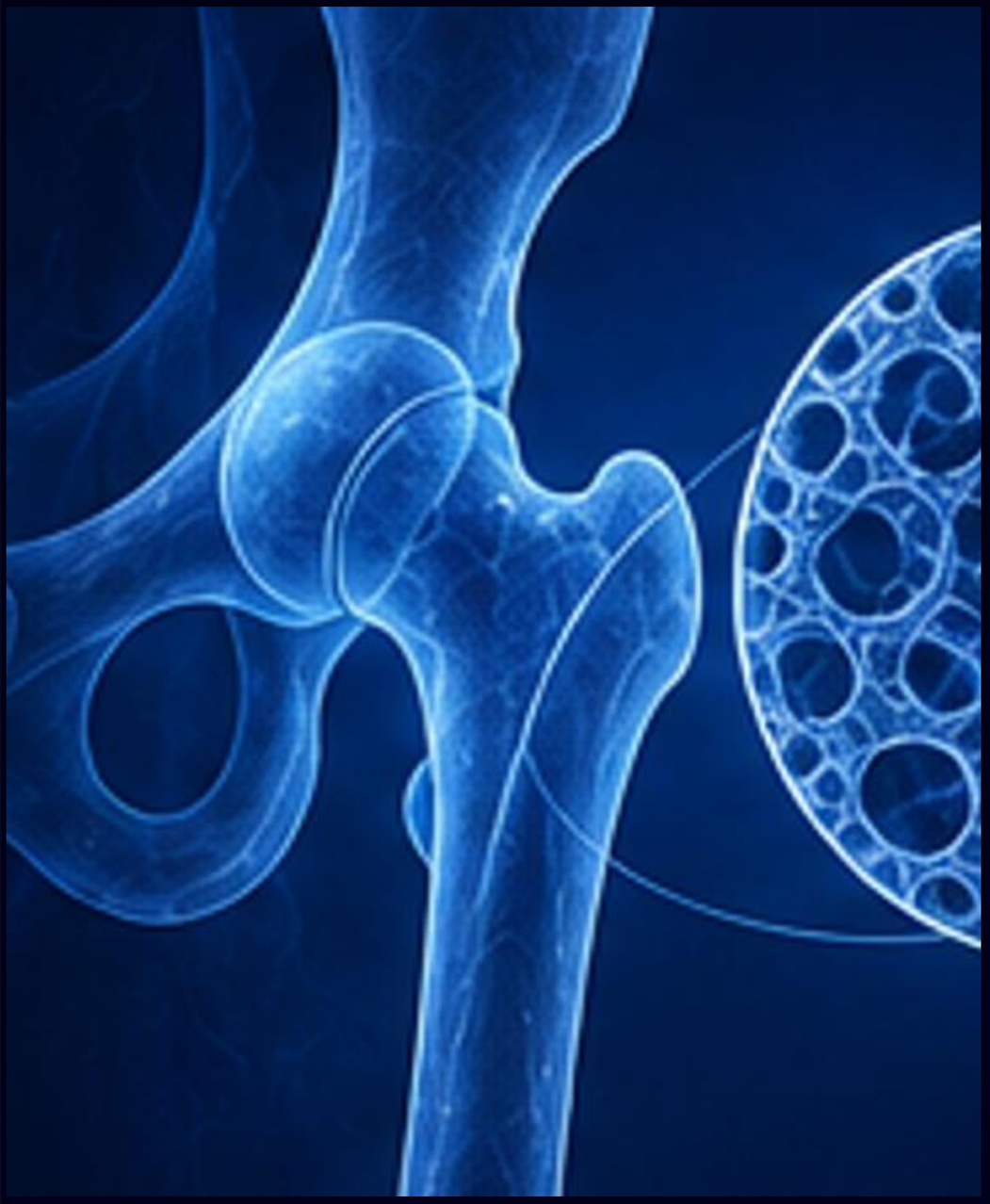
Natural pregnancies after idiopathic POI or most forms of chemotherapy :
do not show any higher obstetric or neonatal risk than

Oocyte donation pregnancies:
are high risk and should be managed in an appropriate obstetric unit.

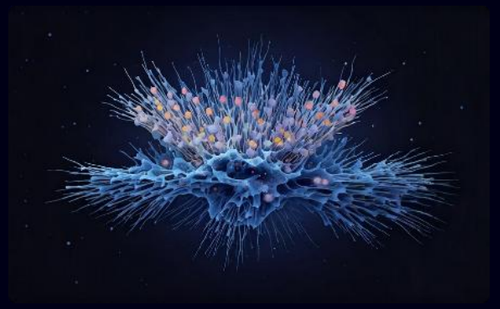
Pregnancies occurring after radiation to the uterus:
are at high risk of obstetric complications and should be managed in An appropriate obstetric unit.

Pregnancies in Turner Syndrome:
are at high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement.



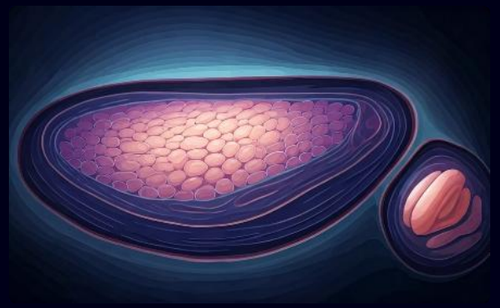


Bone Health:
what should we know?



Affect on BMD:

POI is associated with abnormal bone microarchitecture and reduced BMD.



Fracture risk:

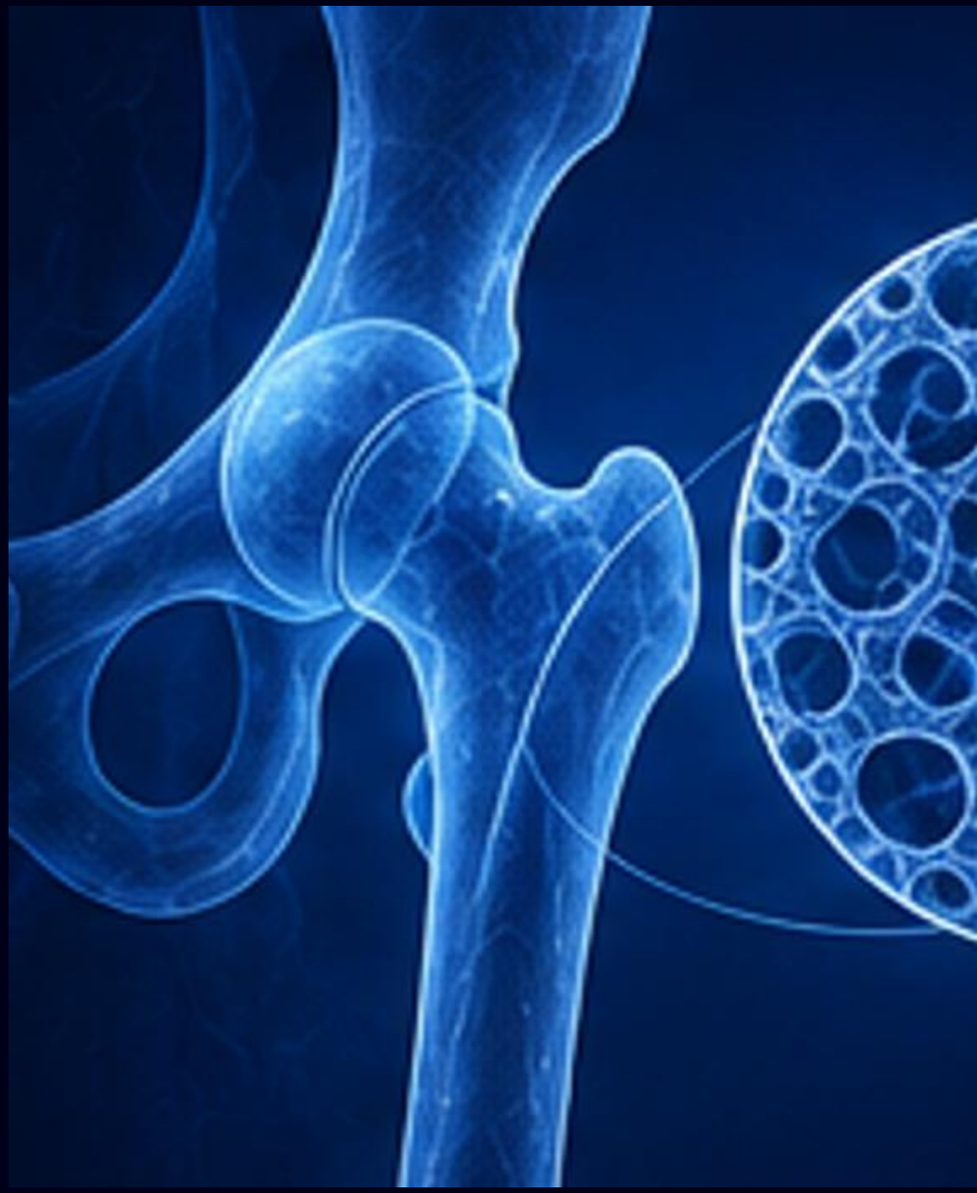
POI may be associated with an increased risk of osteoporosis and fracture later in life.

