Update on Guidelines for POI

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Anschutz

Disclosures

Nothing to disclose

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Objectives

- Review diagnosis and initial assessment of POI
- Discuss sequelae of POI
- Review recommended treatments for POI

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POI Definition and Prevalence

Nomenclature

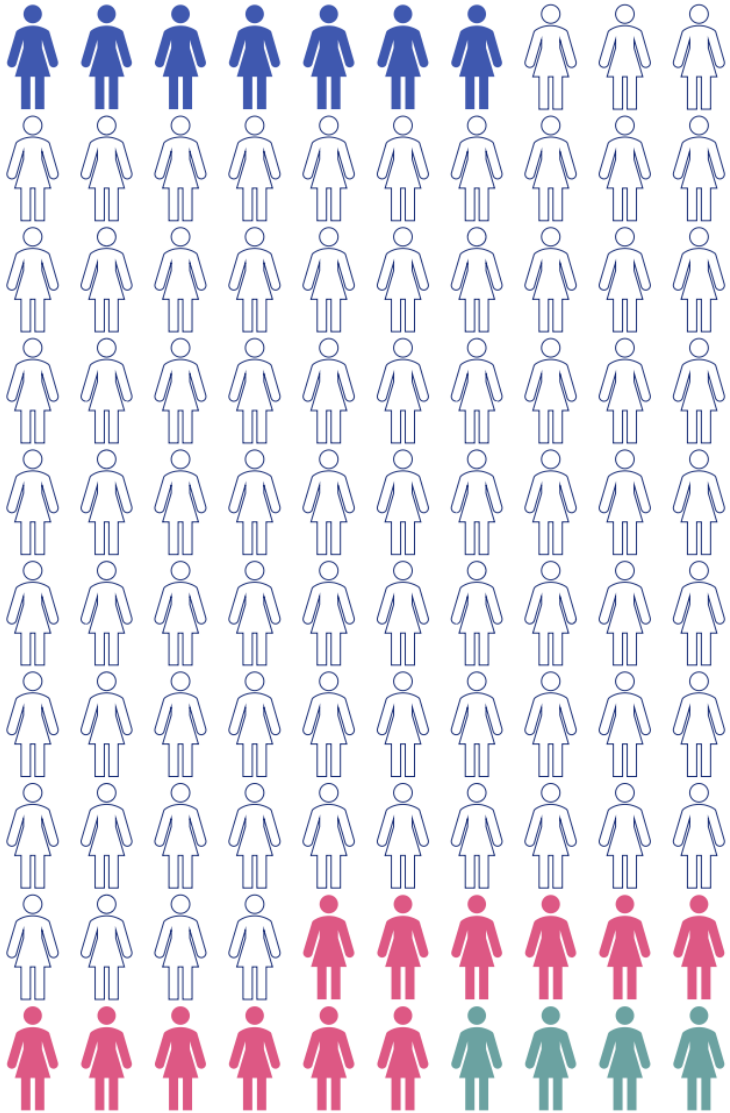
- **Premature ovarian insufficiency**
  - Used by ASRM, ESHRE
- **Primary ovarian insufficiency**
  - Used by ACOG

DIAGNOSIS

- **Amenorrhea or menstrual disturbance x4 months**
- **FSH >25 IU/L**
  - Low estradiol (<50 pg/mL) with elevated FSH supports diagnosis
  - One test is sufficient; can repeat after 4-6 weeks if non-conclusive
- **Rule out other causes of amenorrhea**
  - Pregnancy, PCOS, thyroid dysfunction, hyperprolactinemia, structural
  - May need to discontinue hormonal therapy

PREVALENCE

- Reported as 1% in older literature
- Newer meta-analyses suggest 3.5-3.7% prevalence
- Estimated to affect:
  - 1 in 1,000 before age 30
  - 1 in 10,000 before age 20



ESHRE 2024; Golezar 2019; Li 2023; Panay 2020

RISK FACTORS

- Genetic / family history
- Co-existing medical conditions
- Ethnicity
- Early life factors
- Reproductive factors
- Low BMI
- Lower socioeconomic status
- Lifestyle (smoking, alcohol)
- Infections
- Environmental exposures

For women with a known genetic predisposition or family history of POI, recommend counseling on reduction of risk if applicable

For some risk factors, not clear that adapting lifestyle can change outcomes

Women with RF should be counseled on **fertility preservation**

PREDICTING AGE OF MENOPAUSE

Age

- Best predictor for menopause timing

AMH

- Lower AMH has higher risk of early menopause
- Can help distinguish POI from PCOS, hypothalamic amenorrhea

Genetics

- Newer studies have identified many genes associated with age of menopause
- Will likely be useful in the future

Other factors that are NOT useful

- FSH, inhibin B, FSH/LH ratio
- AFC and ovarian volume
- Menstrual cycle length

Nelson 2023; Laven 2024; ESHRE 2024

Presentation and Evaluation

PRESENTATION

- Typically secondary amenorrhea (80-85%)
- Primary amenorrhea less associated with sx of estrogen deficiency (22% vs 86%)
- Symptoms may be intermittent

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

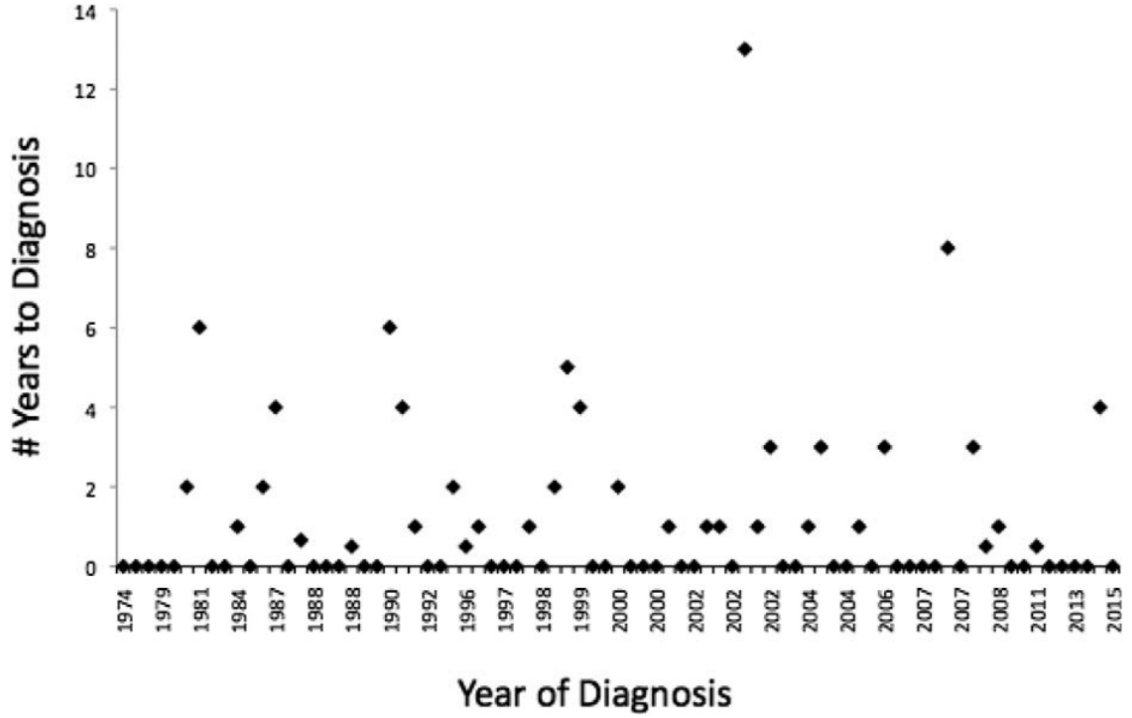
Symptoms may vary in severity depending on the different underlying causes of POI

