From Causes to Consequences: Modern and Evidence-Based Approaches to Managing Morbidity in Premature Ovarian Insufficiency

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Disclosures

Consulting Fee (e.g., Advisory Board): Ferring Pharmaceuticals

Objectives

- To review the definition, global prevalence, and pathophysiology of premature ovarian insufficiency
  - Idiopathic and secondary
- To describe the significant health risks (cardiometabolic, endocrine, quality of life, fertility) associated with premature ovarian insufficiency and the current barriers to implementation of systematic care
- To discuss a lifecourse approach to the management of premature ovarian insufficiency that addresses disease risk mitigation and the role of hormone replacement

Definitions and Nomenclature

- Premature ovarian insufficiency (POI) describes a spectrum of declining ovarian function and reduced fecundity due to a premature decrease in initial follicle number, an increase in follicle destruction, or poor follicular response to gonadotropins before the age of 40
- Primary Ovarian Insufficiency
  - First described in 1942 by Fuller Albright
- The terms primary and premature ovarian insufficiency have both been used
  - Replacing “premature menopause” and “premature ovarian failure”

Evidence-based guideline: Premature Ovarian Insufficiency, Human Reproduction Open, 2024, 2024(4) 1-14
ACOG Committee Opinion 698, Obstetrics and Gynecology 2017;129;e136-141
ACOG Committee Opinion 605, Obstetrics and Gynecology 2014; 123;193-7

Table 3. Clinical States Included in the Spectrum of Primary Ovarian Insufficiency.*

Clinical State	Serum FSH Level	Fertility	Menses
Normal	Normal	Normal	Regular
Occult	Normal	Reduced	Regular
Biochemical	Elevated	Reduced	Regular
Overt	Elevated	Reduced	Irregular or absent

Nelson L NEJM 2009;360:606-614

Definitions and Nomenclature

- POI is characterized by amenorrhea or oligomenorrhea (4-6 months), with elevated gonadotropins and low estradiol
- Premature ovarian insufficiency is a pathologic condition that should not be considered a hastening of natural menopause
  - 50% experience infrequent ovulation and menstrual cycles after diagnosis and 5–10% of whom may achieve spontaneous pregnancies

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Clinical Considerations

- Although women with premature ovarian insufficiency share common health risks with women who are naturally menopausal at later ages, the approach to health maintenance in these women is distinct
  - Contraception is a consideration
  - Hormonal management has a distinct risk benefit profile
  - Beware of extrapolating data from WHI

POI and Early Menopause Prevalence -- An Evolving Picture

- Traditional POI prevalence has been reported to be 1%
- In epidemiologic studies, approximately 10% of women in the general population experience early menopause between 40 and 45 years
- Data from more recent published evidence suggests higher POI prevalence
  - Golezar et al, meta-analysis of 31 studies (2019): Global POI prevalence 3.7%
    - Ages 40-45: 12.2%
    - POI prevalence varied in low (4.3%) and medium (4.9%) Human Development Index countries compared to high HDI countries (4.1%)
    - No apparent trends over time

Golezar S et al. Climacteric 2019;22: 403-411
Cramer D Fertility and Sterility 1995;64: 740-745
Van Noord PAH et al Fertility and Sterility 1997;68: 95-102
Coulam CB et al Am J Reprod Immunol 1983;4: 63-66

POI Prevalence

- Li et al, meta-analysis, 13 studies (2023): Global POI prevalence 3.5%
  - 25,107 POI patients
  - Prevalence of POI differed between regions globally, as well as between developing and developed countries

Li M et al. Climacteric 2023a;26: 95-102

POI Prevalence

Table 2. Subgroup analysis based on the etiopathology, regions, sample size, study type, quality of the study and development level.