treatment options for bone protection and improvement

1. **Risk factor modification:**
   Osteoporosis risk factors should be identified and addressed.

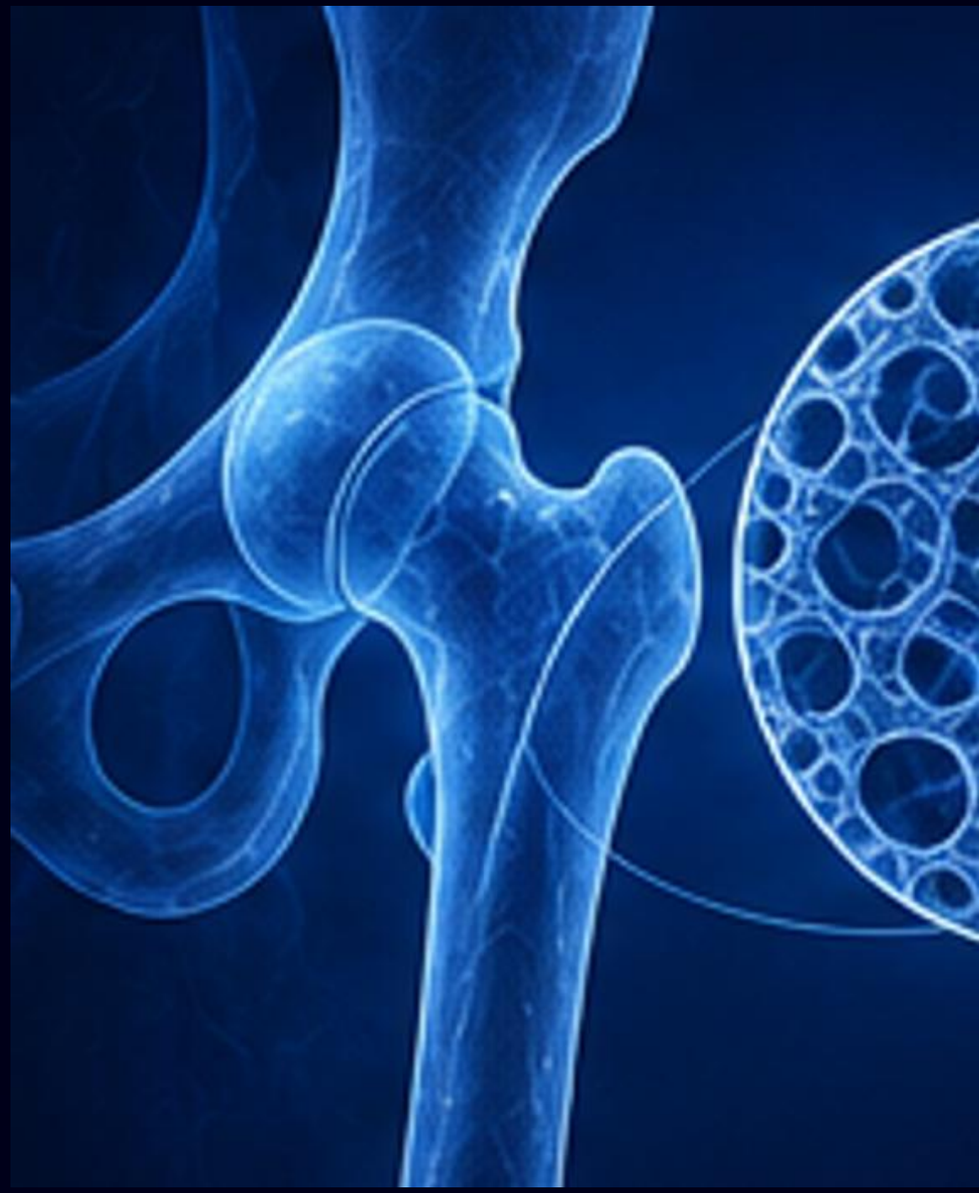
2. **Life style:**
   Having a healthy lifestyle (including weight-bearing exercise, healthy diet, avoiding smoking, and maintaining normal weight) to optimize bone health.

3. **supplementation of calcium and vitamin D:**
   may be required in inadequate vitamin D status and/or calcium intake and may be of benefit in women with low bone mineral density.



HT is foundational

1. **dose of HRT:**
   A daily dose of HRT containing no less than 2 mg oral or 100 µg transdermal estradiol, or equivalent, is suggested to optimize BMD.
2. **Time of HRT:**
   Delayed initiation and non-adherence should be avoided.
3. **What If the combined oral contraceptive is used:**
   a continuous or extended regimen is recommended to provide Continuous estrogen therapy and avoid bone loss.
4. **estrogen alone or bisphosphonate?**
   estrogen replacement first, clinical judgment is particularly important, Particular caution applies to women desiring pregnancy.