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

ESHRE 2024; Bidet 2011

DIAGNOSIS OF POI IS OFTEN DELAYED

- Median time for diagnosis: 2 years
- 25% of women undiagnosed for >5 years
- 50% visit clinician office 3+ times before diagnosis



Sullivan 2016; Hipp 2016

ETIOLOGY

Iatrogenic *Surgery, chemo, radiation*	Genetic	Autoimmune
Infectious *Mumps, HIV*	Metabolic *Galactosemia, 17-OH deficiency*	Toxic *BPA, phthalates, cigarette smoke*

Touraine 2024; ESHRE 2024

GENETIC EVALUATION

FMR1 premutation

- Premutation seen in 1-5% of isolated POI, 13% of familial POI
- Highest risk with 80-100 repeats

Karyotype

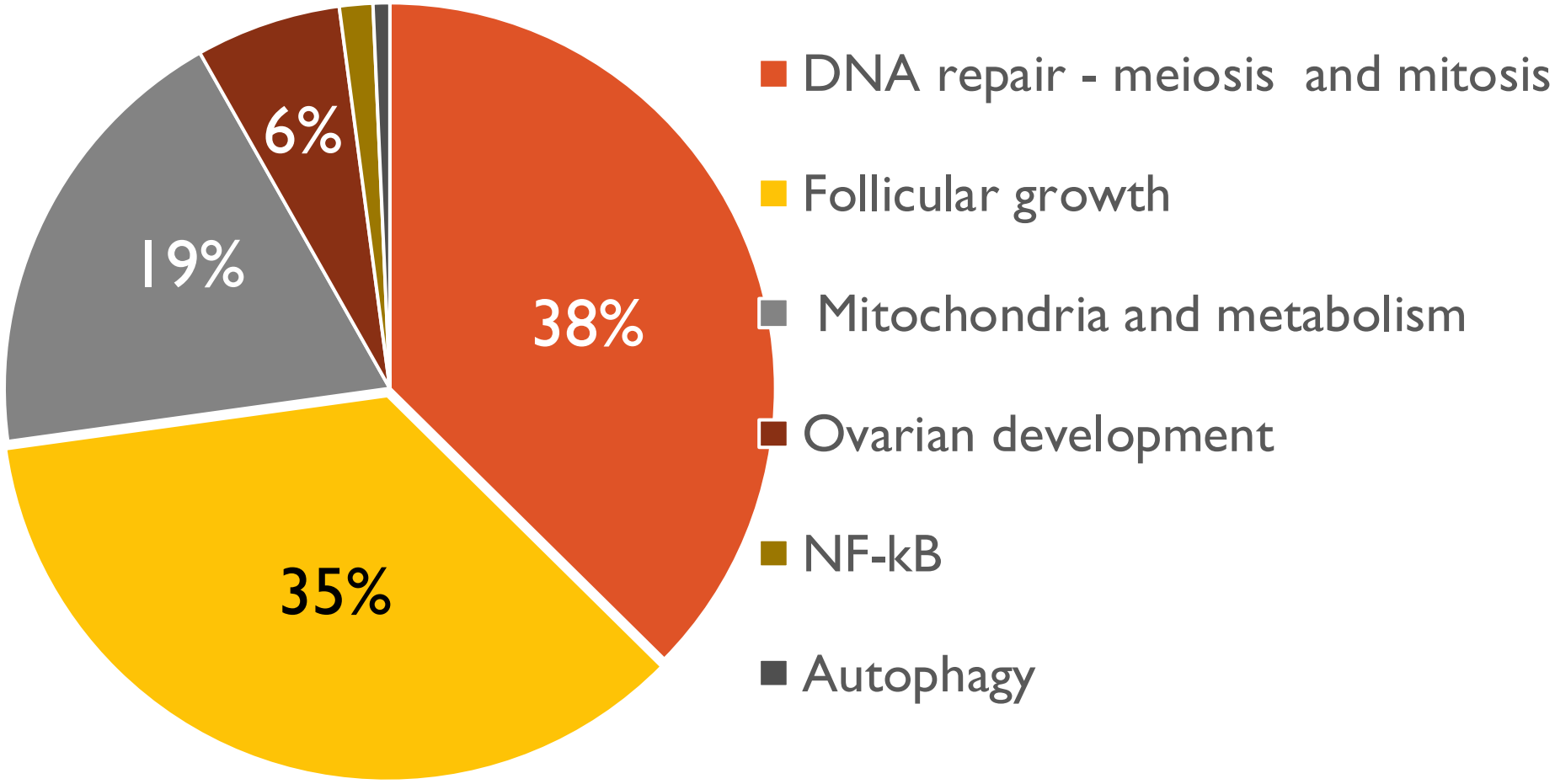
- Chromosomal abnormalities in 10-13%, largely X chromosome
- Turner syndrome affects 25-50 per 100,000 women

Other monogenic disorders

- ~100 mutations identified as pathogenic or likely pathogenic
- 20-30% of patients test positive for one of the identified genes
- More common in primary amenorrhea (29%) and syndromic POI (58%)

ESHRE 2024; Silven 2023; Sullivan 2005; Ke 2023; Heddar 2022; Eskenazi 2023

GENES INVOLVED IN POI



Heddar 2022

SYNDROMES ASSOCIATED WITH POI

Syndrome	Gene	Symptoms
Ataxia telangiectasia	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)	AIRE	Chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal failure
Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)	FOXL2	Autosomal dominant congenital palpebral malformation
Bloom syndrome	BLM	Chromosomal breakage > early onset of aging, short stature, and elevated rates of most cancers
Galactosemia	GALT	Metabolic disease related to glucose metabolism
Perrault syndrome	Multiple	Ovarian dysgenesis and sensorineural hearing loss

AUTOIMMUNE CONCERNS

Adrenal insufficiency

- 6-20% with adrenal insufficiency have POI
- 2-3% of women with POI develop adrenal insufficiency

Thyroid disorders

- Seen in 20% with POI (vs 5-10% in general population)
- Do NOT check TPO abs

Autoimmune polyendocrine syndrome

- Recessive mutation in autoimmune regulator (AIRE) gene
- Sx include adrenal insufficiency, mucocutaneous candidiasis, hypoparathyroidism and 50–60% of these women develop POI

Other

- Has been associated with SLE, celiac disease, vitiligo

ESHRE 2024; Panay 2020

NEXT STEPS AFTER DIAGNOSIS

Testing

Genetic

- FMR1 premutation
- Karyotype
- NGS when available / after comprehensive genetic counseling

