Early or premature menopause: causes and management

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Premature ovarian insufficiency (POI) is a condition defined by loss of ovarian activity before the age of 40 years.
POI is characterised by amenorrhea or irregular menstrual cycles with elevated gonadotropins and low estradiol.

Efforts should be made to reduce the risk of POI.
Modifiable factors may include:
- gynaecological surgical practice
- lifestyle factors such as smoking
- treatment regimens for malignant and chronic diseases.

Women with risk factors for POI are identified and counselled regarding POI risk and fertility preservation

Diagnostic criteria: disordered menstrual cycles (spontaneous amenorrhea or irregular menstrual cycles) for at least 4 months, and an elevated Follicle Stimulating Hormone (FSH) concentration>25 IU/l.
FSH assessment should be repeated after 4-6 weeks if there is diagnostic uncertainty. FSH testing for the diagnosis of POI does not have to be timed to a specific day of the menstrual cycle.

Not recommend diagnosing POI based on serum estradiol concentrations . However, a low estradiol concentration indicates hypoestrogenism, and in combination with an elevated FSH concentration provides additional confirmation of the POI diagnosis.

Anti-Müllerian hormone (AMH) should not be used as the primary diagnostic test for POI.
The guideline group recommends that 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.

Chromosomal analysis testing is recommended for all women with non-iatrogenic POI. STRONG
***FMR1* premutation (Fragile X syndrome gene) testing is recommended for all women with non-iatrogenic POI** STRONG
Where available and after comprehensive genetic counselling, additional genetic testing (e.g., next generation sequencing [NGS]) can be offered to all women with non-iatrogenic POI to identify other potential genes that may cause POI

Premature and early menopause

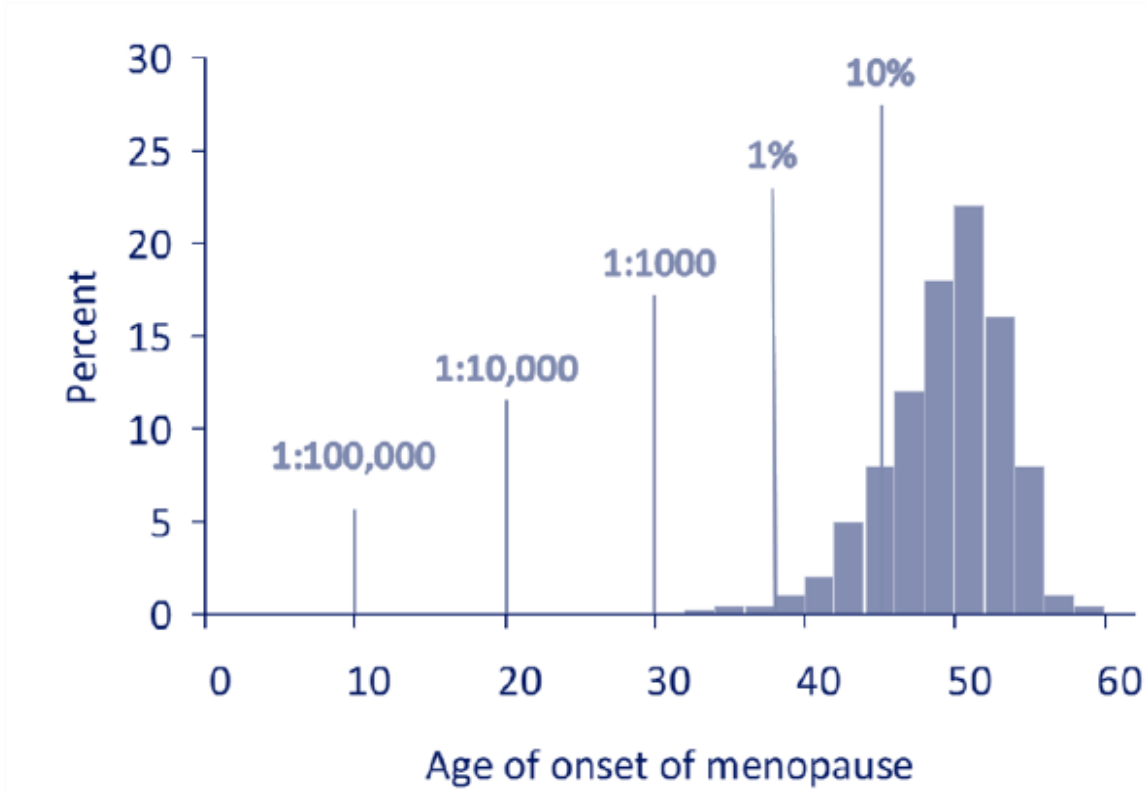
- Ovarian insufficiency (before 40 years) and early menopause (before 45 years), whether natural or induced, is associated with increased morbidity & mortality, when women are untreated with MHT.
- Several recent meta-analyses reported in particular increased cardiovascular morbi-mortality (Grade 1C)
- Several observational studies reported increased neuro-degenarative diseases in these women also, while MHT reduces these risks.(Grade IC)

- Muka T, et al JAMA Cardiol. 2016.
- Rocca JAMA Netw Open 2022

Premature and early menopause

- Data gathered from studies in postmenopausal women aged 50 or more can not necessarily be extrapolated to younger postmenopausal women.
- It is generally recommended to treat these women at least till the normal age of menopause.
- Dosage should be adapted according to symptomatology (*Level 3)*
- *Higher doses might be necessary for adequate osteoporosis treatment (Level 3)*

FIGURE 3 DISTRIBUTION OF AGE AT MENOPAUSE.



A similar global overall prevalence of POI of 3.5% was reported in a more recent systematic review and meta-analysis (Li *et al.*, 2023). The prevalence of POI differed between regions globally, as well as between developing and developed countries. In addition, the trend of prevalence of POI over the past 20 years appears to be on the rise (Li *et al.*, 2023).

Known causes of premature ovarian insufficiency

- **Primary**

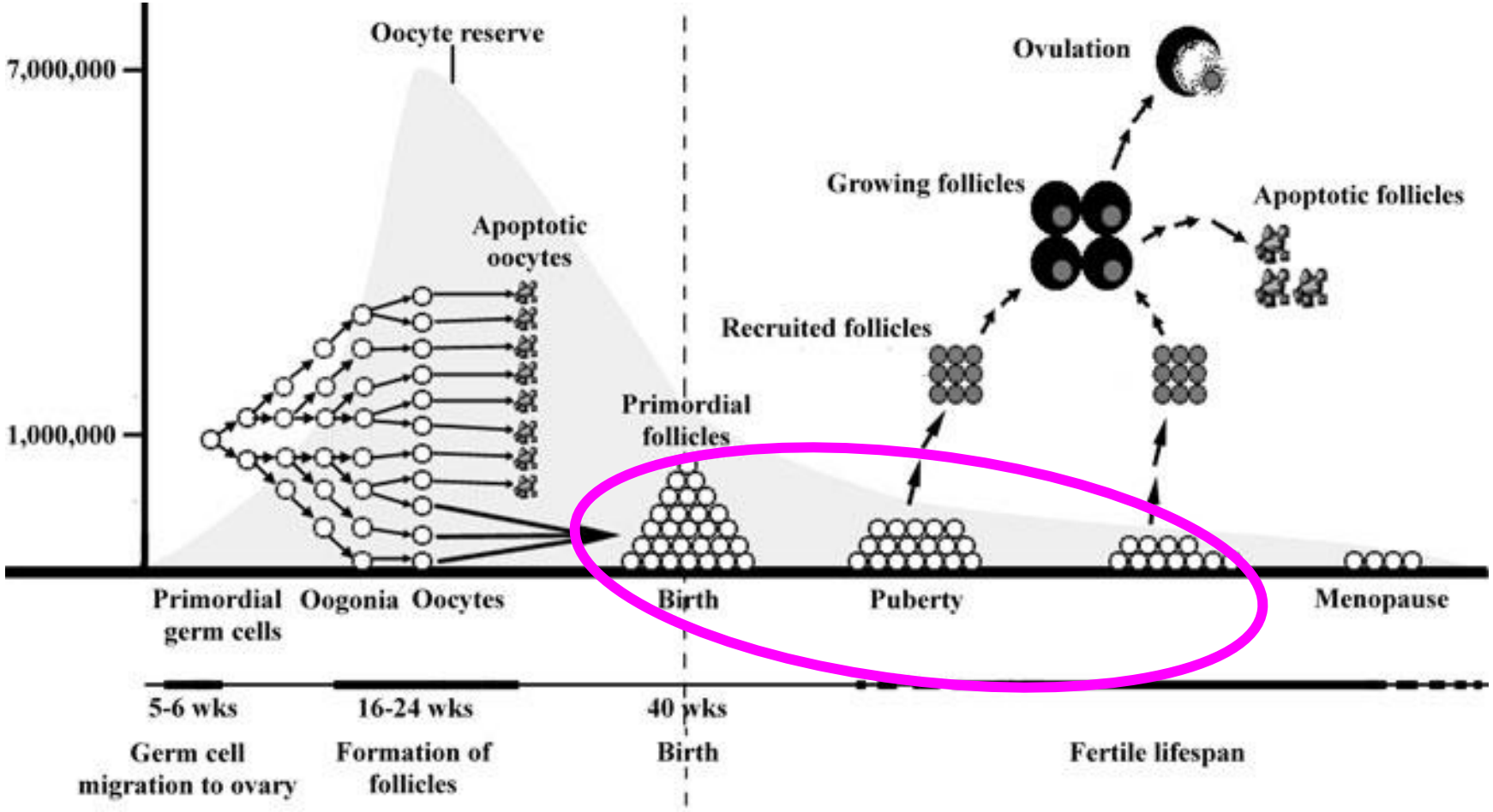
1. Genetic
2. Chromosome abnormalities
3. FMR1 premutations
4. Other gene candidates
5. Enzyme deficiencies
6. Autoimmune diseases