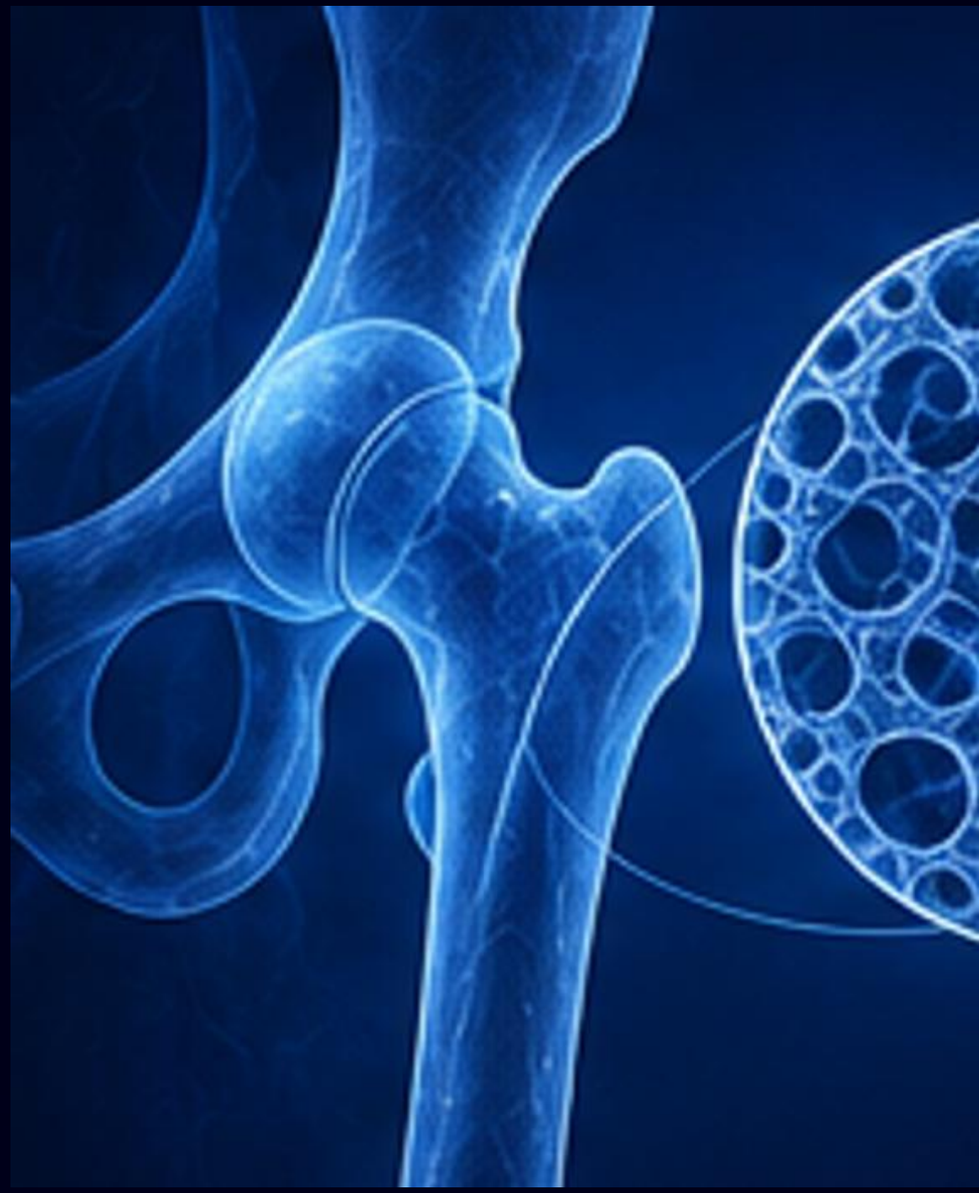
Monitoring of skeletal health

1. **BMD (DXA)**
   at the time of diagnosis of POI for all women.

2. **If BMD is normal:**
   If BMD is normal and adequate systemic HT, repeat no less than 5 ys.

3. **If BMD show steoporosis or low bone density**
   BMD (DXA) should be reassessed every 1–3 years, based on individual risk factors

4. **Caution!**
   decrease in BMD should prompt review of HT and potential factors contributing to bone loss.



Muscle Health:
what should we know?

POI and Muscle health

1

Effect on muscle:

POI may be associated with reduced muscle mass, strength, and performance, which may increase the risk of sarcopenia. So screen for sarcopenia at POI diagnosis.

2

Treatment options for muscle protection & improvemen

Adoption of a healthy lifestyle, prescribing resistance exercise

3

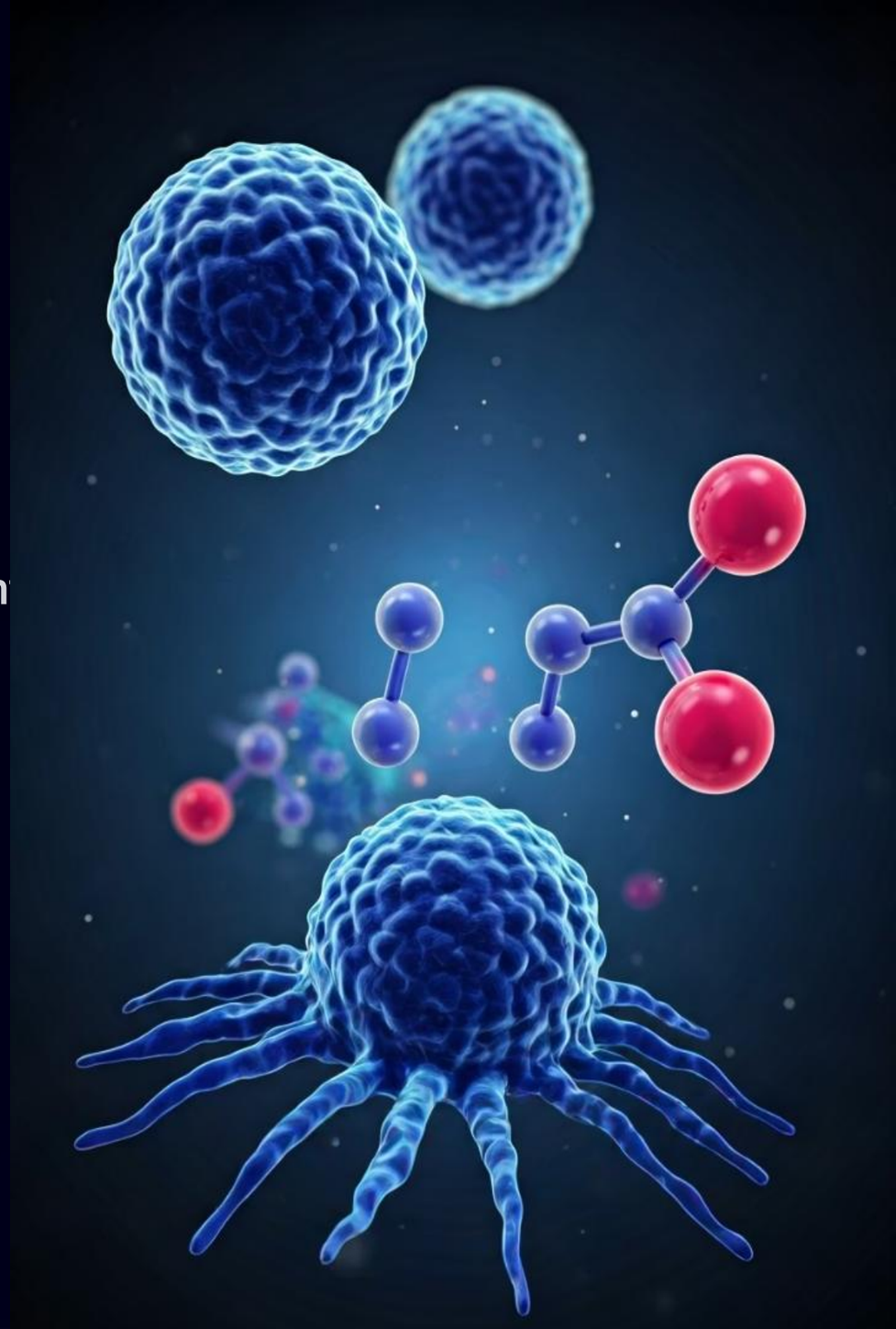
What about HRT

HRT prescribed for other indications may also benefit muscle health

4

testosterone therapy

The effect of other interventions, including testosterone therapy, on muscle health in women with POI is uncertain and therefore they should not be offered.