Characteristic	Number of included studies	Result of heterogeneity		Type of effect model	Result of meta-analysis Combined prevalence (95% confidence interval)
		p-Value	I^2 (%)		
Etiopathology					
Autoimmunity	5	<0.001	84.7	Random	10.5 (6.1–15.0)
Infections	1	–	0.0	Random	13.1 (8.7–17.5)
Iatrogenic cause	2	0.453	0.0	Random	11.2 (9.3–13.1)
Idiopathic cause	3	<0.001	91.1	Random	2.1 (1.7–2.6)
Region					
Europe	6	<0.001	94.3	Random	2.3 (1.9–2.8)
Asia	4	<0.001	89.9	Random	3.3 (2.1–4.5)
North America	2	<0.001	0.0	Random	11.3 (9.5–13.1)
South America	1	–	0.0	Random	5.4 (4.0–6.8)
Sample size					
<1000	8	<0.001	83.9	Random	11.1 (8.1–14.1)
>1000	5	<0.001	95.3	Random	2.2 (1.9–2.5)
Study type					
Cross-sectional	8	<0.001	94.2	Random	4.8 (3.7–6.9)
Cohort	5	<0.001	97.5	Random	3.6 (2.9–4.3)
Quality of study					
High	9	<0.001	96.1	Random	2.8 (2.4–3.2)
Moderate	3	<0.001	90.1	Random	11.2 (3.2–19.1)
Low	1	–	100	Random	10.2 (7.4–13.0)
Development level					
Developed country	9	<0.001	96.4	Random	3.1 (2.6–3.6)
Developing country	4	<0.001	77.7	Random	5.3 (3.0–7.6)
Overall	13	<0.001	96.1	Random	3.5 (3.0–4.0)

Li M et al. Climacteric 2023a;26: 95-102

POI Prevalence Race and Ethnicity

- The Study of Women's Health Across the Nation (SWAN)
  - 1.1% prevalence of POI overall
    - 1% Caucasian
    - 1.4% of African American
    - 1.4% of Hispanic
    - 0.5% of Chinese
    - 0.1% of Japanese