- **Secondary**

1. Chemotherapy and radiotherapy
2. Bilateral oophorectomy or surgical menopause
3. Infections

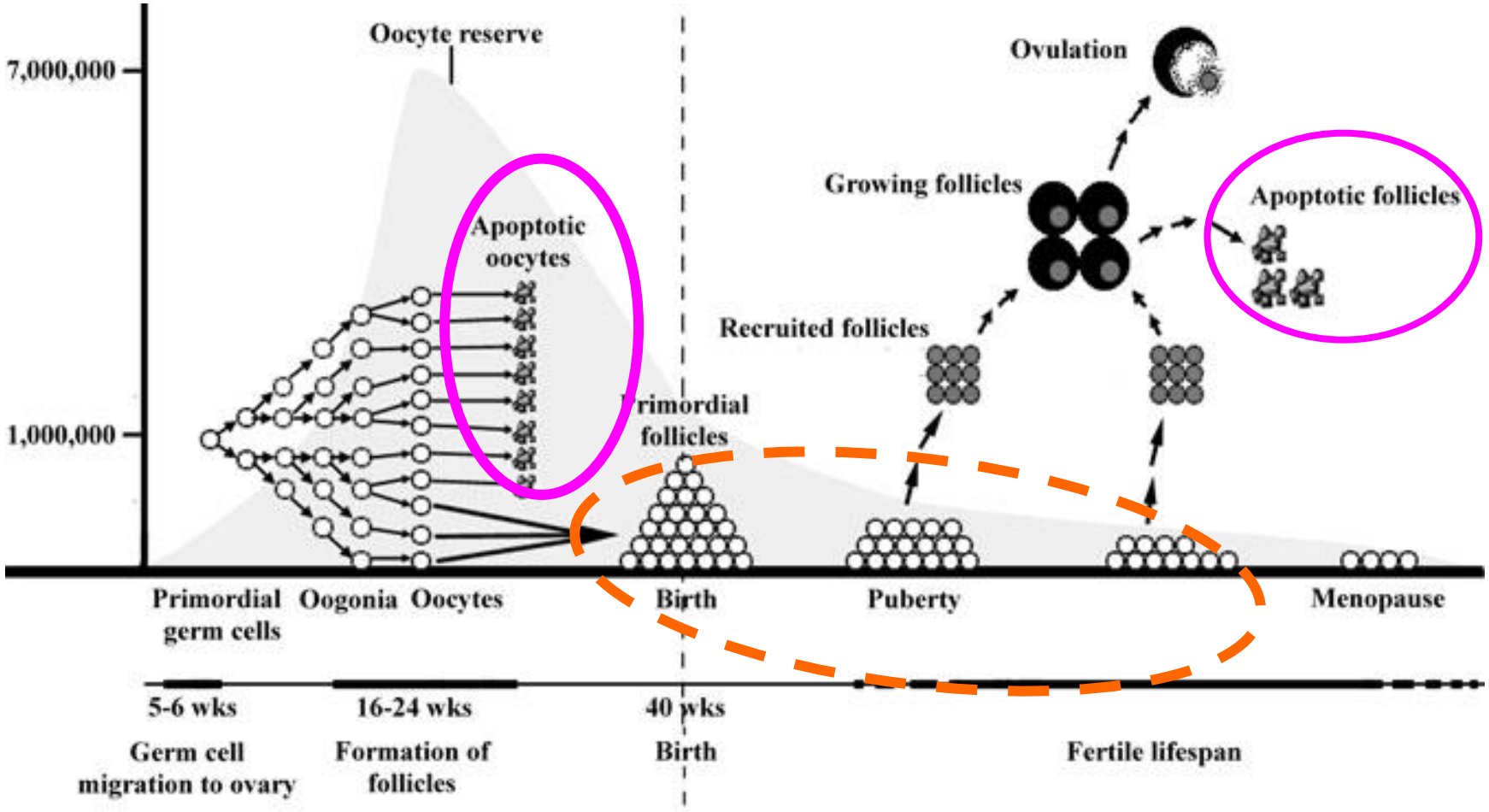
POI

Reduction of the pool (ex oncologic treatment)



POI

Apoptosis ex/ Turner syndrome)



POI

Folliculogenesis block (ex/ FSHR mutation)

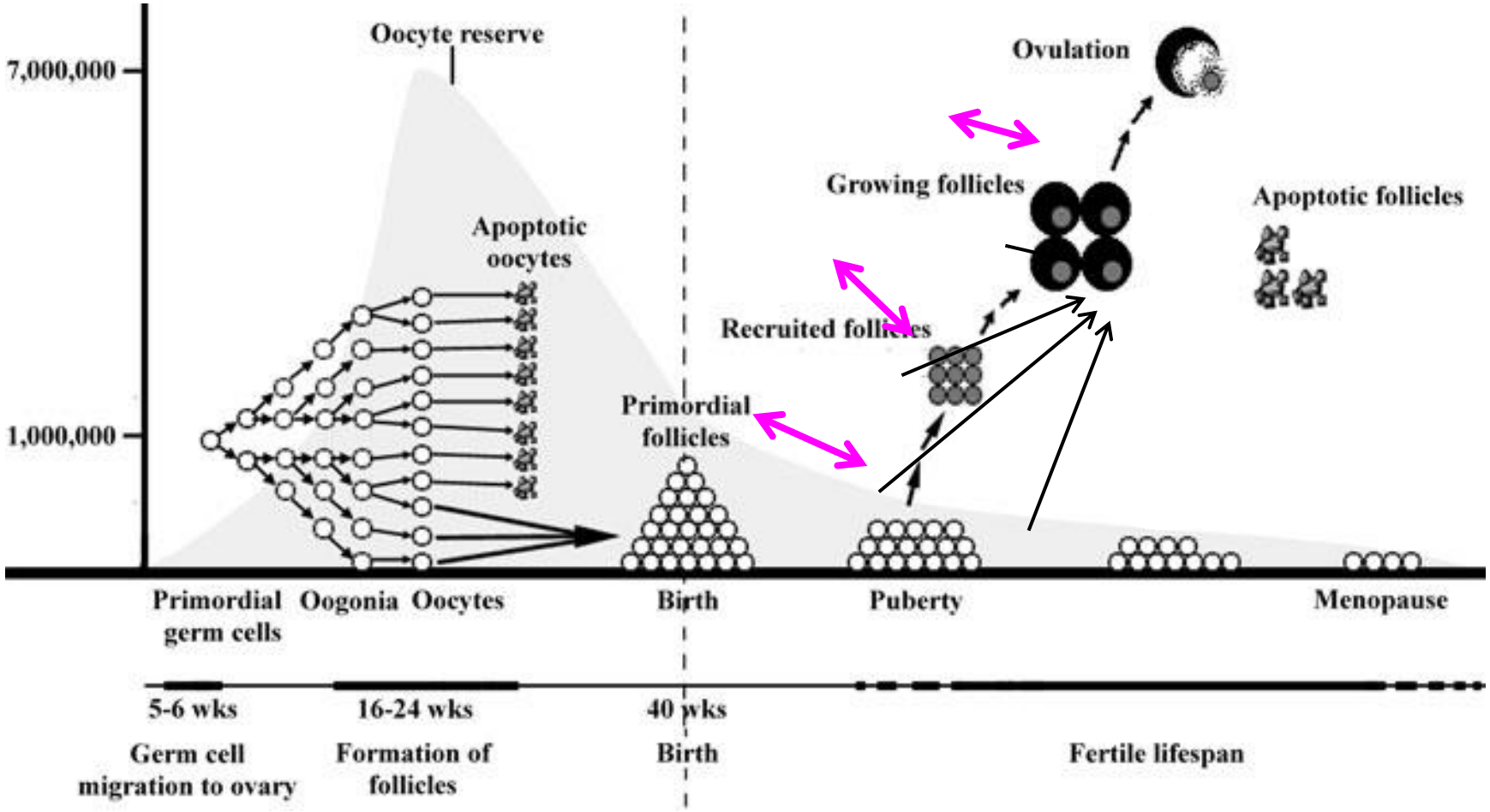
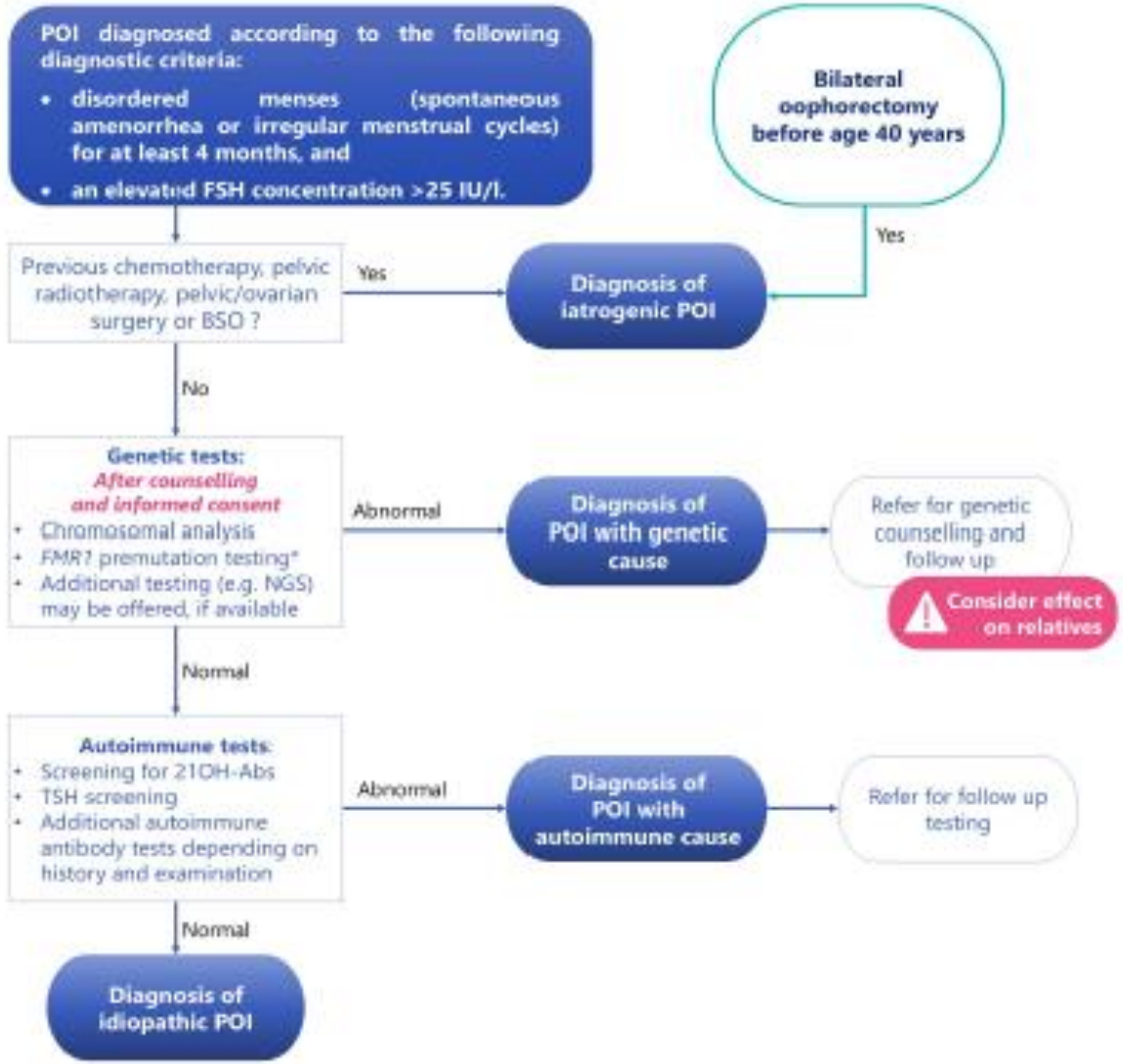


FIGURE 6 SUMMARY OF THE RECOMMENDATIONS ON DIAGNOSIS AND TESTING TO ESTABLISH A CAUSE FOR POI



**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: 21OH-Abs, 21-hydroxylase autoantibodies; BSO, bilateral salpingo-oophorectomy; FSH, follicle stimulating hormone; NGS, next generation sequencing; TSH, thyroid stimulating hormone.

Table 1. Classes of chemotherapy, their action and infertility risk.