Consequences of POI for the cardiovascular system

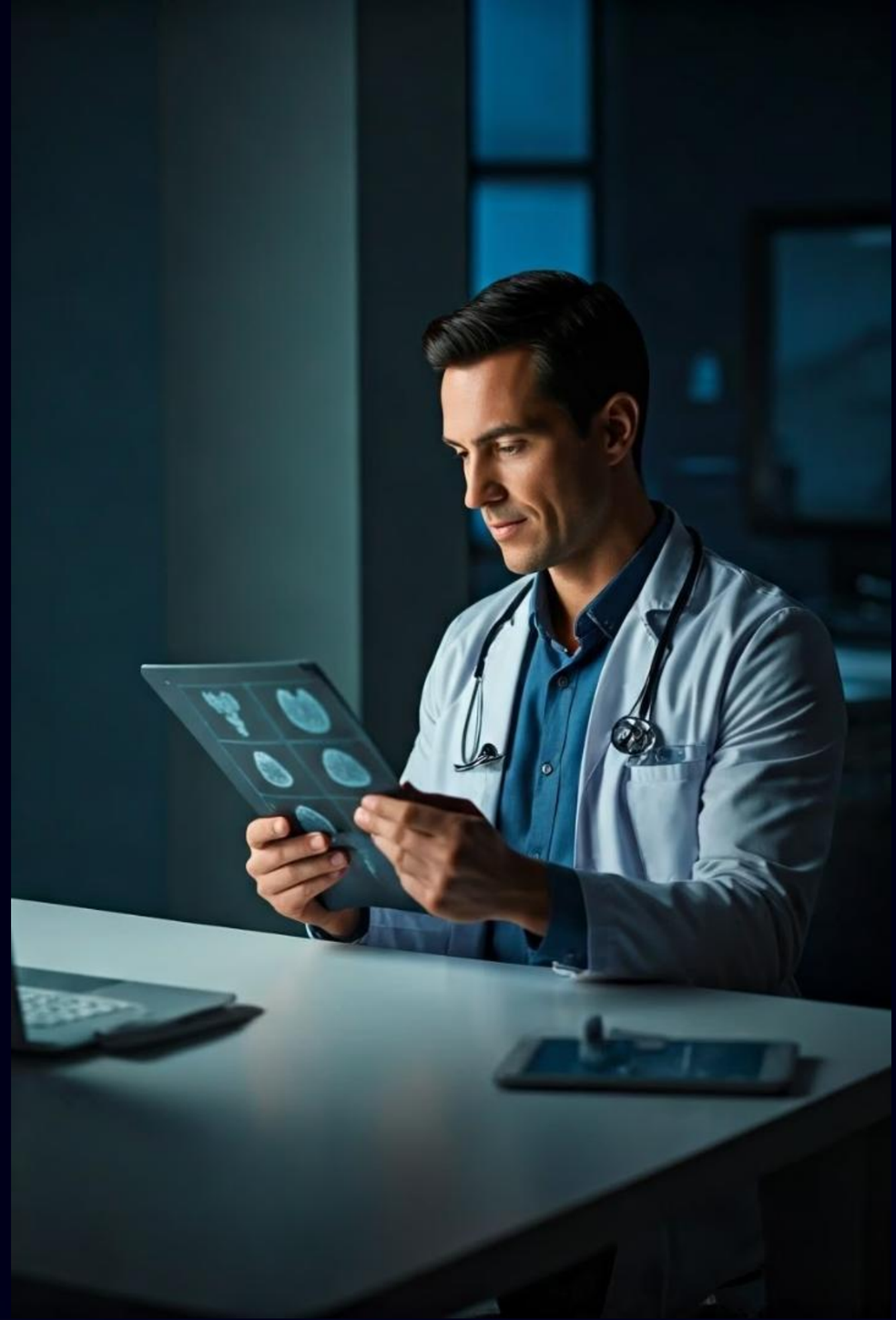
POI is a cardiovascular risk state

1. **increased risk of CVD**
   including CAD, HF and stroke.

2. **Turner Syndrome**
   All women diagnosed with Turner Syndrome should be evaluated by a cardiologist, especially prior to and during pregnancy.

3. **Is estrogen therapy cardio-protective?**
   Estrogen therapy has beneficial cardiometabolic effects, which can influence cardiovascular disease risk.

4. Non-use of HT is associated with an increased risk of CVD events and mortality, and HT is therefore recommended until the usual age of menopause.



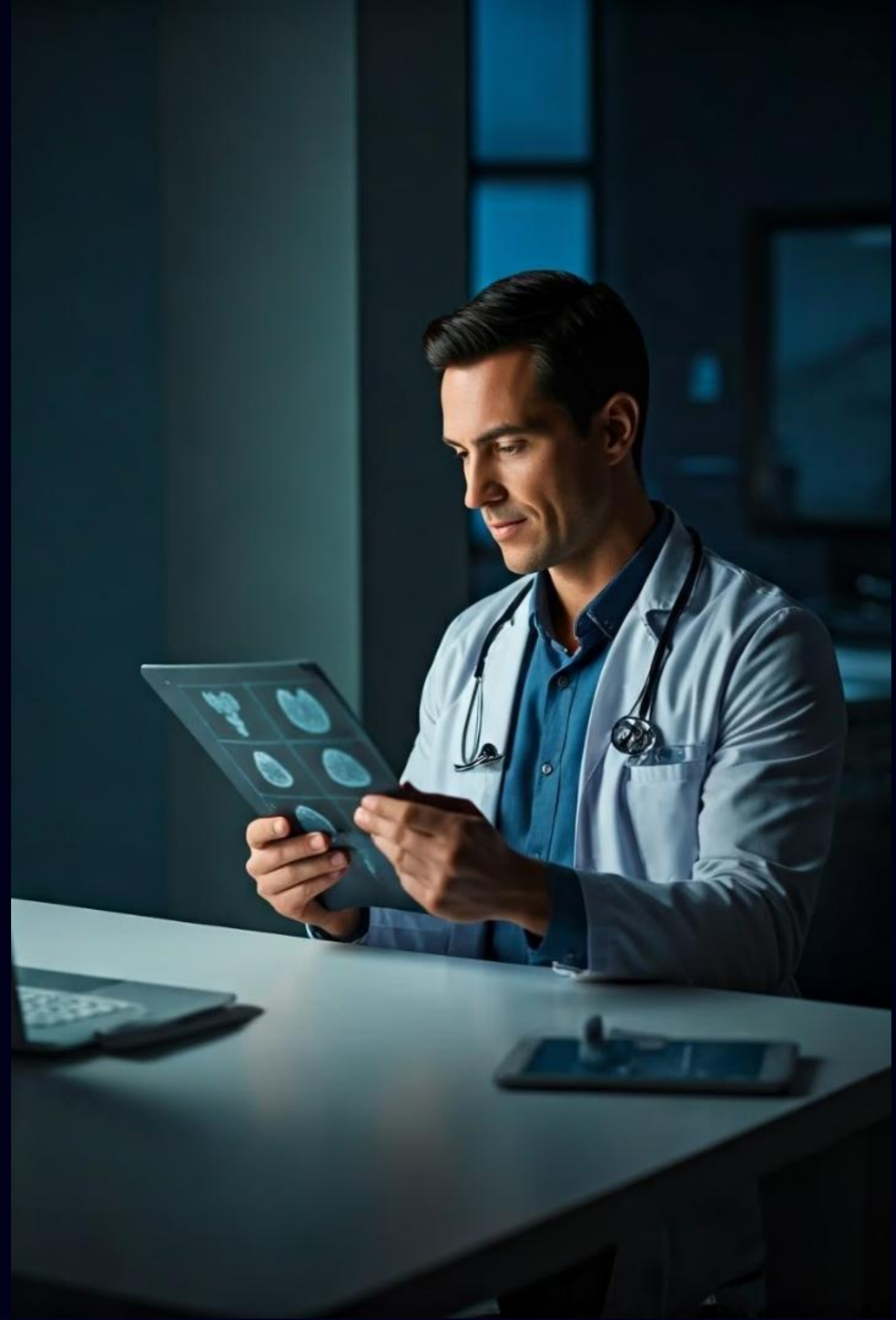
Monitoring CV risk factors

1. **Baseline cardiovascular risk assessment**
   At diagnosis of POI

2. **Modifiable risk factors:**
   behavioral change (including avoiding smoking, heart healthy diet, regular physical activity, and maintenance of normal body weight.