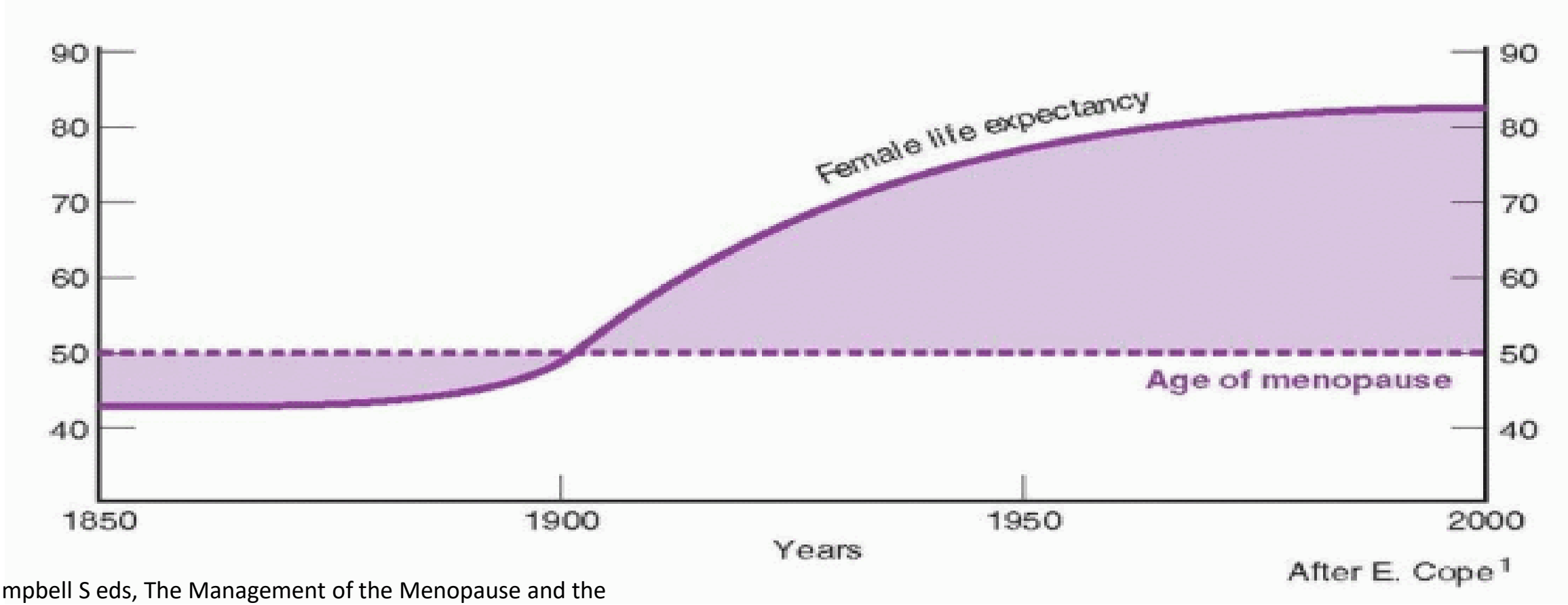
Harlow BL et al. Maturitas 2000;35:3–9

Menopausal Timing

Investigators	Age of Menopausal Onset
Massachusetts Women's Health Study (US)	Median 51.4 years
Study of Women's Health Across the Nation (US)	Median 51.4 years
Penn Ovarian Aging Study (US)	Mean 50.9 years
Treloar et al (US)	Mean 49.5 years
Van Noord et al (Netherlands)	Mean 50.2 years
Meschia et al (Italy)	Mean 50.9 years
Kapur et al (India)	Mean 46.8 years

McKinlay SM et al, 1992
Treloar et al, 1974; Freeman et al, 2012
Meschia M et al, 2000; Kapur P et al, 2009
van Noord PAH et al, 1997

Menopausal Timing and Life Expectancy



In: Campbell S eds, The Management of the Menopause and the Postmenopausal years, Univ Park Press, Baltimore 1976

Common Causes and Pathophysiology

- Spontaneous
  - Idiopathic –90%
  - Monosomy X/Mosaicism – Turner Syndrome
  - Fragile X Premutation Carrier (FMR1)
  - Autoimmune
    - Isolated
    - In association with polyglandular failure
- Iatrogenic
  - Chemotherapy/Stem Cell Transplant
    - Alkylating agents
  - Radiation therapy
    - Exposures higher than 10-12 Gy to pelvis
  - Bilateral Salpingoophorectomy

Risks Factors for Symptoms and POI/Early Menopausal Onset

- Family History
  - Six fold increase in likelihood of early menopause when a mother, sister, aunt or grandmother is effected
- Medical History/Medical Treatments
- Smoking
  - Hastening by 1-4 years
  - Heavy Smoking
  - Genetic variation in CYP genes may play a role in susceptibility
  - Increased prevalence and severity of vasomotor symptoms

Butts et al, 2014; Barbieri et al, 1995; Westoff et al, 2000
Freour et al 2008; El-Nemr, et al 1998; Cramer et al 1995
Luborsky et al, 2002; Gallichio et al, 2006
Freeman et al, 2001; Whiteman MK et al, 2003