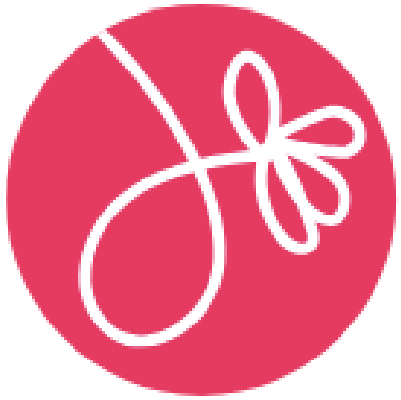
Autoimmune

- 21-hydroxylase antibodies
  - Endocrinology referral if positive
- TSH (q5 years)
- NO ovarian antibodies

Psychological support

Family counseling

SUPPORT GROUPS



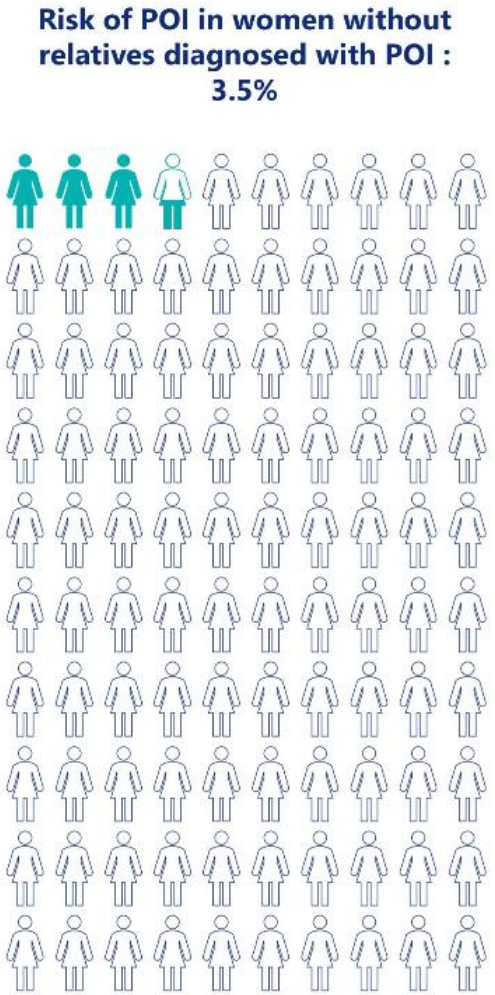
daisy network

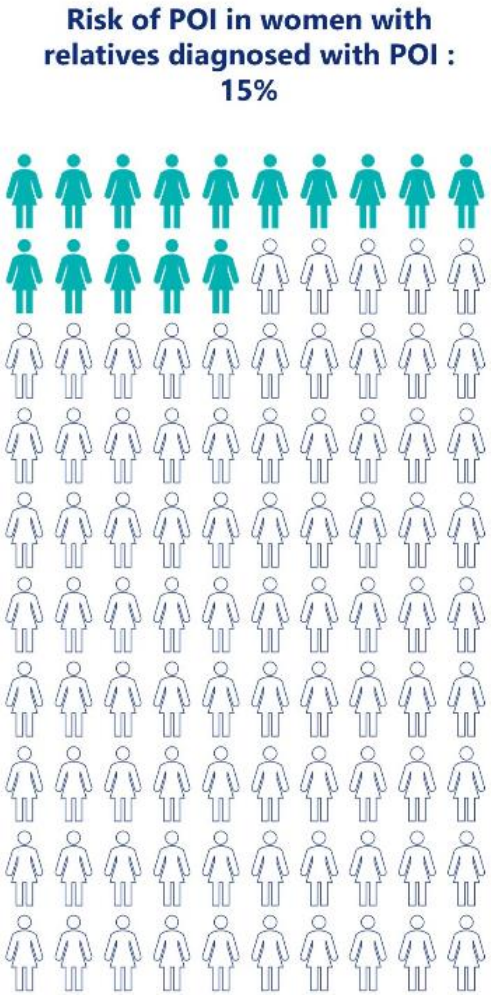
resolve

THE NATIONAL INFERTILITY ASSOCIATION

FAMILY COUNSELING

- Increased risk of POI
- No ways to predict or prevent
- Discuss signs and symptoms
- Effect of hormonal treatment
- Fertility preservation options





Sequelae of POI

SEQUELAE OF POI

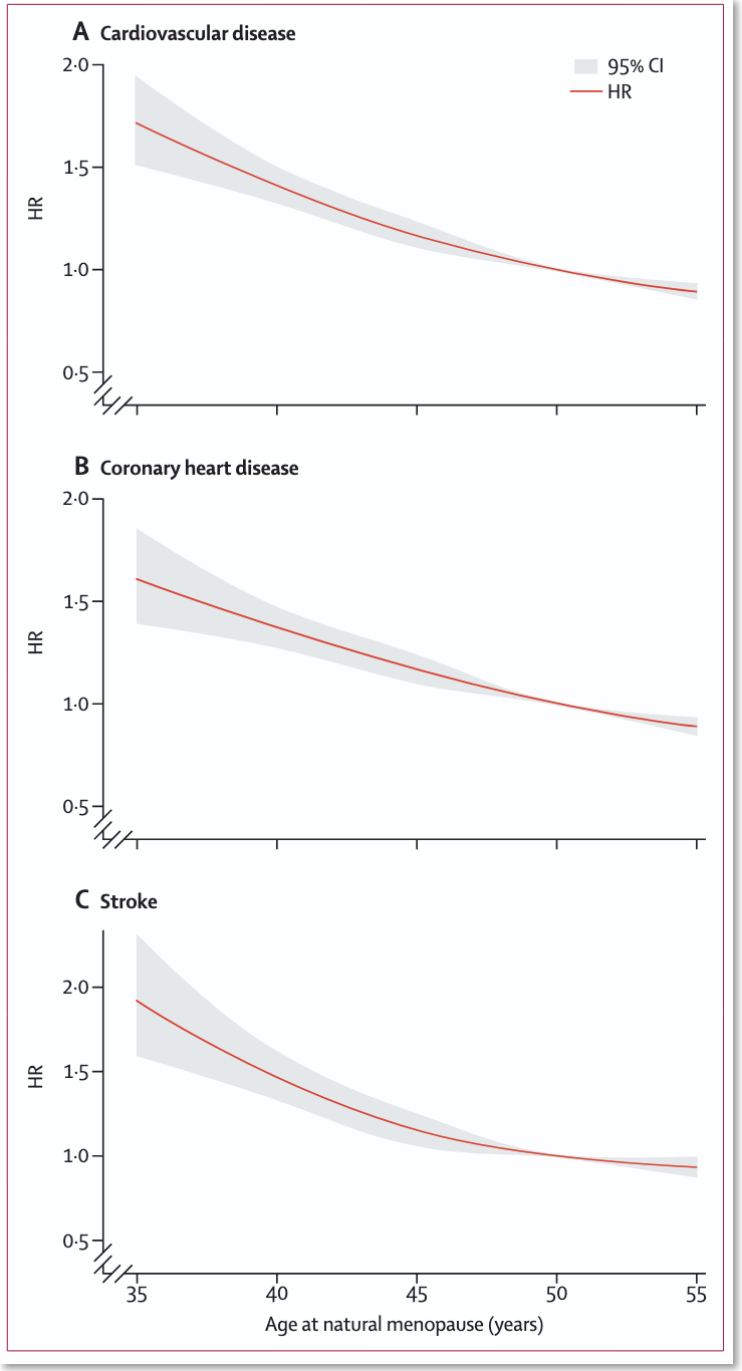
- Cardiometabolic disease
- Bone health
- Cognition
- Psychological health
- Vasomotor / menopausal symptoms
- Sexual function
- Fertility