3. **Ongoing monitoring:**
   All women with POI should have (at least) annual monitoring of BP, weight, and smoking status

4. **DM and Dyslipidemia:**
   All women with POI should have a lipid profile and DM screening at diagnosis.
   Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia, hyperglycaemia, and additional risk factors or global cardiovascular risk.

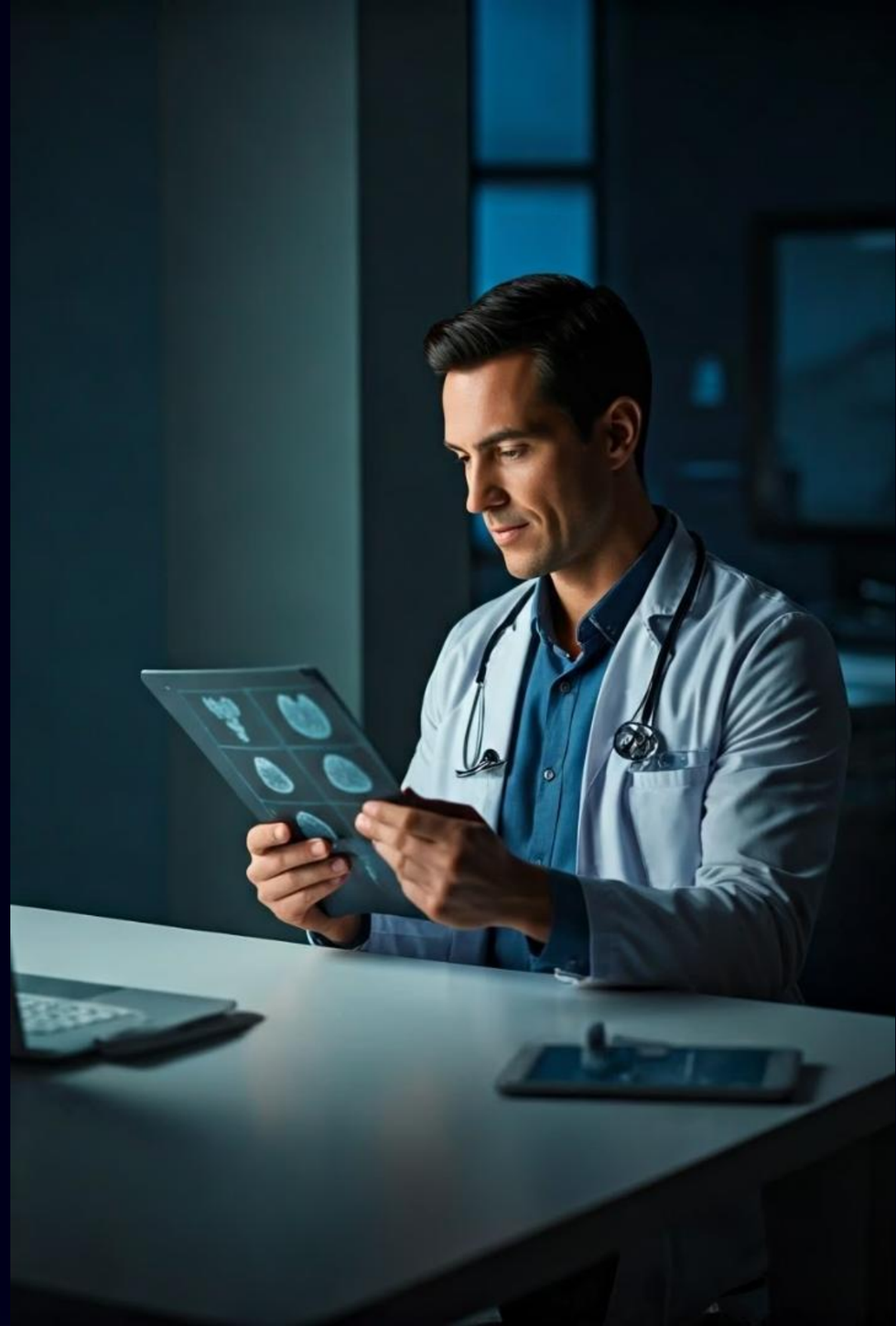


Consequences of POI on psychological wellbeing and quality of life

psychological wellbeing and quality of life

1. We should offer assessment of psychological health and QOL to all women with POI

2. Personalized care, including psychological support should be accessible to women with POI.



The Neglected Aspects of POI

Sexual and genitourinary health

Don't stop at vaginal dryness.

Ask about:

Libido, dyspareunia, vaginal dryness, genitourinary syndrome, relationship/psychosexual consequences

The guideline group recommends personalized management using the biopsychosocial model for the impact of POI on sexuality.

HCPs should be aware that HT prescribed to women with POI for other indications may improve sexual function, although the effect is generally small.

Testosterone: what is the evidence?

Iatrogenic POI

Testosterone treatment should be considered in women with hypoactive sexual desire disorder when other biopsychosocial etiologies are excluded. (Strong recommendation)

Noniatrogenic POI

estosterone treatment could be considered in women with hypoactive sexual desire disorder when other biopsychosocial etiologies are excluded. (Conditional recommendation)

Safety

although short term treatment with transdermal testosterone at premenopausal physiological doses is safe, longer term safety data are lacking

Transdermal testostrone

Treatments of GU symptoms in POI

Iatrogenic POI

vaginal estrogen therapy should offer to improve genitourinary and sexual symptoms.

Women with POI may be offered vaginal estrogen therapy if genitourinary symptoms are not fully relieved by using systemic HT

Vaginal lubricants and moisturizers

can be used for treatment of vaginal discomfort and dyspareunia in women with POI and can be combined with other treatments.