Class of agent	Examples	Mechanism of action	Infertility risk
Alkylating agents	Cyclophosphamide Mechlorethamine Chlorambucil Busulfan Melphalan	The active metabolites form cross-links with DNA with resultant inhibition of DNA synthesis and function. DNA double strand breaks and resultant P63-mediated apoptotic death in human primordial follicles [8]	High risk
Platinum-based compounds	Cisplatin Carboplatin	Covalently binds to DNA to form intra- and interstrand DNA cross-links, leading to DNA breakage during replication. This inhibits DNA transcription, synthesis and function. Specific toxicity has not been shown in human primordial follicles	Intermediate risk
Antimetabolites	Methotrexate 5-fluorouracil Cytarabine	Inhibition of DNA, RNA, thymidylate and purine synthesis. No DNA damage in human follicles, hence not gonadotoxic	Low risk
Vinca alkaloids	Vincristine Vinblastine	Inhibition of tubulin polymerization and disruption of microtubule assembly during mitosis. This arrests mitosis during metaphase and leads to cell death. No DNA damage in human follicles, hence not gonadotoxic	Low risk
Anthracyclin antibiotics	Daunorubicin Bleomycin Adriamycin (doxorubicin)	Inhibition of DNA synthesis and function. It interferes with DAN transcription. It inhibits topoisomerase II, which leads to DNA breaks. It also forms toxic oxygen-free radicals, which induce DNA strand breaks, thereby inhibiting DNA synthesis and function. Doxorubicin induces DNA double strand breaks P63-mediated apoptotic death in human primordial follicles [8]	Low risk (except adriamycin: intermediate risk)

Disorders leading to ovarian insufficiency

Ovarian follicle dysfunction

Signalling defect

- Follicle-stimulating-hormone-receptor mutation (*FSHR*)
- Luteinising-hormone-receptor mutation (*LHR*)
- Pseudohypoparathyroidism type 1a (*GNAS*)

Enzyme deficiency

- Isolated 17-α-hydroxylase or 17,20-lyase deficiency (*CYP17A1*)
- Aromatase deficiency (*CYP19*)

Autoimmunity

- Autoimmune lymphocytic oophoritis
- Polyglandular autoimmune syndrome, including adrenal, thyroid, or thymic disease
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (*AIRE*)

De Vos et al., Lancet 2010

Ovarian follicle depletion

Insufficient initial follicle number

- Blepharophimosis, ptosis, and epicanthus inversus syndrome (*FOXL2*)
- 46,XY gonadal dysgenesis (*SRY* and others)
- Other syndromes and genes associated with an insufficient initial follicle number that have not been described

Spontaneous accelerated follicle loss

- Turner's syndrome: full blown and mosaic variants (unknown)
- Trisomy or polysomy X, or mosaic variants
- Macrodeletions Xp or Xq
- Autosomal or X translocations

De Vos et al., Lancet 2010

90% idiopathic

genes located

on the X chromosome

on chromosome 21 (AIRE)

on chromosome 11 (FSH β, ATM)

on chromosome 3 (BEPS)

on chromosome 2 (FSHR – LHR)

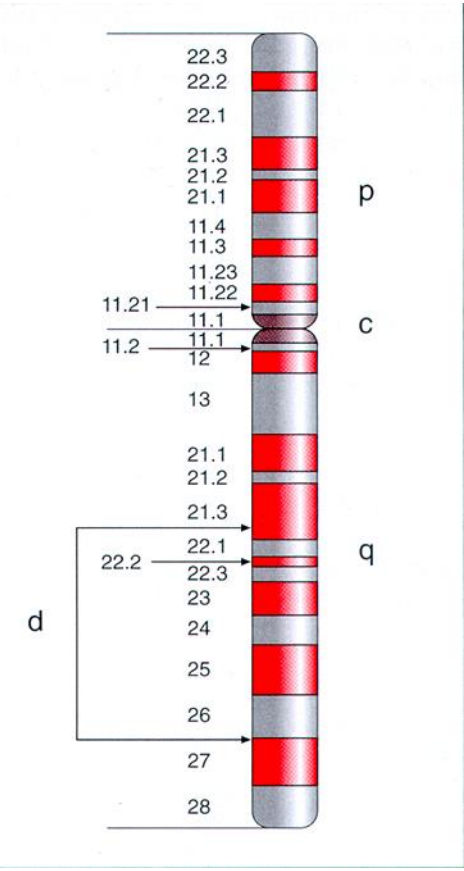


TABLE III SYNDROMES ASSOCIATED WITH POI (LIST BASED ON QIN 2015, HUHTANIEMI 2018, AND VERPOEST 2023)

Syndrome	OMIM	Gene(s)	Further information
Acromesomelic chondrodysplasia with genital anomalies	#609441	BMPR1B	Particular features: Severe brachydactyly with radial deviation of the fingers, ulnar deviation of the hands, fusion of the carpal/tarsal bones, aplasia of the fibula, bilateral clubfeet with small broad feet and short toes
Ataxia telangiectasia	#208900	*ATM*	Progressive cerebellar degeneration, telangiectasias, immunodeficiency, recurrent infections, insulin-resistant diabetes, premature aging, radiosensitivity, and high risk for epithelial cancers in surviving adults.
Autoimmune polyendocrine syndrome type I (APS-1)	#240300	*AIRE*	Rare autoimmune condition including chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal failure. Some patients also present with POI. It results from mutations in the AIRE gene, with complex transmission: recessive autosomal in some variants, and dominant in others. Also called Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED)
Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)	#110100	*FOXL2*	Prevalence: ~1–9/100,000 Transmission: Autosomal dominant Rare congenital palpebral malformation It is in some cases associated with POI; in which case it is known as type-1 BPES.

TABLE III SYNDROMES ASSOCIATED WITH POI (CONTINUED)

Syndrome	OMIM	Gene(s)	Further information
Bloom syndrome	#210900	*BLM*	Chromosomal breakage leading to early onset of aging, short stature, and elevated rates of most cancers.
Fanconi anemia	#227650 #227645 #614082	*FANCA* *FANCC* *FANCG*	Particular features: Pancytopenia, small stature, microcephaly, ear anomalies, heart defects, kidney malformations, radial aplasia and thumb deformities, intellectual disability, café-au lait spots
Fragile X syndrome	#300624	*FMR1*	Attention deficits, hyperactivity, social deficits, anxiety disorder, deficits in cognitive flexibility.
Galactosemia	#230400	*GALT*	A metabolic disease related to abnormal glucose metabolism. The culprit gene in this form showing recessive autosomal transmission is GALT. The POI is due to accumulation of galactose in the ovaries, leading to oocyte apoptosis. Acute neonatal life-threatening symptoms are observed (e.g., vomiting, poor feeding, lethargy, metabolic acidosis, jaundice, abnormal clotting, liver failure) but adults are also affected in milder forms.
GAPO	#230740	*ANTXR1*	Particular features: Growth retardation, alopecia, pseudoanodontia, optic atrophy, high forehead, midface hypoplasia
Hutchinson-Gilford progeria	#176670	*LMNA*	Particular features: Progeria, short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, cardiomyopathy
Nijmegen breakage syndrome	#251260	*NBN*	Particular features: Prenatal growth retardation, progressive mental deterioration, microcephaly, recurrent infections, increased risk for neoplasia such as lymphoma
Perrault syndrome	#233400 #614926 #614129 #615300 #616138 #605608 #612425 #609947 #607435 #611584 #611974 #601498 #606982 #614917	*HSD17B4* *HARS2* *LARS2* *CLPP* *C10orf2* *CLDN14* *SGO2* *KIAA0391* *ERAL1* *MRPL50* *MRPS7* *PEX6* *GGPS1* *RMND1*	Associated with ovarian dysgenesis and sensorineural hearing loss. Like the hearing loss, the dysgenesis is extremely variable, but systematic. Identifying new candidate genes should shed light on the pathophysiology of the hearing loss and of POI in this syndrome
PMM2-CDG CDG-1 (a previously known as congenital disorder of glycosylation type 1a)	#212065	*PMM2*	Cerebellar dysfunction (ataxia, dysarthria, dysmetria), non-progressive cognitive impairment, stroke-like episodes, peripheral neuropathy with or without muscle wasting, absent puberty in females, small testes in males, retinitis pigmentosa, progressive scoliosis with truncal shortening, joint contractures, and premature aging
Progressive external ophthalmoplegia, PEO	#157640	*POLG*	Particular features: Ptosis, progressive external ophthalmoplegia, sensorineural hearing loss, axonal neuropathy, muscle weakness, ataxia, dysarthria, dysphagia, and late onset Parkinsonism
Proximal symphalangism, SYM1	#185800	*NOG*	Ankylosis of the proximal interphalangeal joints. Particular features: symphalangism, hearing loss
Pseudohypoparathyroidism Pseudohypoparathyroidism type 1A (PHP 1A)	#103580	*GNAS*	Particular features: Brachydactyly, short stature, hypocalcaemia and hyperphosphatemia, hypothyroidism, obesity. An endocrine disease characterised by resistance to parathyroid hormone and other hormones such as TSH and GnRH. Particular features: Brachydactyly, short stature, hypocalcaemia and hyperphosphatemia, hypothyroidism, obesity.
Retinal dystrophy with or without extraocular anomalies	#617175	RCBTB1	Particular features: Retinal dystrophy, goiter, intellectual disability, hypogonadism
Rothmund–Thomson syndrome, RTS	#268400	*RECQL4*	Cutaneous rash, sparse hair, small stature, skeletal and dental abnormalities, cataracts, premature aging, and an increased risk for cancer, especially malignancies originating from bone and skin tissue.
SF1-related XX-DSD	#612964	*NR5A1/SF1*	Particular features: Adrenal insufficiency

TABLE III SYNDROMES ASSOCIATED WITH POI (CONTINUED)

Vanishing white matter disease, ovarioleukodystrophy	#603896 #615889	*EIF2B* *AARS2*	Neurological disorder characterized by involvement of the white matter of the central nervous system. When Leukodystrophies associated with premature ovarian failure referred to as ovarioleukodystrophy.
Werner syndrome	#277700	*WRN*	Premature aging of the skin, vasculature, and bone and elevated rates of certain cancers, particularly sarcomas.
Woodhouse-Sakati syndrome	#241080	*C2orf37*	Particular features: Alopecia, deafness, hypogonadism, diabetes, intellectual disability
WT1-related XX-DSD	#194070	*WT1*	Particular features: Nephropathy, diaphragmatic hernia
XRCC4-related disorder	#616541	*XRCC4*	Particular features: Short stature, microcephaly, developmental delay, diabetes mellitus

Rationale for genetic testing

Identifying the genetic cause of POI can be helpful for patients and families by enabling (Heddar *et al.*, 2022):

- potential psychological benefits including providing a cause of POI rather than the term "idiopathic."
- better understanding of prognosis, including fertility, thus facilitating counselling and personalised management.
- appropriate co-morbidity screening with involvement of multidisciplinary teams (e.g. oncogeneticists). Before genetic testing, it is important to inform patients that sometimes POI can be the first sign of other related health conditions in a syndrome and that a comprehensive assessment by a multidisciplinary team may be necessary.
- family screening, including male siblings (Huhtaniemi *et al.*, 2018), facilitating fertility preservation and co-morbidity screening in members not yet affected.
- development of novel prevention or treatment strategies (Yang *et al.*, 2021, Heddar *et al.*, 2022, Ke *et al.*, 2023).