CARDIOMETABOLIC DISEASE

- ↑ risk of CVD, coronary artery disease, stroke
  - 5.7/1000 woman-years without POI
  - 8.8/1000 for non-surgical POI
  - 11.3/1000 for surgical POI
- Interaction may be bi-directional
  - E2 <50 pg/mL > ↑ risk of coronary artery disease
  - ↑ premenopausal RF for heart disease > earlier menopause

➢ Vascular disease may be partially causative of POI

➢ Early menopause may reflect accelerated aging



Honigberg 2019, Ley 2017, Zhu 2019 ; Bairey Merz 2003, Kok 2006, Stuenkel 2012

BONE HEALTH

- Decreased BMD and higher rates of fracture
  - Femoral neck osteopenia in 67% with POI vs 16% controls
  - 1.5-3 fold higher fracture risk with POI
- Differential risk persists long-term
- Bone loss begins rapidly after onset of amenorrhea

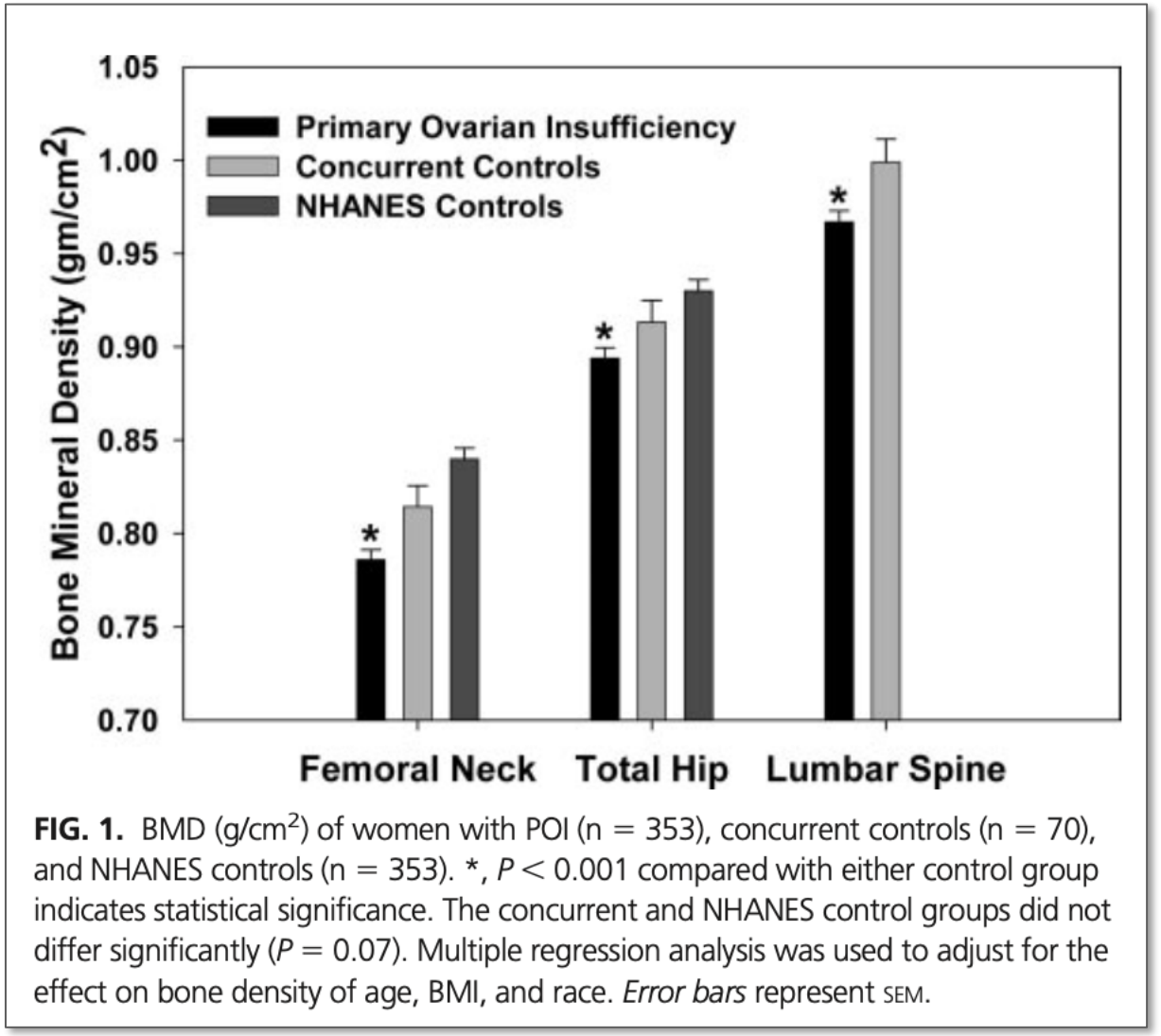


FIG. 1. BMD (g/cm^2) of women with POI (n = 353), concurrent controls (n = 70), and NHANES controls (n = 353). *, $P < 0.001$ compared with either control group indicates statistical significance. The concurrent and NHANES control groups did not differ significantly ($P = 0.07$). Multiple regression analysis was used to adjust for the effect on bone density of age, BMI, and race. *Error bars* represent SEM.

Anasti 1998; Popat 2009; Popat 2014; van Der Voort 2003; Sullivan 2016

COGNITION

- Natural menopause before age 45 may be associated with increased risk of dementia
- Premenopausal oophorectomy associated with greater risk of cognitive impairment

Karamitrou 2023; Rocca 2007; Rocca 2021

PSYCHOLOGICAL WELLBEING

- Higher rates of depression among women with POI
  - Most women report depression dx before POI dx
  - 26% reported depression prior to menstrual irregularities
- Lower QoL reported in women with POI

Allshouse 2015; Schmidt 2011; ESHRE 2024

SEXUAL FUNCTION

- Multiple issues including:
  - Reduced sexual arousal
  - Decreased lubrication
  - Increased genital pain
  - Lower levels of satisfaction

TABLE 2. *Mean FSFI scores of the women with POF and the women in the control group (n = 58 in each group)*

	POF group		Control group		
Domain	Mean ± SD	Median	Mean ± SD	Median	*P*
Desire	3.5 ± 1.1	3.6	3.6 ± 1.1	3.6	NS
Arousal	3.7 ± 1.2	3.8	4.2 ± 1.0	4.4	0.0176
Lubrication	4.2 ± 1.3	4.2	5.0 ± 1.2	5.4	0.0012
Orgasm	4.0 ± 1.3	4.0	4.6 ± 1.2	4.8	0.0136
Satisfaction	4.3 ± 1.3	4.8	4.9 ± 1.1	5.0	0.0124
Pain	4.3 ± 1.3	4.4	5.0 ± 1.0	5.2	0.0037
Total	24.0 ± 6.0	24.0	27.3 ± 4.8	27.7	0.0047

All cells/data refer to Wilcoxon signed-rank test.
FSFI, Female Sexual Function Index; POF, premature ovarian failure; NS, not significant.