laser or thermal energy

It is not recommended as standard care for GU symptoms

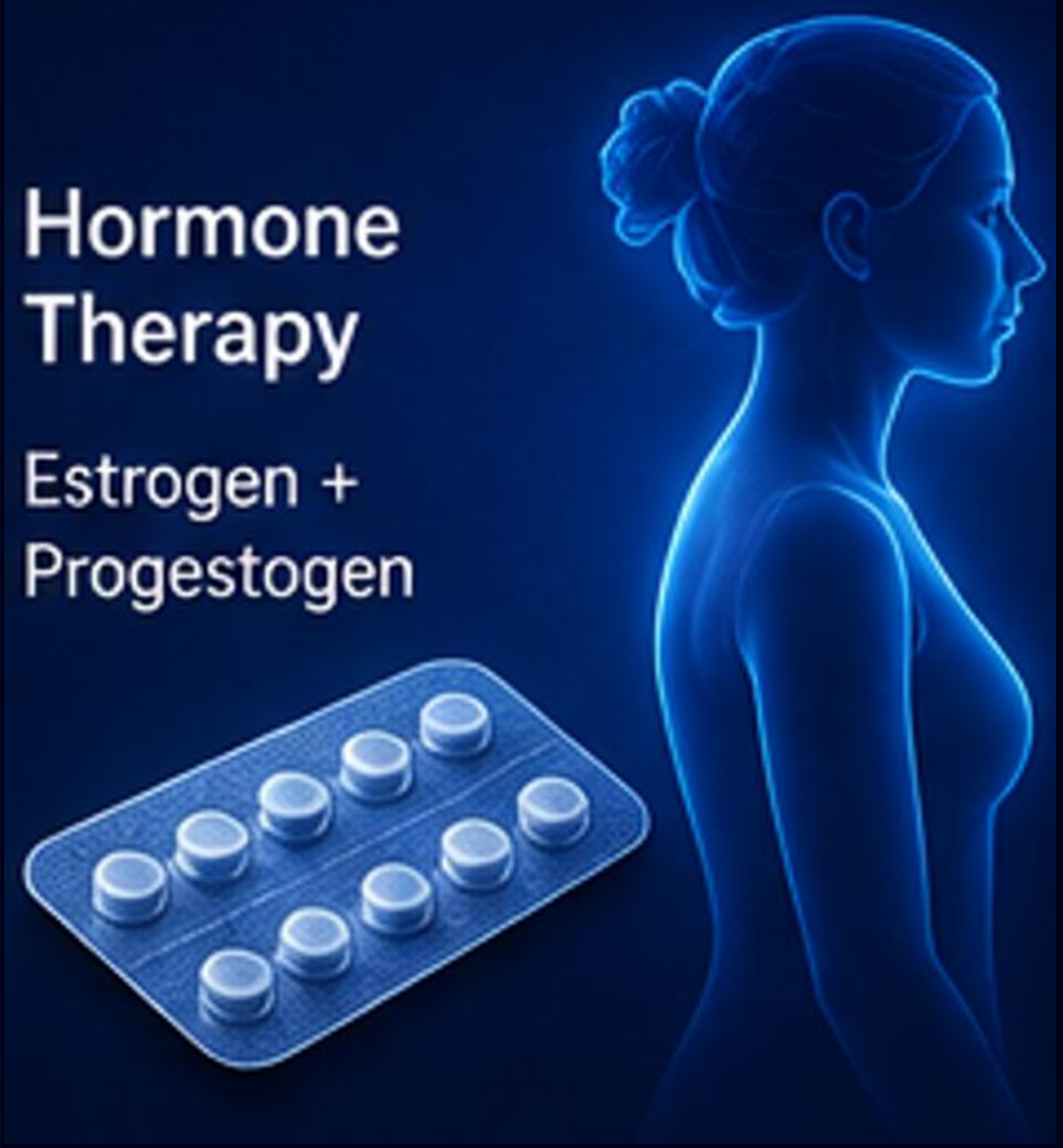
POI effects on cognition

POI is associated with an increased risk of cognitive impairment and dementia.

The possible effect on cognition and dementia, Parkinsonism and other neurologic diseases should be discussed when planning BSO under the age of 45 years, especially for women at an average risk of ovarian cancer.

HT is recommended in women with POI until the usual age of menopause to reduce the possible risk of cognitive impairment and dementia.

The guideline group recommends that women with POI should be encouraged to adopt a healthy lifestyle to reduce the risk of cognitive impairment and dementia.



POI Treatment

Hormone therapy (HT) in POI

HT until what age?

HT is recommended 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.

When reaching menopause age:

consider the need for continued HT based on a personalized risk–benefit assessment and current evidence.

Contraception:

We should know that HRT does not provide contraception.

Intermittent ovarian function and desiring natural pregnancy:

recommendations for HRT remain unchanged and do not impact chances of natural conception. A sequential HRT regimen is recommended.

Recommendations of hormone therapy for POI.

Age Range	Medications and Comments
12–13 years	If no secondary sexual characteristics and elevated FSH: initiate low-dose estrogen. Estradiol (E2): • Transdermal: 12.5 μg/day (patch) • Oral micronized E2: 0.5 mg/day
12.5–15 years	Gradually increase the estrogen dose every 6-months until reaching adult doses. Estradiol (E2): • Transdermal: 25, 50, 100 μg/day (adult dose: 75–100 μg/day) • Oral E2: 0.5, 1.0, 1.5, 2.0 mg/day (adult dose: 2–4 mg/day)
14–16 years	Initiate progestogen after 2-years or upon first withdrawal bleeding (whichever occurs first), or based on ultrasound showing endometrial response. Progestogen for 14-days/month: • Oral micronized progesterone: 200 mg/day • Dydrogesterone: 5–10 mg/day • medroxyprogesterone acetate (Provera): 10 mg/day
16–50 years	Full-dose estrogen and progestogen therapy. Estradiol (E2): • Oral: 2–4 mg/day • Transdermal patch: 75–100 μg/day • Transdermal gel (sachet): 1.5–2 mg/day • Transdermal gel (0.75 mg/pump): 3–4 dose/day; Transdermal spray (1.53 mg/spray): 3–4 dose/day Progestogen: • Sequential regimen (14 consecutive days/month): • Oral micronized progesterone: 200–400 mg/day • Dydrogesterone: 10–20 mg/day • medroxyprogesterone acetate (Provera): 10 mg/day • Norethisterone: 10 mg/day • Continuous regimen (daily use): • Oral micronized progesterone: 200–400 mg/day • Dydrogesterone: 10–20 mg/day • medroxyprogesterone acetate (Provera): 5 mg/day • Norethisterone: 5 mg/day • LNG-IUD (52 mg) • Continuous combined oral contraceptive with 30 μg ethinylestradiol (especially when pregnancy risk exists and is not acceptable)
Above 50 years	Hormone therapy should follow postmenopausal guidelines and individual considerations

Risks of Hormone therapy

1

Breast Cancer

- ✓ there is no evidence that HT use increases their risk of breast cancer
- ✓ HT is not recommended in women with a history of breast cancer

2

BRCA1/2 mutations

Women with BRCA1/2 mutations without a personal Hx of breast cancer should be advised that HT is an option after risk reducing BSO.

3

prevent endometrial hyperplasia/cancer.

A progestogen should be given in combination with estrogen therapy to all women with an intact uterus.

4

Progesterone dose

the dose of progestogen is increased when higher doses of estrogen therapy are used.

Clinical pearls in HT

1

Unscheduled bleeding

In women with POI, as with any women using HT, unscheduled bleeding requires assessment.

2

POI with history of endometriosis

should be treated with combined estrogen–progestogen HT, even after hysterectomy, to avoid recurrence or malignant transformation.

3

Migraine

- ✓ should not be considered a contraindication to HRT use in POI
- ✓ change dose, route, or regimen if migraine worsens during HRT

4

Women with POI and migraine with aura should be advised to use transdermal estrogen as this may be the lowest-risk route.