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

***FMR1* premutation (Fragile X syndrome gene) testing is recommended for all women with non-iatrogenic POI**

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

Screening for 21-hydroxylase autoantibodies (21OH-Abs) should be performed in women with POI of unknown cause.

Screening for anti-ovarian autoantibodies should not be used to diagnose autoimmune POI.

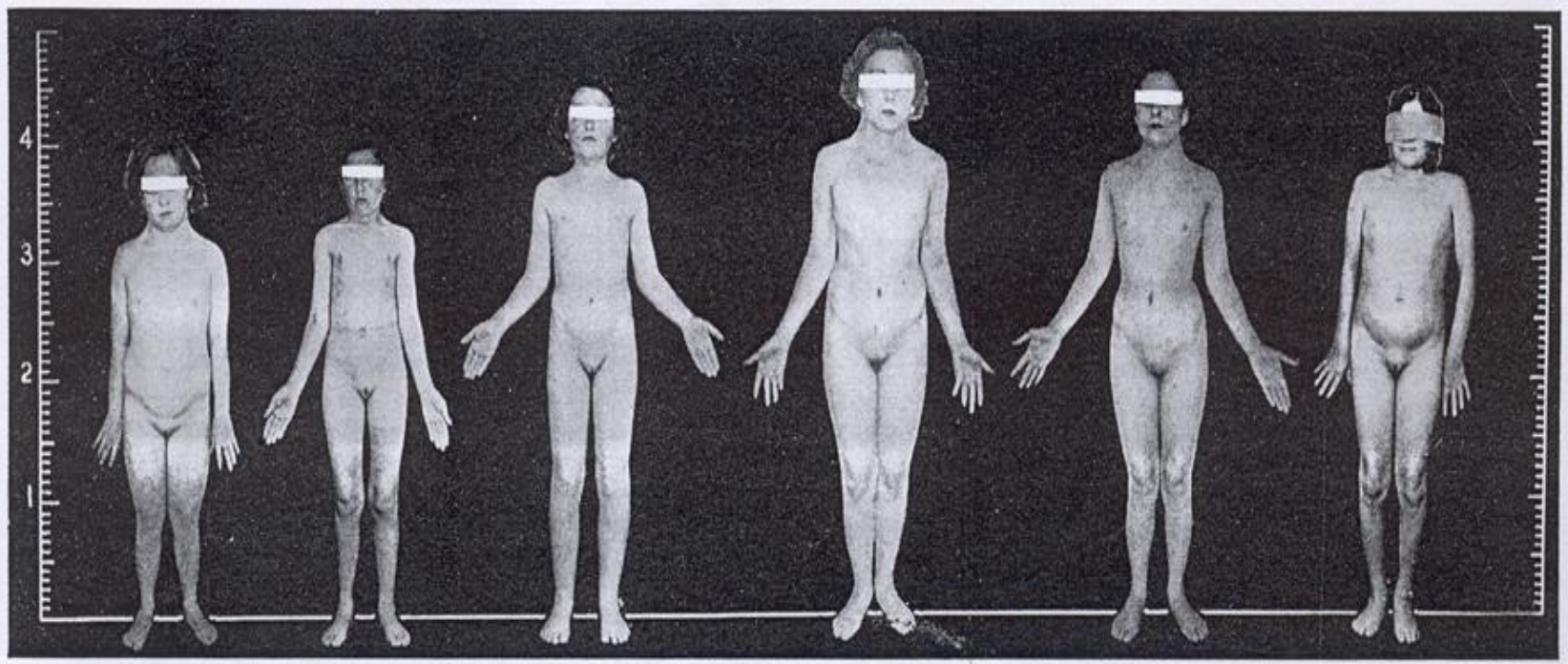
Thyroid function should be assessed by measuring Thyroid Stimulating Hormone (TSH) at POI diagnosis.

TSH measurement should be repeated every 5 years or when symptoms arise.

A SYNDROME OF INFANTILISM, CONGENITAL WEBBED NECK, AND CUBITUS VALGUS[1]

HENRY H. TURNER
From the Endocrine Clinic of the Out-Patient Department of the University Hospital, University of Oklahoma School of Medicine
OKLAHOMA CITY, OKLAHOMA

Endocrinology, 1938



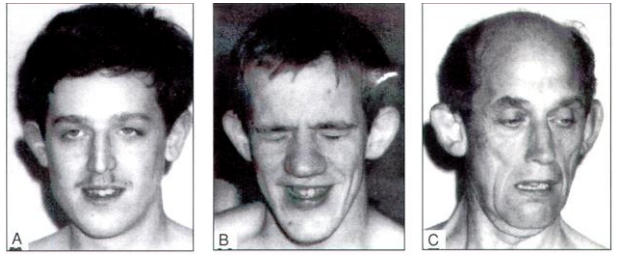
Case 3 Case 7 Case 6 Case 2 Case 1 Case 5

Fig. 1. Patients illustrating the syndrome of infantilism, webbed neck, and cubitus valgus.

X chromosome : gene FMR

- Gene Xq 27.3 protein FMR1 : fragile mental retardation
- Mutations = more than 200 CGG repeats in the 5' untranslated region of the FMR gene
- ***Fragile X-associated tremor/ataxia syndrome*** *(FXTAS)*
- Premutations = 50-200 repeats POF

(Schwartz, 1994 ; Conway, 1997)



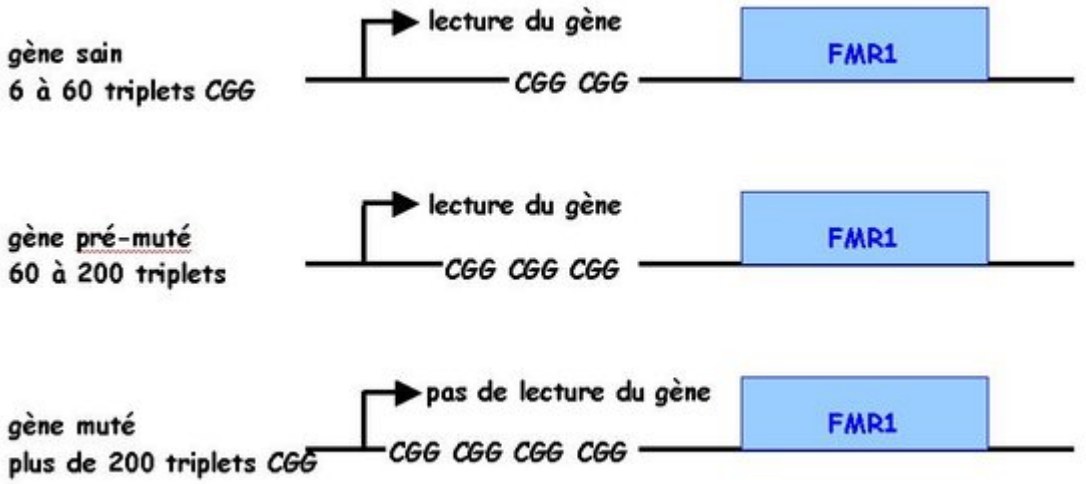


FIGURE 5. SUMMARY OF DATA ON SYMPTOMS OF POI. PREVALENCE DATA ARE BASED ON 2 RETROSPECTIVE STUDIES AND LIMITED TO THOSE WITH A PREVALENCE OF 30% OR MORE (ALLSHOUSE *ET AL.*, 2015, HUANG *ET AL.*, 2021). FURTHER DETAILS ON PREVALANCE OF SYMPTOMS ARE AVAILABLE IN THE TEXT.

POI symptoms	Reported by women with POI
Mood swings (sometimes with melancholia/mental fog)	7 out of 10
Insomnia	5 out of 10
Sexual problems	5 out of 10
Fatigue	5 out of 10
Hot flushes/sweating	5 out of 10
Hair loss	5 out of 10
Dry eyes	5 out of 10
Cold intolerance	5 out of 10
Joint clicking	5 out of 10
Headaches	3 out of 10
Vertigo	3 out of 10
Muscle/joint pain	3 out of 10
Palpitations	3 out of 10
Tingling in limbs	3 out of 10

Symptoms may intermittently disappear due to fluctuating ovarian function

Symptoms may vary in severity depending on the different underlying causes of POI

Some women with POI may not experience any symptoms, for examples those with primary amenorrhea

POI consequences

- premature morbidity and mortality.
- impaired endothelial function, ischemic heart disease, ischemic stroke,
- a higher incidence of osteoporotic fractures,
- impaired cognition and
- diminished sexual well-being

Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis

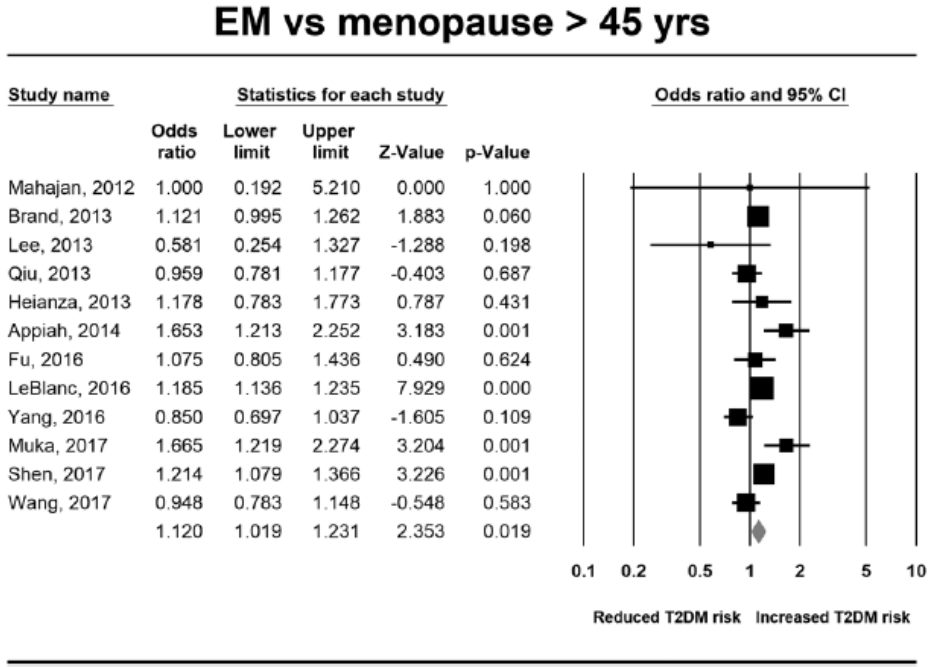
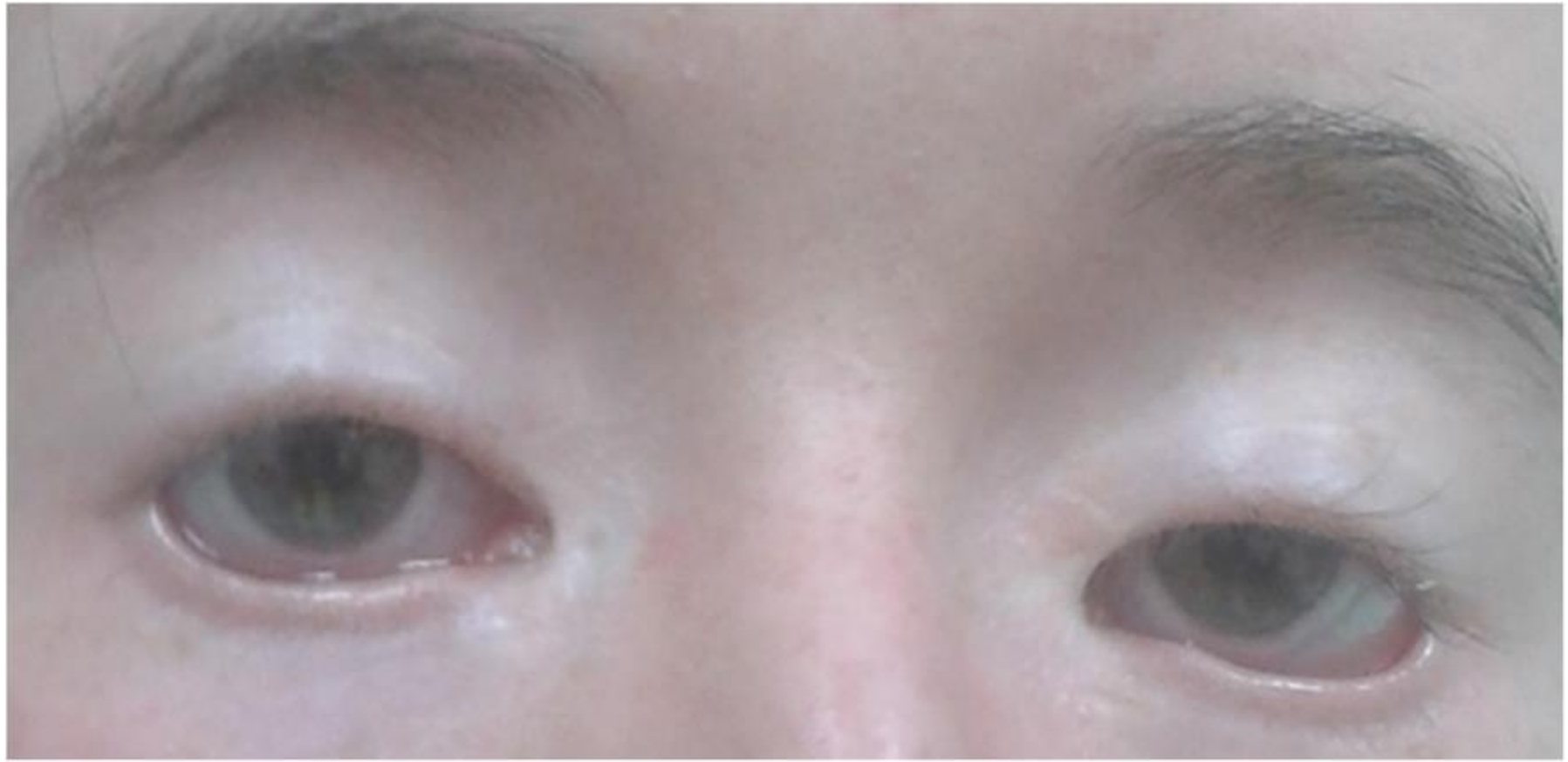


Figure 2

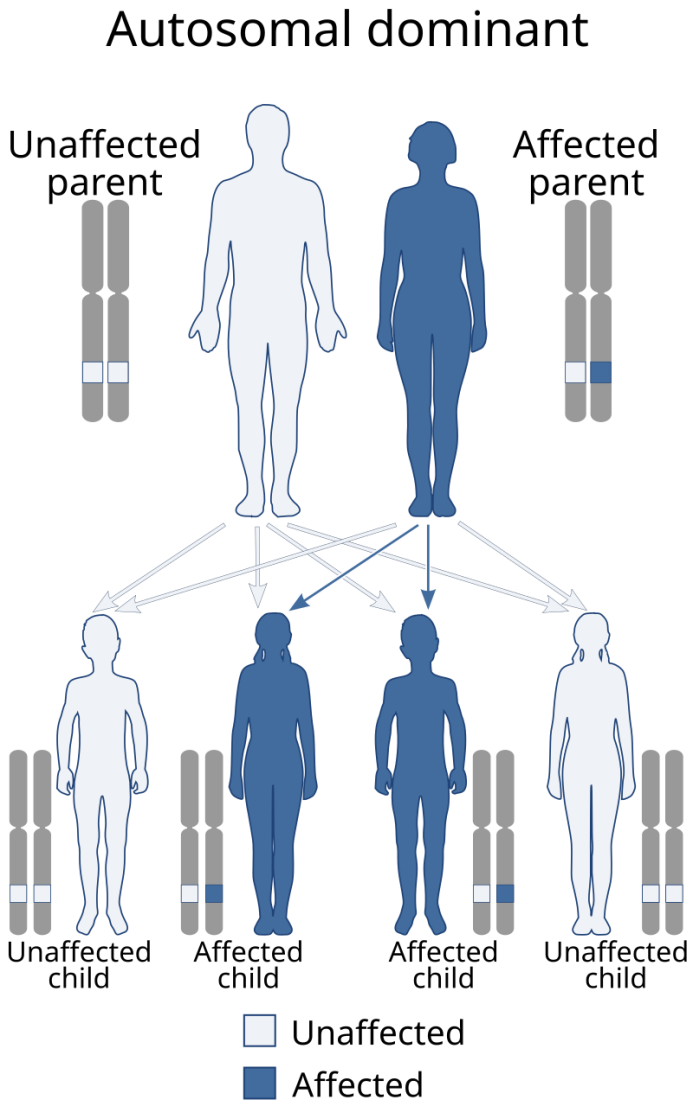
Forest plot of the comparison between early menopause (EM) and menopause >45 years.

Panagiotis Anagnostis, European Journal of Endocrinology 2018

Lisa 14 years



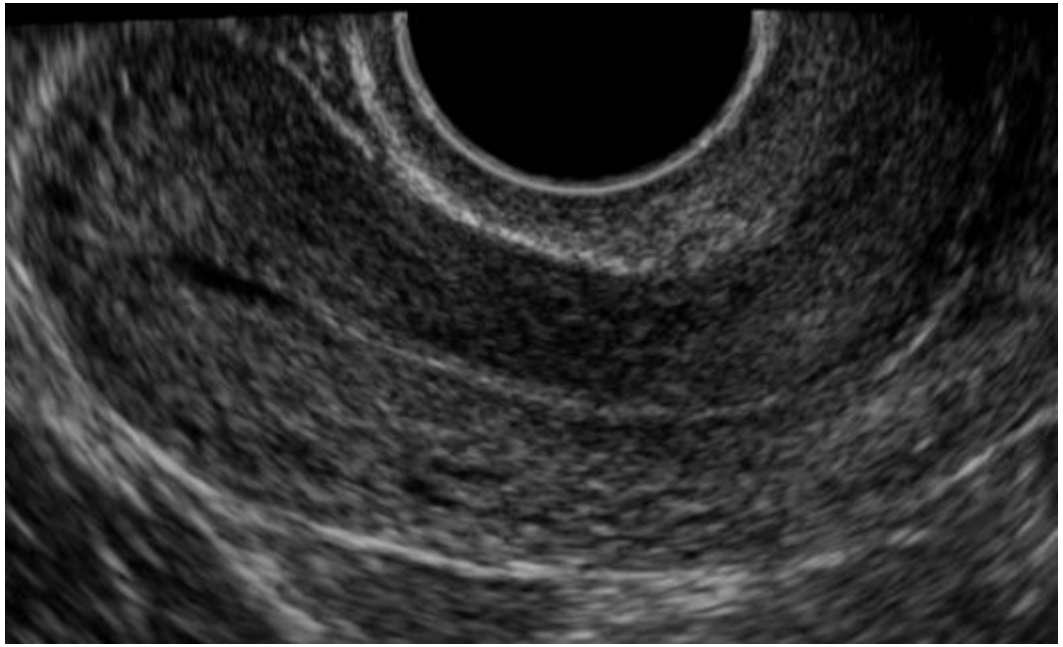
Blepharophimosis Epicanthus Ptosis Syndrome



BPES is caused by a mutation in the gene *FOXL2*, located at 3q23 (band 23 on the long arm of chromosome 3)

Type 1 BPES is distinguished by including premature ovarian insufficiency (POI) in females, which causes menopausal symptoms and infertility in patients as young as 15 years old.

Isabelle 14 years



LH 25 UI/L
FSH 60 UI/L
PRL 7 ng/ml
Oestradiol : 15 ng/L

Normes
LH : 1,9 à 76 UI/L
FSH : 2,5 à 33 UI/L
PRL : 1 à 28 ng/ml
Oestradiol : 20 à 356 ng/L