- Higher rates of vaginal atrophy
  - Does NOT correlate with reported sexual pain or lubrication

Kalantaridou et al 2004; de Almeida et al 2011; Pacello et al 2014

MENOPAUSAL SYMPTOMS

- Many symptoms overlap with age-appropriate menopause
- Presenting complaints include:
  - Mental fog (77%)
  - Vasomotor symptoms (39%)
  - Bleeding complaints (14%)
  - Low energy, low libido, low mood, vaginal dryness for most others

Allshouse 2015; Benetti-Pinto 2011

FERTILITY

- Around 25% will have intermittent ovarian function
  - Most likely in 1st year after diagnosis
  - Predictive: low FSH, high E2, antral follicles, fam hx, secondary amenorrhea
- Unassisted conception reported in 3-10%

Bidet 2011; Bachelot 2017; Fraison 2019; Cambray 2023

Treatment

PRINCIPLES OF HORMONAL TREATMENT

- Provide ***replacement*** of physiologic hormones
- Used for both ***treatment*** and ***primary prevention***
- May be needed for puberty induction, fertility treatments

ESHRE 2024; NAMS 2022

ESTROGEN

- Replace at a physiologic level
- Ideally, use non-oral 17β-estradiol
- Titrate doses to symptoms

Consider starting with transdermal estradiol 0.1mg

ACOG CO 698, ESHRE 2024; Panay 2020; Costa 2023

PROGESTERONE

- Expert opinion recommends **cyclic** monthly progesterone
- Micronized progesterone: **lower breast cancer and cardiovascular risk**
- Medroxyprogesterone acetate – only use with adequate contraception
- Can use LNG-IUD if contraception needed

Consider oral micronized progesterone 200 mg daily for 12 days a month or LNG-IUD

WHAT ABOUT OCPS?

- Estradiol is better at increasing bone density
- Transdermal estradiol has a more favorable CV profile

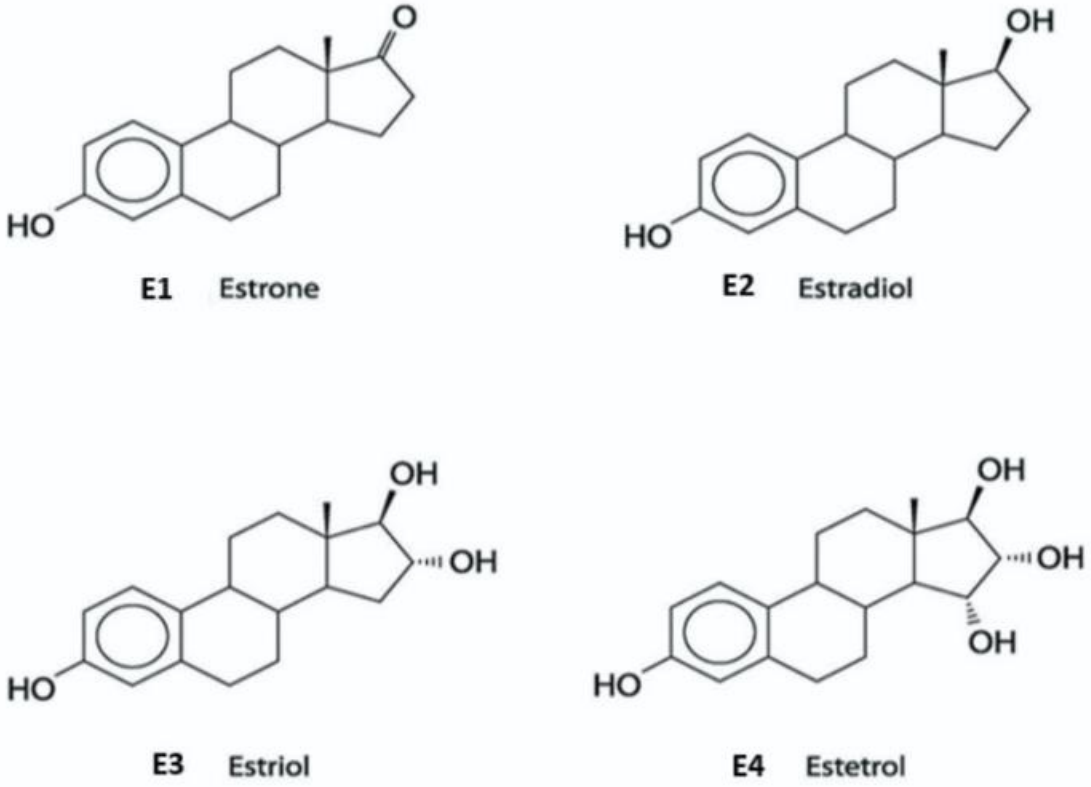
Consider OCPs for…

Contraception	If fertility not desired, need reliable contraception
Cost	Transdermal HRT can be more expensive than OCPs
Social Factors	Young women may decline menopause treatments

- If OCPs, consider continuous use

Cartwright 2016; Crofton 2010; Langrish 2009; Fine 2022

ESTETROL



- High oral bioavailability
- Half life of 24-32 hours
- Limited effect on hemostasis
- Beneficial effects on lipids, carbohydrate metabolism, bone turnover
- May have antitumor effects in breast cancer

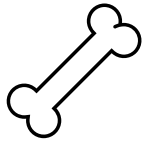
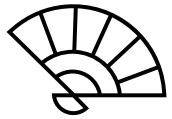
Coelingh Bennink 2025; Creinin 2024; Panay 2026; Gerard 2022

TESTOSTERONE

- Consider use for HSDD, particularly with iatrogenic POI
- No proven benefit for cognition, QoL, self-esteem, mood, bone health
- If used, recommend transdermal dosing > premenopausal level
  - Check T levels to avoid supratherapeutic dosing

Popat 2014; Guerrieri 2014; Davis 2019; Stuursma 2022

HORMONAL TREATMENT BENEFITS

	Symptom	Effect
	Cardiovascular	Endothelial function normalized in 6 months
	Bone health	BMD normalized in 3 years
	Vasomotor	Significant decrease in symptoms
	Sexual function	Improvement in sexual discomfort
	Cognition	May have benefit with immediate initiation