Specific Considerations

iatrogenic POI after SCC of the cervix: HT does not increase the risk of recurrence and is recommended

iatrogenic POI after cervical adenocarcinoma: HT may be associated with a slightly increased risk of recurrence and a personalized approach is recommended.

iatrogenic POI due to early-stage low-risk endometrial Adenocarcinoma: can consider HT

iatrogenic POI due to epithelial ovarian cancer: HT can be considered

Specific Considerations

iatrogenic POI after non-epithelial ovarian cancer: HT is uncertain & is used in a personalized approach

iatrogenic POI after Hormone dependent ovarian or uterine tumors: HT should be avoided

Non-hormonal therapies

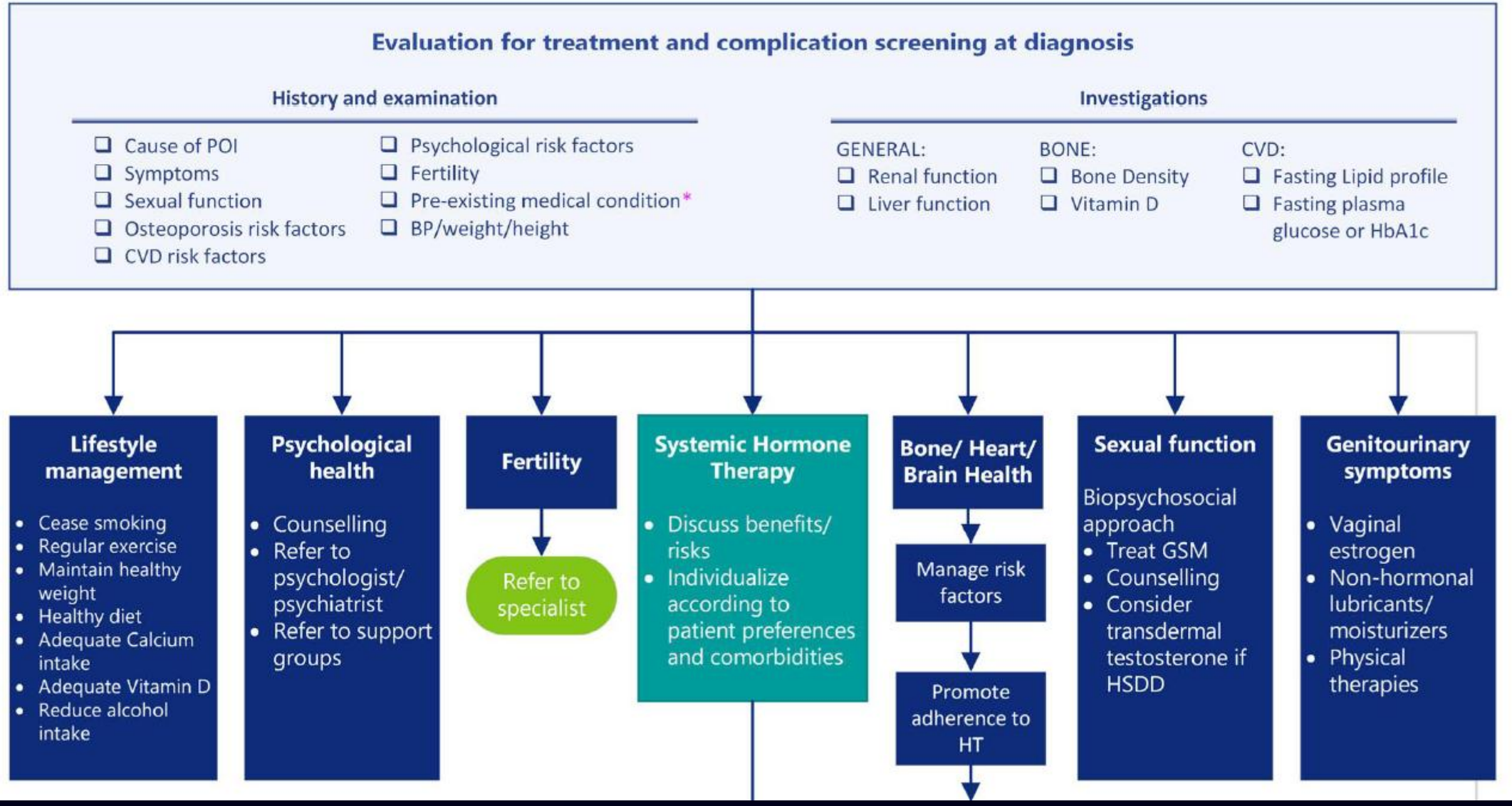
1. Complementary therapies should not be used to replace HT as there is insufficient evidence on their effectiveness for prevention of longterm sequelae of POI.

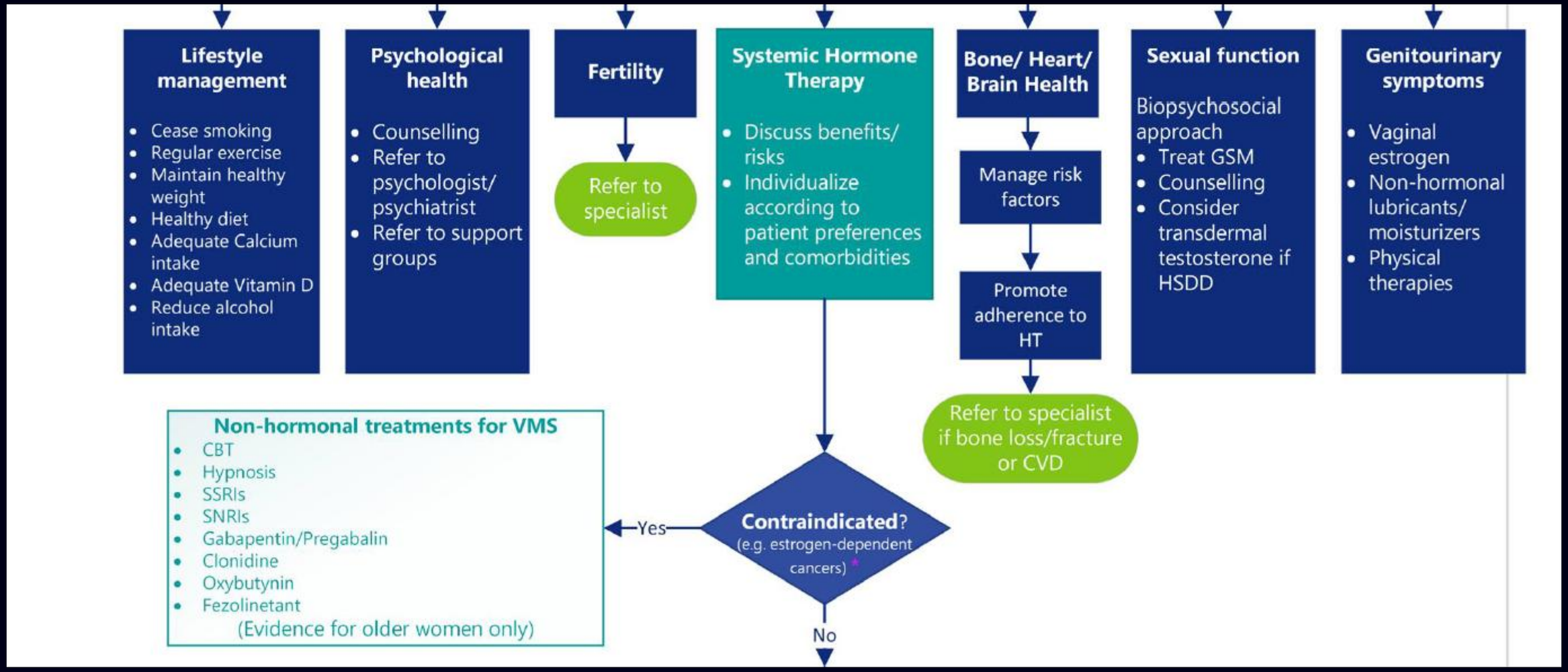
2. **Chinese herbal medicine:**
the evidence for benefit is limited but the intervention does not appear to cause significant harm in the short term