Leila 17 y

LH 25 UI/L
FSH 60 UI/L
PRL 7 ng/ml
Oestradiol : 15 ng/L

Normes
LH : 1,9 à 76 UI/L
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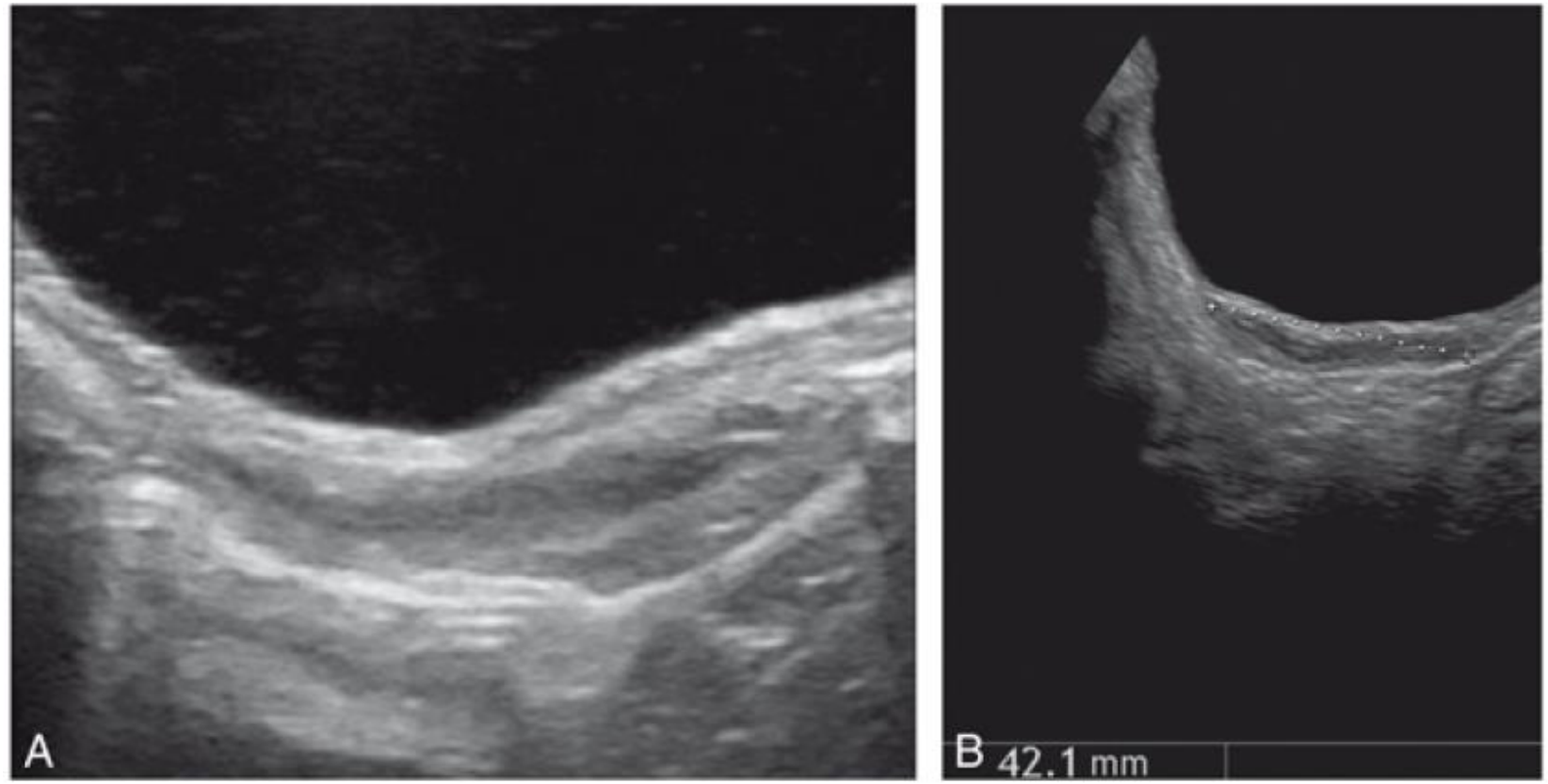

A
B 42.1 mm

Primary amenorrhea with impuberism (in 3 sisters)
Parents first cousins
No autoimmunity detected
Severe osteoporosis
Normal karyotype, no premut X Fra
MCM9 mutation

Menopause and cancer

Menopause and cancer: desire for children? fertility preservation, an open door to the future

Menopause after preventive surgery (women at high risk of cancer)

Menopause after cancer: the short- and long-term consequences of hormone deficiency:

Health and quality of life: tailored, individualized care

Particular context: rapid onset of non-physiological menopause, young patient

Vasomotor symptoms
Cognitive functioning, brain fog
Vaginal dryness
Mood symptoms
Urinary complaints
Uterine bleeding
Sleep
Attractiveness
Sexual activity
Anxiety
Depression
HRQoL associated with chronic conditions

H. P. G. Schneider & M. Birkhäuser (2017) Quality of life in climacteric women, Climacteric, 20:3, 187-194

Premature Ovarian Insufficiency (POI)

2024

The guideline development group on Premature Ovarian Insufficiency

FIGURE 7 SUPPORTIVE CARE FOR WOMEN WITH POI WHEN A DIAGNOSIS IS MADE, OUTLINING WHAT HCPS COULD OFFER IN TERMS OF PROVIDING SUPPORT OR REFERRING TO ADDITIONAL REOURCES. FOR DELIVERING THE DIAGNOSIS OF POI, HCPS COULD CONSIDER THE SPIKES PROTOCOL FOR GUIDANCE (BAILE *ET AL.*, 2000).

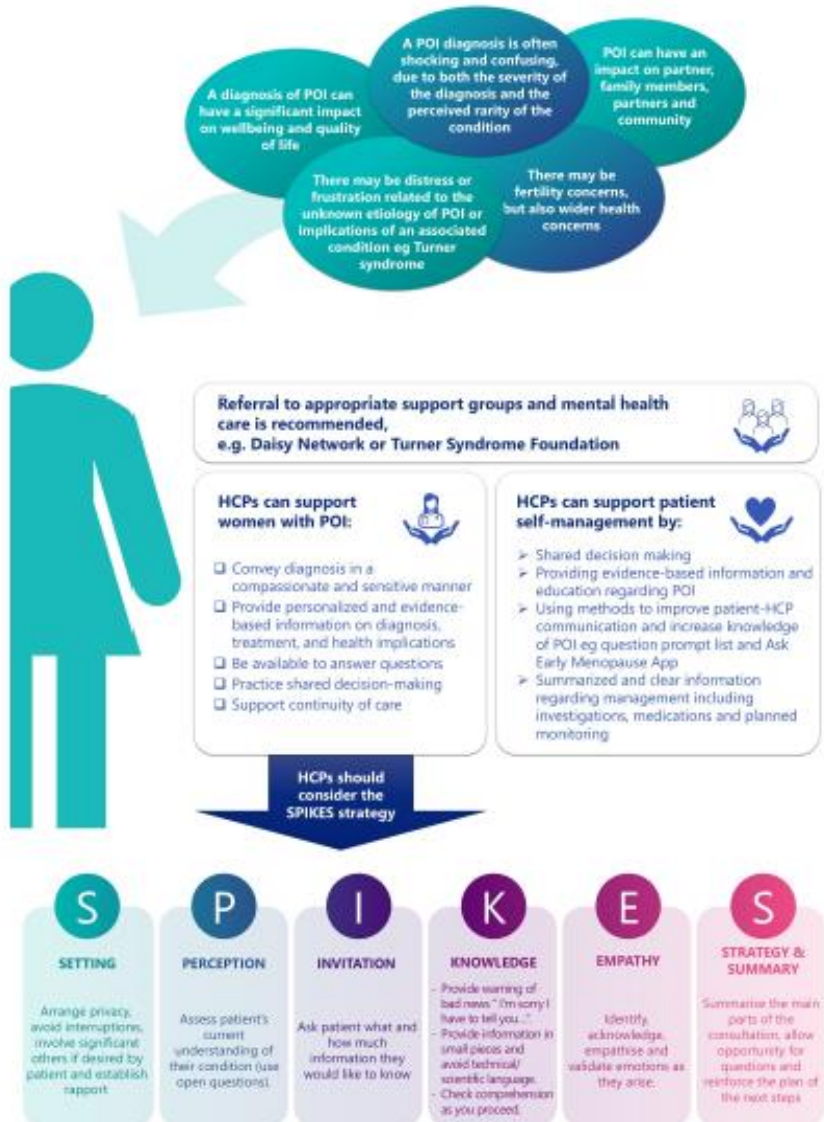


FIGURE 9. SUMMARY OF INFORMATION FOR FAMILY MEMBERS OF WOMEN WITH POI

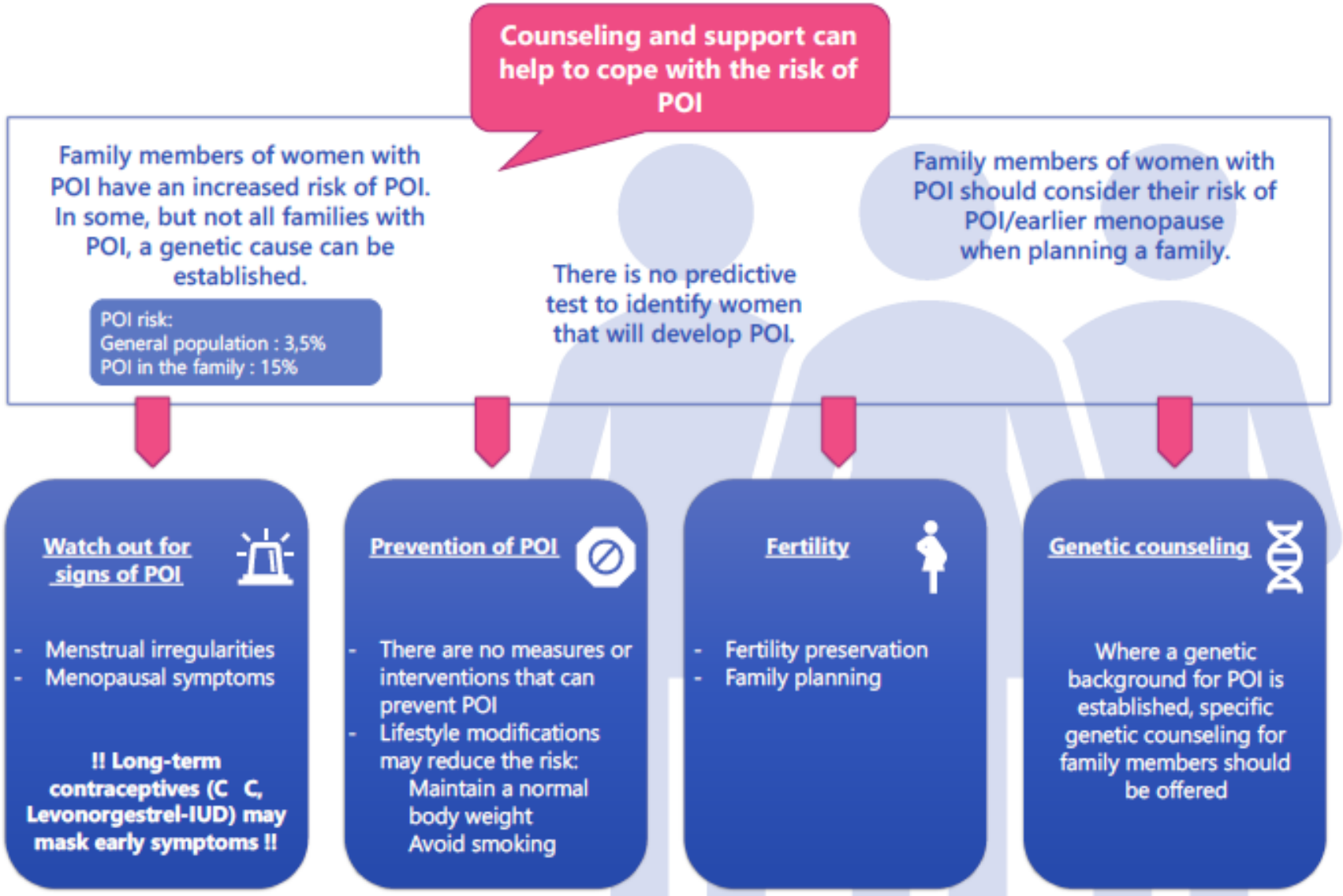


TABLE IV SUMMARY – ASSESSING FITNESS FOR PREGNANCY IN POI

	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

FIGURE 10 MANAGEMENT ALGORITHM FOR BONE HEALTH IN WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY (POI) (ADAPTED FROM (KIRIAKOVA *ET AL.*, 2019), REPRODUCED WITH PERMISSION).

Women with Premature Ovarian Insufficiency

Initial Bone Health Evaluations

Risk factors for low BMD# with POI

- Primary amenorrhea.
- Longer duration of POI
- >1year delay in diagnosis.
- Age <20 years at onset of irregular menses
- Childhood cancer survivors with hypogonadism and:
  - Hypothyroidism AND growth hormone deficiency.
  - Previous treatment with chemotherapy/ glucocorticoids (higher cumulative dose)/
  - Cranial irradiation.