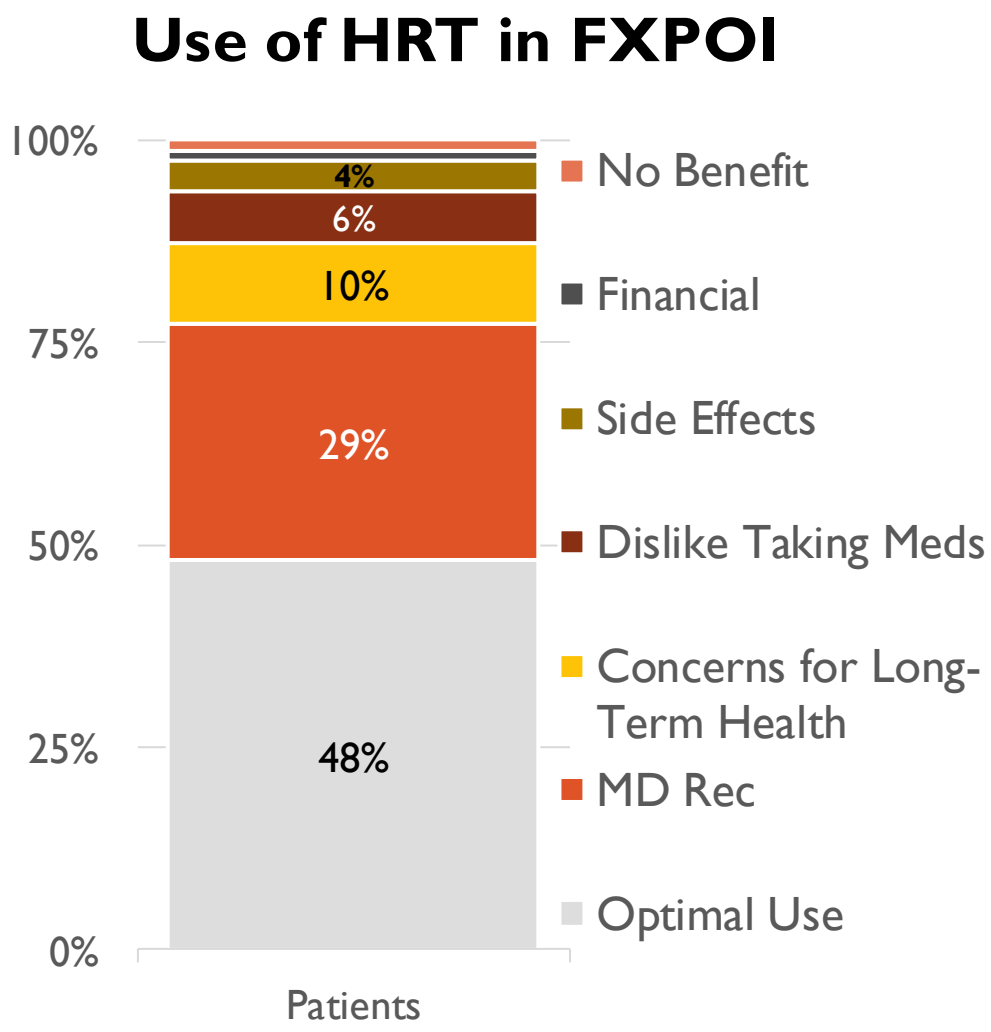
Popat 2014, Kalantaridou 2004; Vermeulen 2017; NAMS 2022

HORMONAL TREATMENT RISKS

Hormone	Risks	
Estrogen	**CONTRAINDICATED** with h/o breast cancer	
	Breast cancer	• Slight increase in risk with OCPs • Likely no increase over age matched controls
	CV events	Transdermal does not increase BP
	VTE	2-3x increased risk with oral formulations
	Gallbladder	~2x increased risk of cholecystectomy
Progesterone	• May increase risk of breast cancer (particularly progestins)	
Testosterone	• No risks identified over12 month exposure period • Long term risks of testosterone use are unknown	

Cushman 2007; Chlebowki 2020, Cordina-Duverger 2013, Jiang 2017; Popat 2014; Guerrieri 2014; Davis 2019; Morch 2017

ADHERENCE TO HORMONE THERAPY



- Discontinuation reasons:
  - Lack of perceived benefit
  - Fear of breast cancer
- BMD loss seen after discontinuation

Hipp 2016; Bachelot 2016

HORMONAL THERAPY AFTER CANCER

- Recommended after squamous cell cancers, stem cell transplantation
- Do NOT use after breast cancer or hormone-dependent uterine or ovarian tumors

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/progestoger
POI following hematopoietic stem cell transplantation	✓ Recommended	Not increased	Individualised HT / pubertal induction

ESHRE 2024

CESSATION OF HORMONAL THERAPY

Discontinue physiologic levels of replacement around 51yo

Can continue normal postmenopausal dosing if needed

OTHER TREATMENT CONSIDERATIONS

Cardiovascular	• Address modifiable risks (smoking, HTN, diabetes) • Annual screening – BMI, BP, lipids, A1c, tobacco use
Bone health	• Get DEXA with diagnosis • Avoid bisphosphonates if considering pregnancy • Supplement calcium and vitamin D
Vasomotor	• Possible addition of nonhormonal medications
GSM	• Add vaginal therapies

NONHORMONAL THERAPIES FOR VASOMOTOR SYMPTOMS

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

- No RCTs specific to POI
- Some data to support CBT, hypnosis, stellate ganglion block
- No good data for other complementary therapies

FERTILITY

- Recommend naturally occurring hormones if pregnancy desired
- Oocyte / embryo donation is the most effective option

Emerging options

- Ovarian tissue cryopreservation
- In vitro maturation
- In vitro activation
- Platelet-rich plasma injection
- Stem cells
- Oogonial stem cells
- Laparoscopic ovarian activation

ESHRE 2024; Panay 2020; Pereira 2020; Kim 2024; Rosario 2021

Thank you!

Questions?