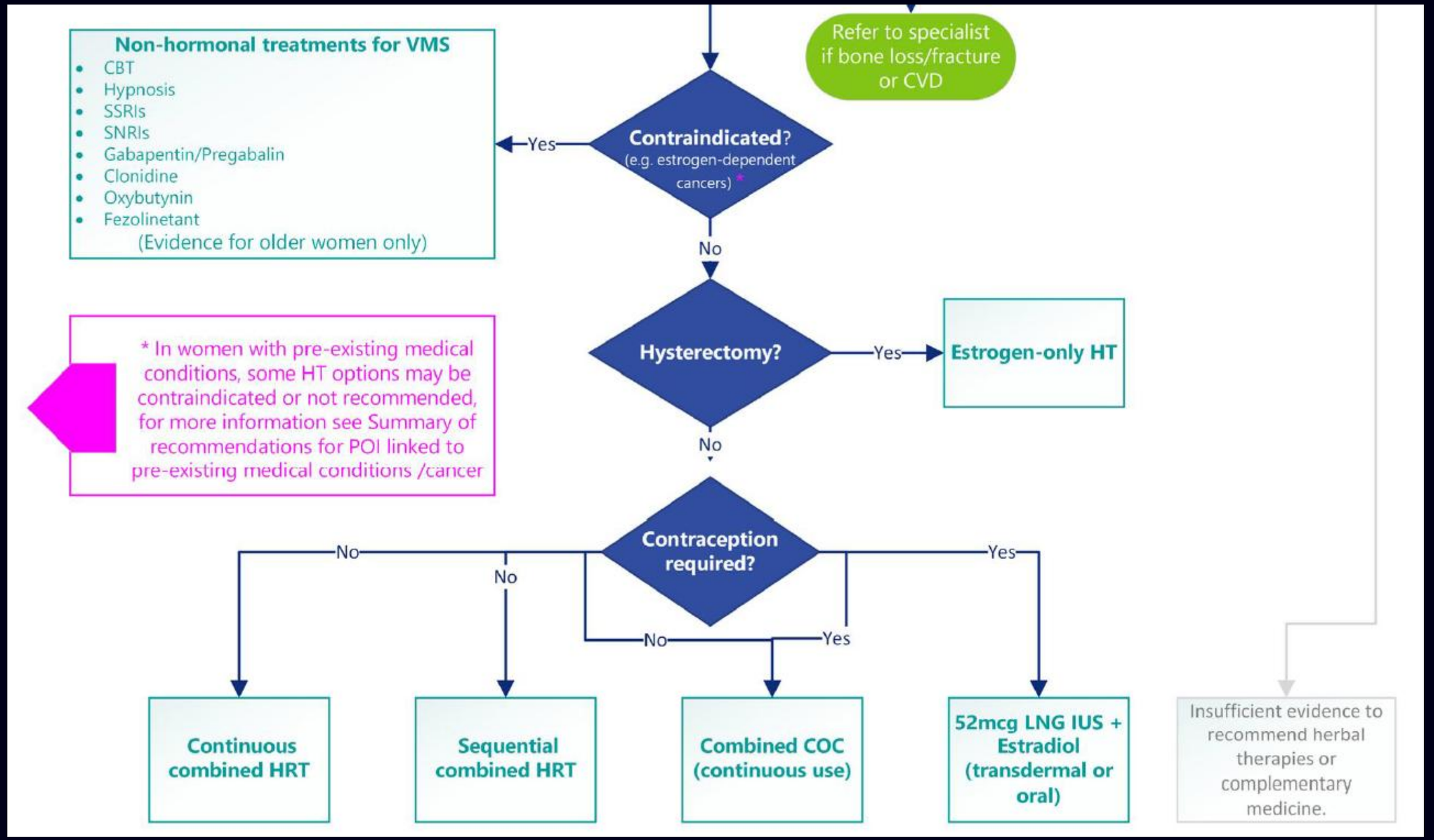
3. **Acupuncture:**
The evidence does not suggest a benefit from adding acupuncture to HT.

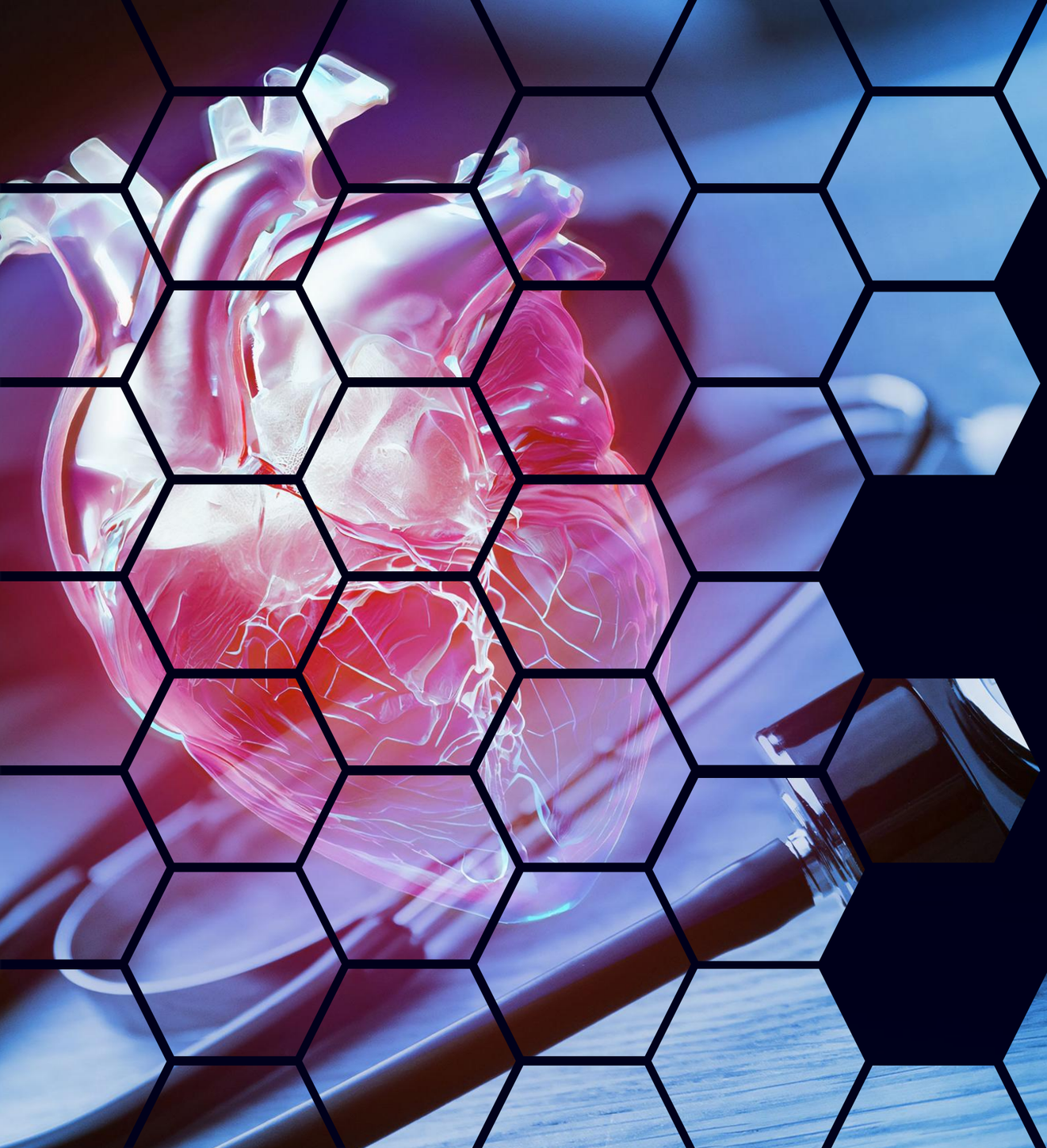
4. **Other nutrient supplements and herbal medicines:**
there is insufficient evidence to support their use

Management algorithm for premature ovarian insufficiency (POI)









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