General risk factors for low BMD#†

Non-modifiable

- Age.
- Prior fragility fracture.
- Family history of osteoporosis.
- Parental history of fracture.
- Ethnicity

Modifiable and lifestyle

- Height loss> 3cm
- Multiple falls.
- Low physical activity or immobility.
- Low body weight (BMI<18 kg/m^2)
- Low muscle mass and strength.
- Poor balance.
- Vitamin D insufficiency.
- Protein or calcium undernutrition.
- Smoking.
- Alcohol >2 standard drinks/day.

Diseases associated with low BMD# +/- POI.

- Rheumatoid arthritis.
- Hyperthyroidism.
- Hyperparathyroidism.
- Chronic kidney disease.
- Coeliac disease or malabsorption.
- Diabetes mellitus.
- Myeloma or MGUS.#
- Bone marrow/ organ transplant.
- HIV# infection.
- Depression.

Medications associated with low BMD#

- Glucocorticoids.
- Excess thyroid hormone replacement.
- Aromatase inhibitors.

Blood and urine tests

- UEC, CMP, LFT, TSH, 25-hydroxy vitamin D#
- Bone turnover markers: not currently recommended for routine use.
- If reduced bone mass is present, also consider the following to screen for secondary causes of osteoporosis: serum PTH#, coeliac serology, serum electrophoresis and 24-hour urine calcium excretion.

Imaging

- **DXA:** Indicated at initial diagnosis for all women with POI where available, especially if long duration of POI or other osteoporosis risk factors present. Use Z-score ≤ -2 to define low bone mass and T-score ≤ -2.5 to define osteoporosis. [1,2]
- **Plain imaging:** Lateral radiographs of lumbar and thoracic spine or DXA-based Vertebral Fracture Assessment (VFA) should be considered on an individual basis particularly if concerns regarding height loss, back pain, chronic diseases associated with low BMD# and current or past glucocorticoid use.

Management

Maintain healthy lifestyle. (Low-moderate quality evidence)

- Weight-bearing exercise.
- Avoidance of smoking.
- Maintenance of normal body weight.
- Balanced diet containing the recommended intake of calcium and vitamin D – dietary supplements may be required if inadequate intake.
- Avoid excess alcohol.

Hormone therapy (Low-moderate quality evidence)

- **Offer estrogen therapy to all women diagnosed with POI unless contraindicated.**
- Consider patient preference for route and method of administration, contraceptive needs, and co-morbidities.
- HRT at higher doses (2 mg oral or 100mcg transdermal oestradiol per day or equivalent) is associated with BMD gains. Combine estrogen with a progestogen for women with an intact uterus.
- If the COC is used, then continuous use is preferred to maintain BMD.
- Continue hormone therapy until at least the time of anticipated natural menopause (approx. 50 years), then reassess.

Anti-resorptive therapy (Low-moderate quality evidence)

- Other pharmacological treatments, including bisphosphonates, should only be considered with advice from a specialist.

Further Assessment

Subsequent assessment of bone health	Specialist referral
• If BMD* is normal and adequate systemic estrogen replacement is maintained, the value of repeated DXA* within 5 years is low. • If low bone mass is diagnosed or where a greater rate of BMD loss is expected (e.g. non-adherence to hormone therapy or presence of other risk factors) then repeat DXA* in 1-3 years [3].	• A decrease in BMD* on subsequent scans (bone loss >5% and/or >0.05g/cm^2) should prompt review of estrogen therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate. • Development of a fragility fracture should prompt specialist referral

FIGURE 11 FACTORS ASSOCIATED WITH DEVELOPMENT OF ADVERSE MUSCULOSKELETAL HEALTH OUTCOMES IN THE NON-POI POPULATION. ADAPTED FROM (KIRK *ET AL.*, 2020) AND USED WITH PERMISSION (OPEN ACCESS CREATIVE COMMONS CC BY LICENCE).

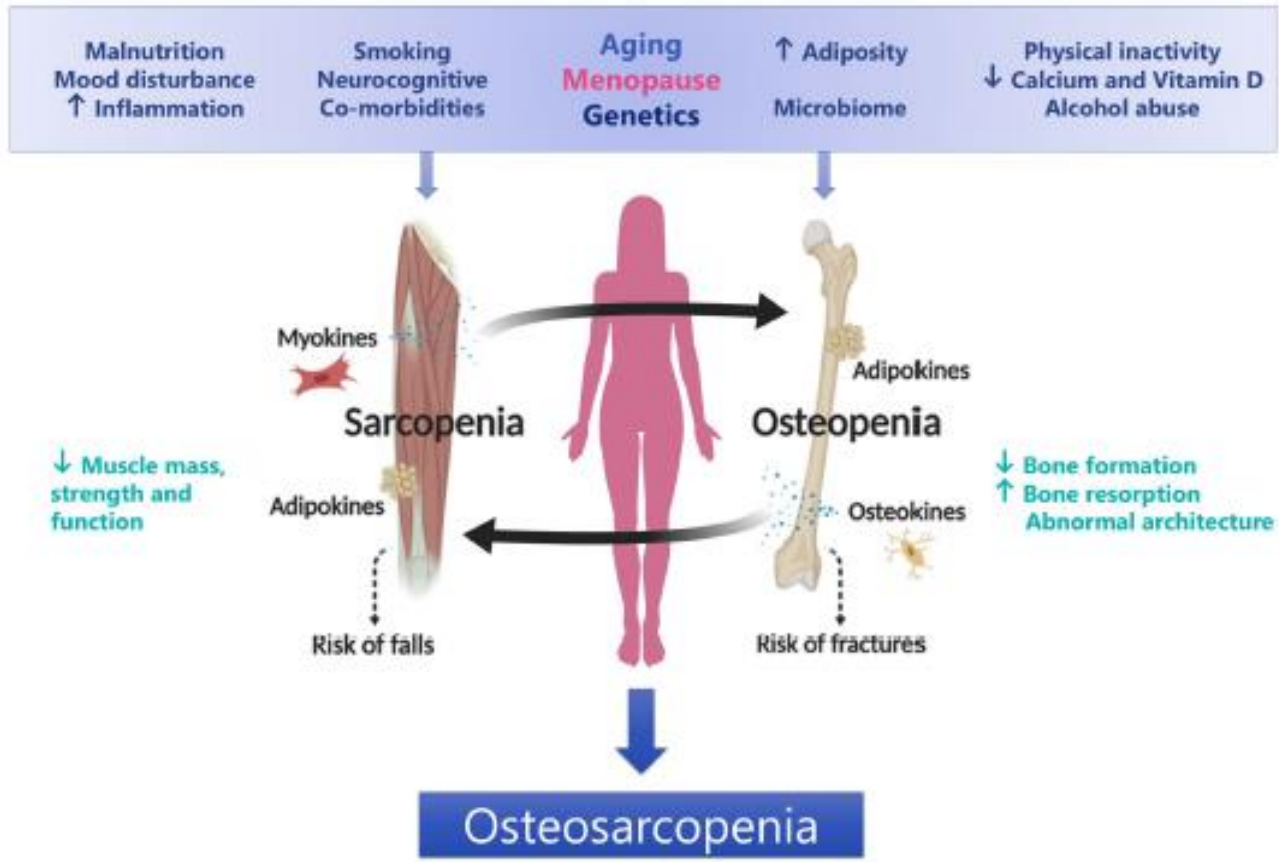


FIGURE 13. INTERNATIONAL SOCIETY FOR THE STUDY OF WOMEN'S SEXUAL HEALTH PROCESS OF CARE FOR THE IDENTIFICATION OF SEXUAL CONCERNS AND PROBLEMS IN WOMEN (REPRODUCED WITHOUT ADAPTATION OR ALTERATION FROM (PARISH *ET AL.*, 2019))

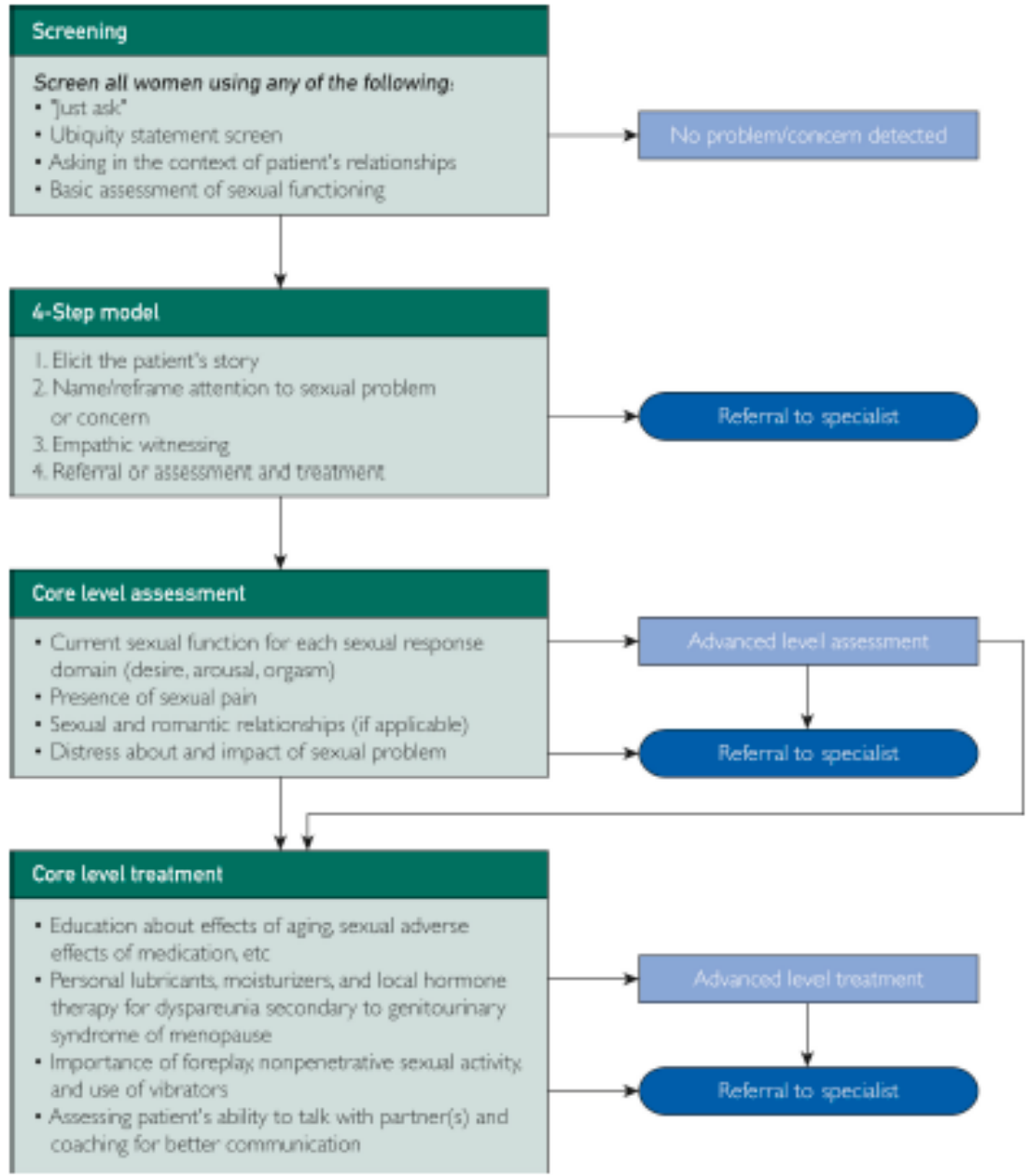


TABLE V SUMMARY OF INDICATIONS FOR HORMONE THERAPY (HT) IN WOMEN WITH POI

Symptoms or Sequelae of POI	Indication for HT	Supporting recommendation
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