Citations

Citations

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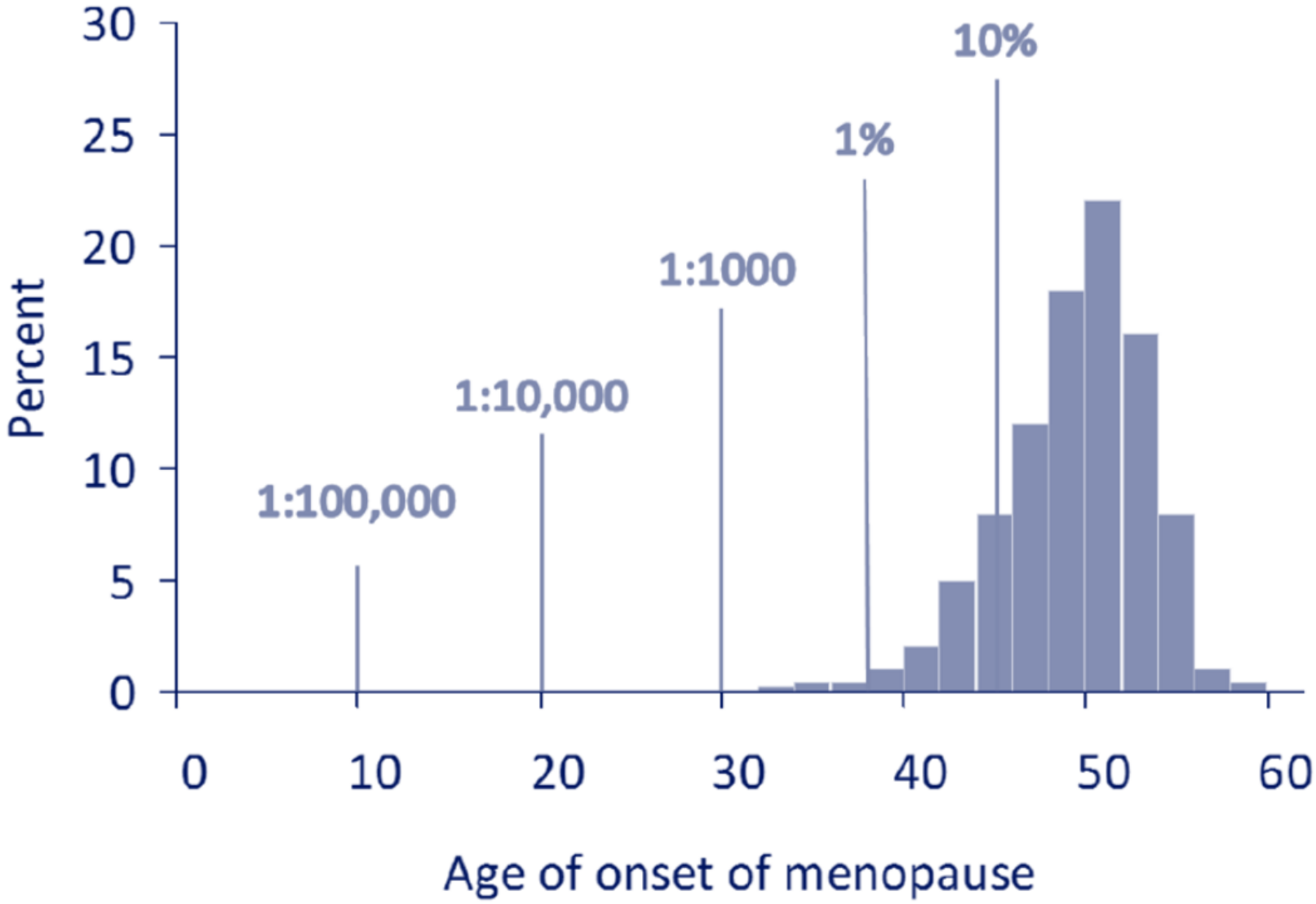
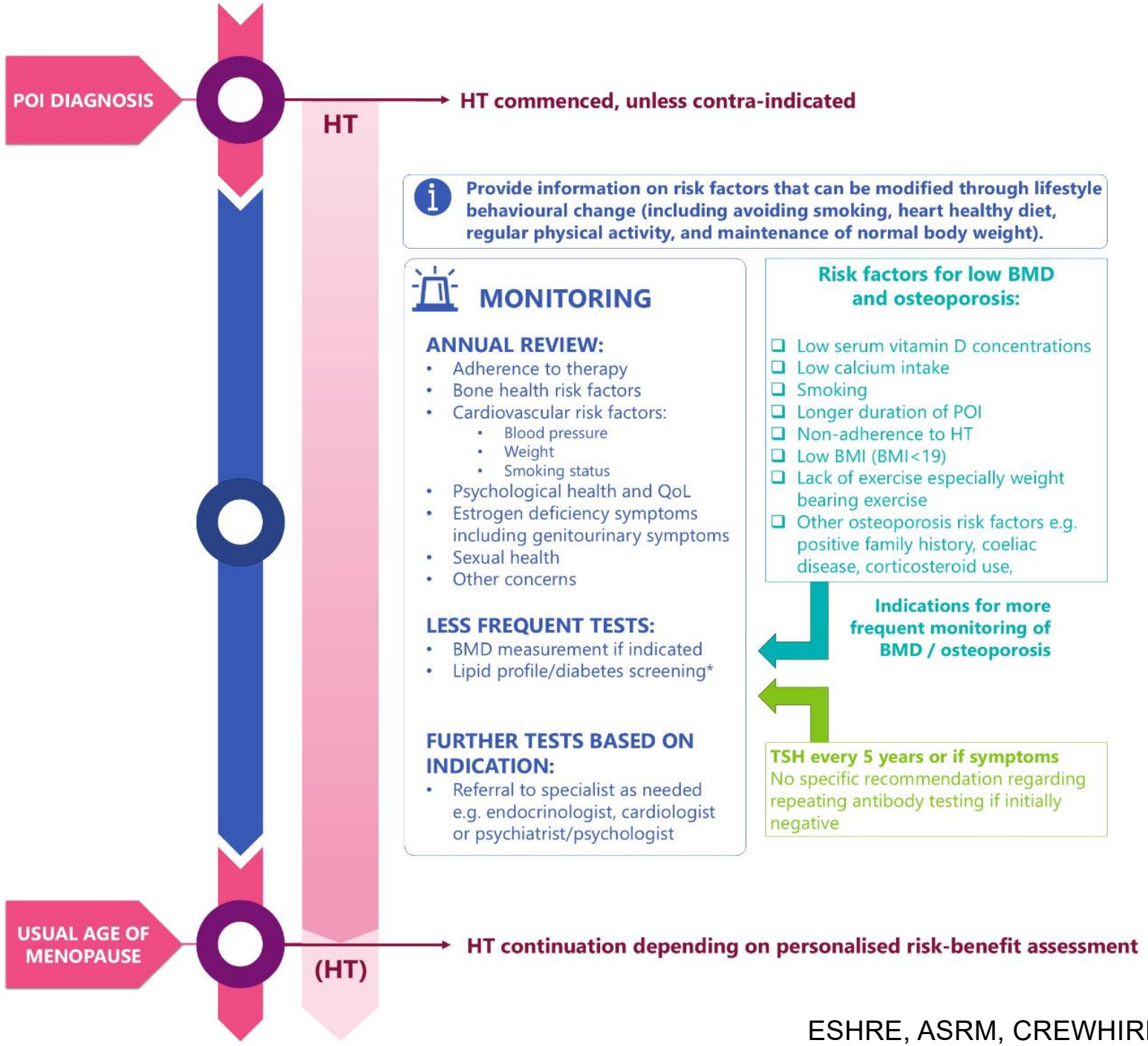
Appendix

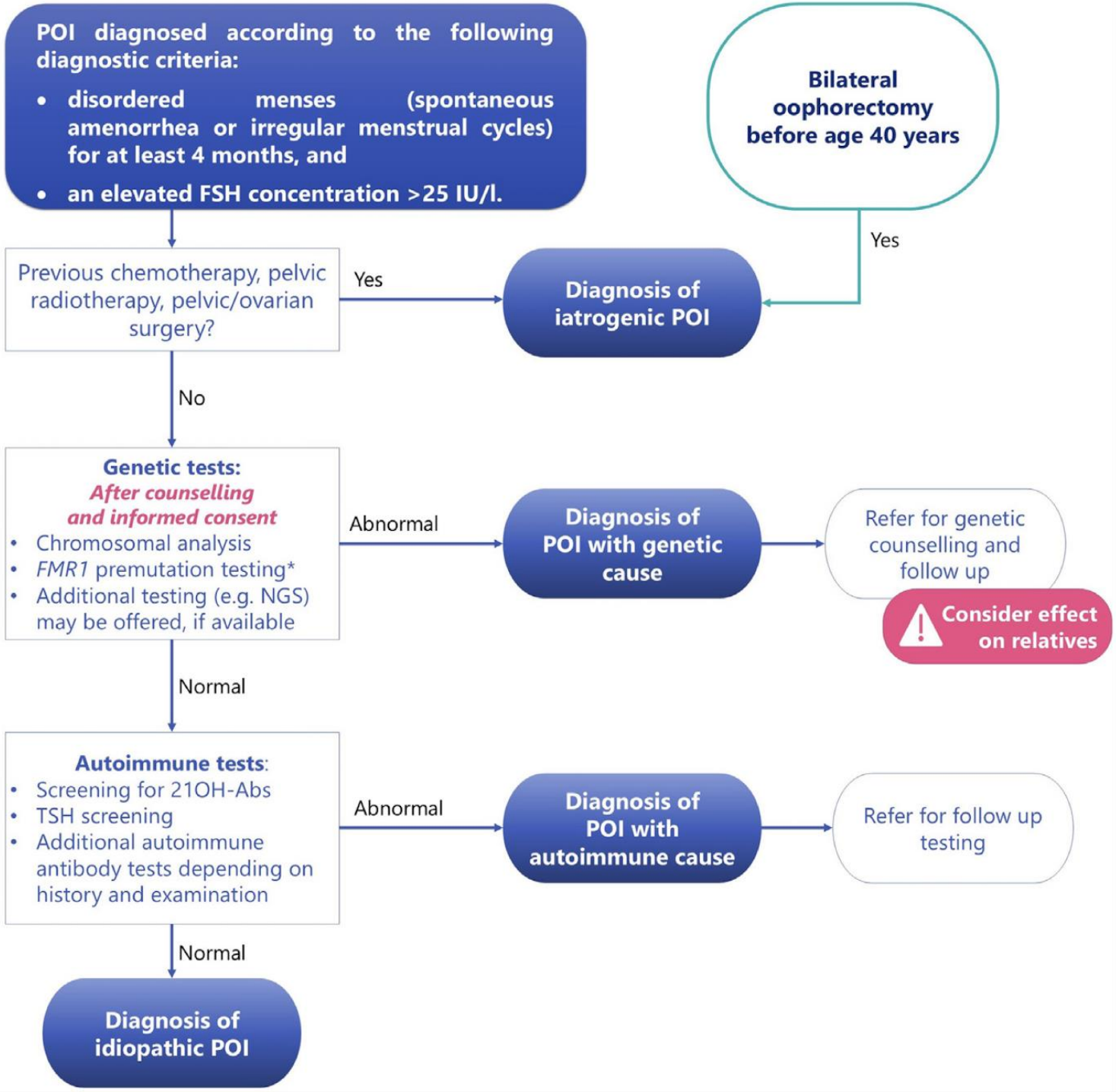
Menopause Age of Onset





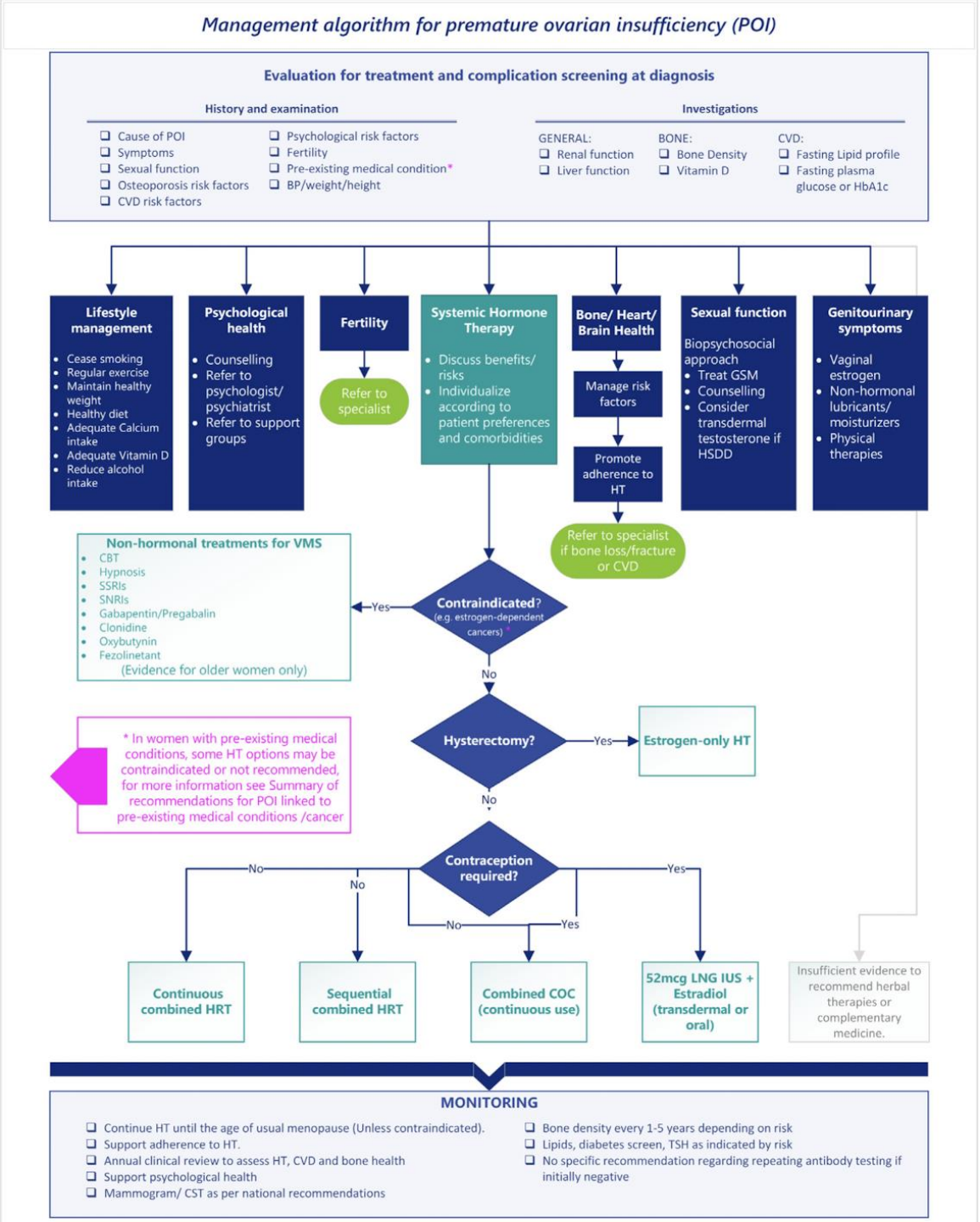
ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI 2024

Diagnosis of POI



ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI 2024

Management of POI



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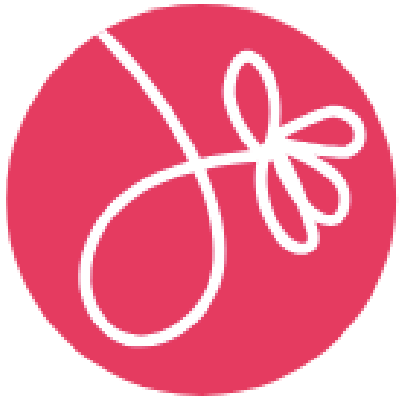
SUPPORT GROUPS



daisy network

resolve

THE NATIONAL INFERTILITY ASSOCIATION

PUBERTY INDUCTION

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.

Speroff 9th edition; Klein 2019; ESHRE 2024

POISE TRIAL

- Multicenter trial in England and Scotland
- Women with POI randomized to COC or HRT
- Primary outcomes: BMD at 2 years post randomization
- Monitoring x5 years, assess bone health, CV markers, sexual function, QOL
- Expected to run through 2029

PRE-PREGNANCY EVALUATION

	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