TABLE VI SUMMARY OF RECOMMENDATIONS FOR HT IN WOMEN WITH POI WITH POTENTIAL HIGHER RISKS LINKED TO COMORBIDITIES

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

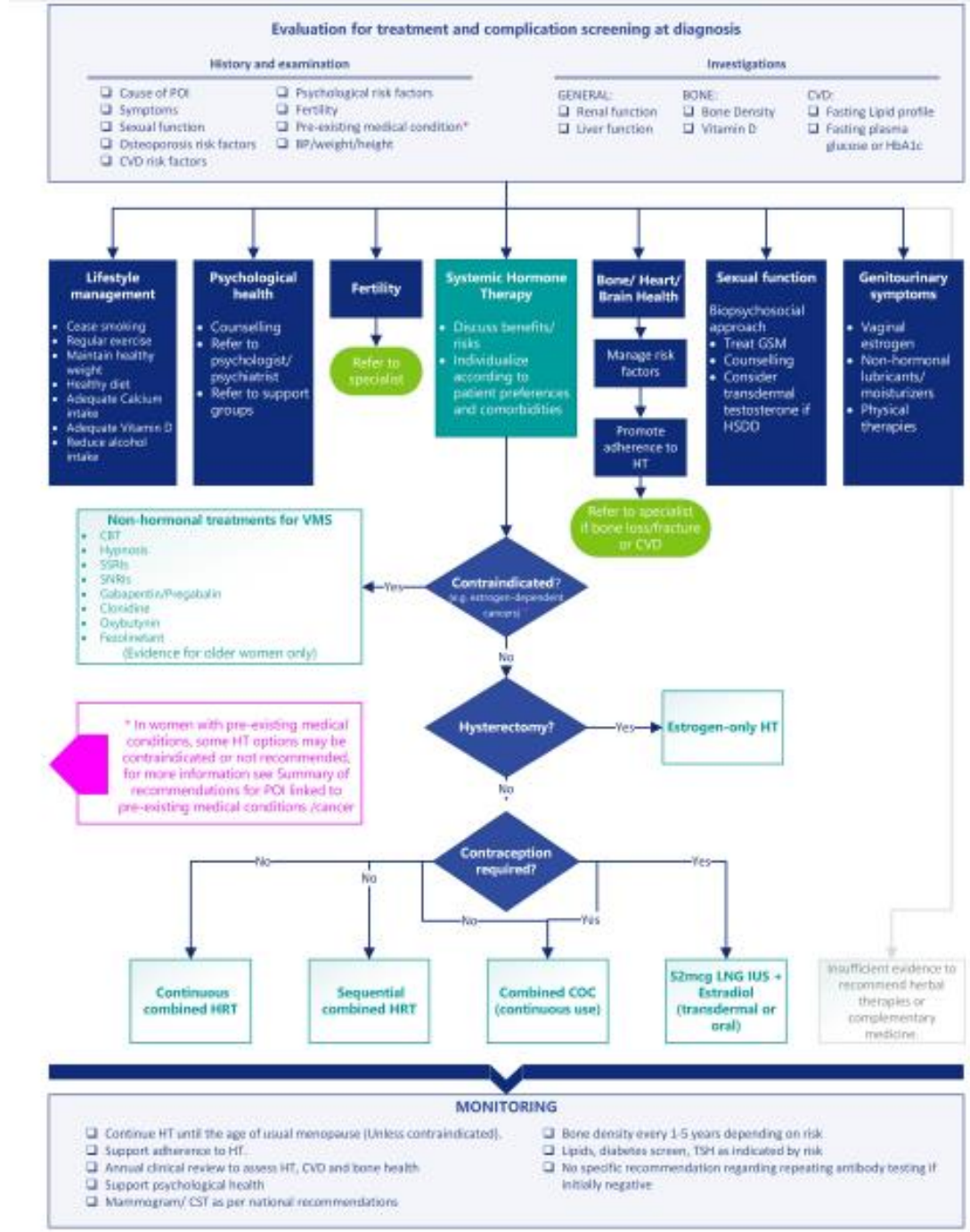
POI after cancer and HT

HT does not increase the risk of recurrence of squamous cell carcinoma of the cervix and is recommended for women with iatrogenic POI due to treatment of squamous cell carcinoma.	STRONG	⊕
HT may be associated with a slightly increased risk of recurrence of cervical adenocarcinoma and a personalised approach considering individualised HT risk and benefits is recommended.	STRONG	⊕
HCPs could consider HT in women with iatrogenic POI due to early-stage low-risk endometrial adenocarcinoma, as there is no evidence that it increases the risk of cancer recurrence.	CONDITIONAL	⊕
HCPs could consider HT in women with iatrogenic POI due to epithelial ovarian cancer.	CONDITIONAL	⊕
The effect of HT on the risk of recurrence of non-epithelial ovarian cancer is uncertain and it is suggested that HCPs use a personalised approach to prescribing HT including consideration of tumour hormone receptor status.	CONDITIONAL	⊕
HT should be avoided in women with hormone dependent ovarian or uterine tumours including uterine sarcoma, endometrioid carcinoma, ovarian clear cell carcinoma, ovarian granulosa cell tumour, or sex cord-stromal tumours.	STRONG	⊕
Women should be informed of the risks of iatrogenic POI and risks and benefits of HT before bilateral salpingo-oophorectomy to reduce cancer risk (RRSO).	STRONG	⊕
It is recommended that personalised HT or pubertal induction be commenced in girls/women with POI following hematopoietic stem cell transplantation or other gonadotoxic therapies.	STRONG	⊕

TABLE VIII SUMMARY OF RECOMMENDATIONS FOR POI LINKED TO GYNECOLOGICAL/BREAST CANCER

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

Figure 14 Management algorithm for POI



OVARIAN INSUFFICIENCY (POI)' REGIMENS (ADAPTED FROM (PANAY *ET AL.*, 2020), REPRODUCED WITH PERMISSION)

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**

TABLE X ESTROGEN SUBSTITUTION THERAPY FOR PUBERTY INDUCTION IN ADOLESCENCE (ADAPTED FROM (GRAVHOLT ET AL., 2017, KLEIN ET AL., 2018))

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.

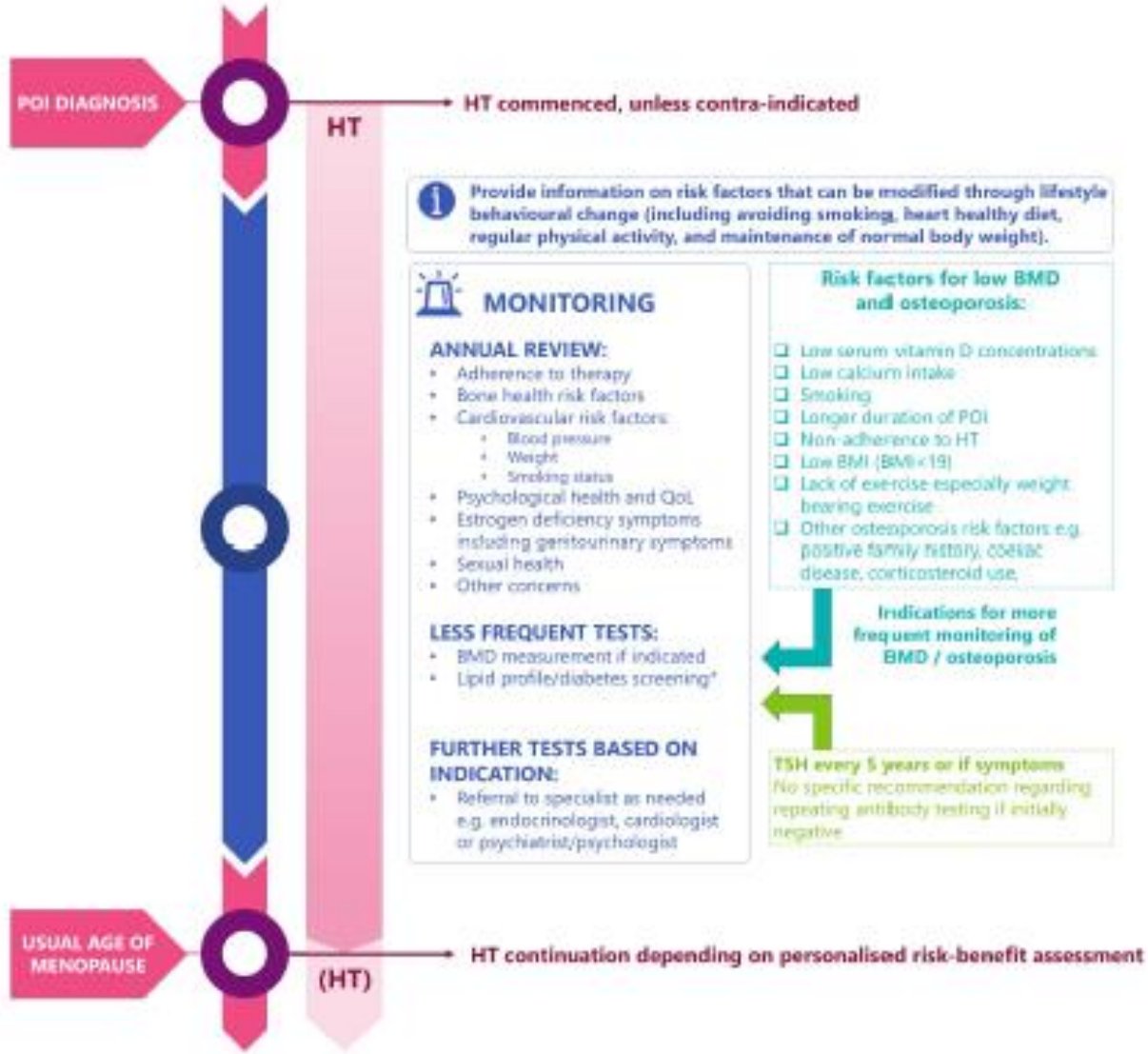
TABLE IX NONHORMONAL OPTIONS FOR MANAGEMENT OF VASOMOTOR SYMPTOMS (ADAPTED FROM (NORTH AMERICAN MENOPAUSE SOCIETY., 2023) WITH PERMISSION).

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

FIGURE 15. SUMMARY OF MONITORING OF WOMEN WITH POI FROM DIAGNOSIS TO USUAL AGE OF MENOPAUSE



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