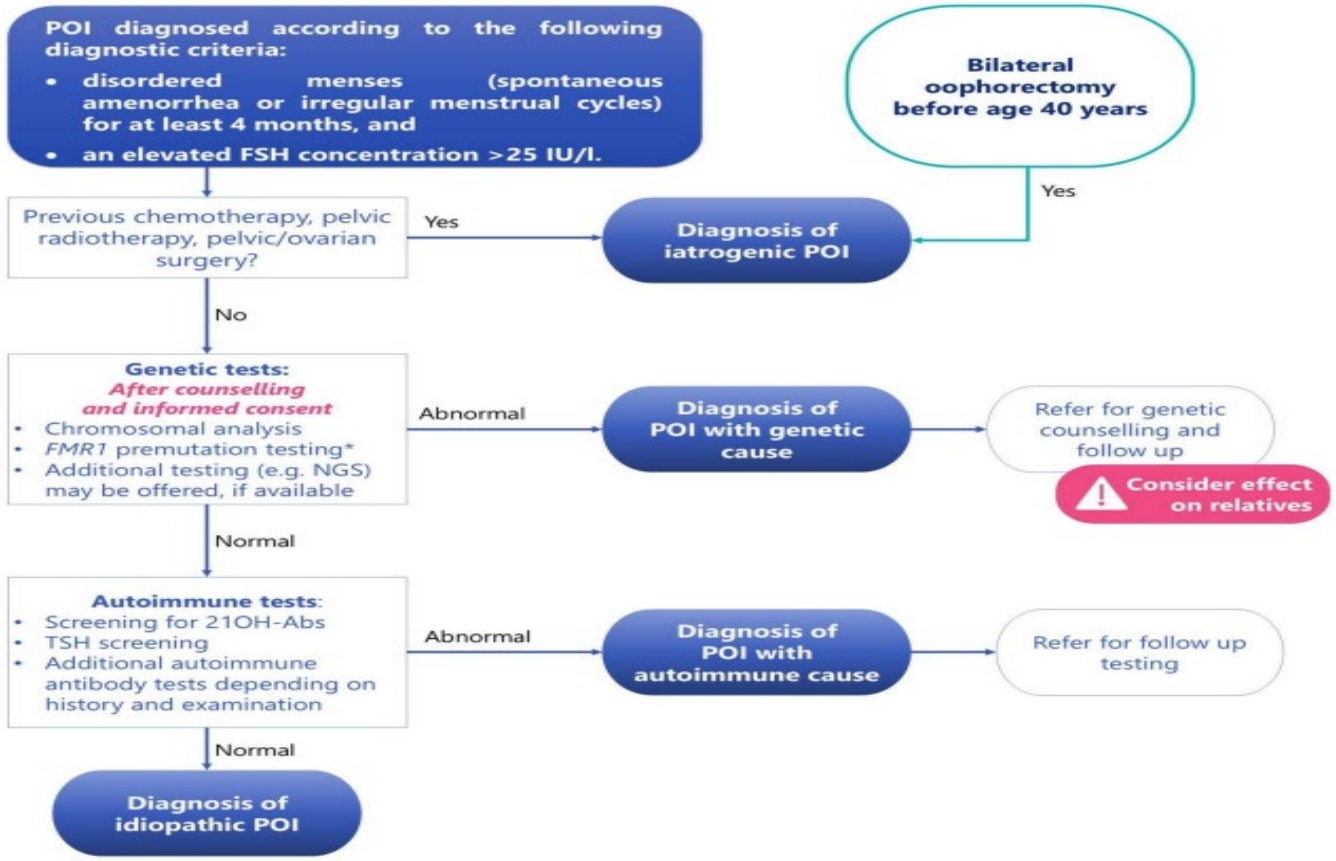


Figure 2. Summary of the recommendations on diagnosis of premature ovarian insufficiency (POI), as well as the recommended further testing to establish a cause for POI. *Fragile X premutation testing is indicated in all women diagnosed with POI. This needs to be performed as a specific test as multigene panels and NGS are not useful in detecting FMR1 premutation. 21OH-Abs, 21-hydroxylase autoantibodies; BSO, bilateral salpingo-oophorectomy; NGS, next-generation sequencing; TSH, thyroid-stimulating hormone.

Evidence-based guideline: Premature Ovarian Insufficiency, Human Reproduction Open, 2024, 2024(4) 1-14

Primary Work Up

- **Diagnosis**
  - Gonadotropins and estradiol – On more than one occasion at least 4 weeks apart
  - **AMH tends to be very low (except in autoimmune causes) but lacks diagnostic specificity**
  - BhCG, TSH, and prolactin
  - Pelvic ultrasound
- **Etiology**
  - **Karyotype (regardless of age)**
  - Fragile X Premutation Testing
    - 1-5% of women with isolated POI/14% of women with familial POI
  - Adrenal Antibodies
    - 21 Hydroxylase, positive 3-5% of the time
    - Positivity warrants additional testing given risk of adrenal insufficiency (2-3% of women with POI will develop autoimmune insuff)
    - **Antiovarian antibodies are not reliable and should not be measured**
  - Additional testing individualized
    - CAH due to rare enzyme deficiency
    - Autoimmune polyendocrine syndrome (APS-1)

Symptoms and Associated Health Risks

- **Symptoms**
  - Vasomotor symptoms
  - Urogenital atrophy symptoms
  - Infertility
    - 5-10% lifetime probability of pregnancy
  - Dysfunctional uterine bleeding
- **Health Risks**
  - Thyroid disease – Up to 20%; Hashimoto Thyroiditis
  - Low bone mass/osteoporosis – up to 3 fold higher risk
    - Risk of hip fracture 1.5-3 fold higher
  - Cardiovascular disease risk
  - Reduced life expectancy without HRT due to cardiovascular disease

ACOG Committee Opinion 698, "Hormone Therapy in Primary Ovarian Insufficiency" Obstet Gynecol 2017;129:e134–41

POI and Multimorbidity

The association between primary ovarian insufficiency and increased multimorbidity in a large prospective cohort (Canadian Longitudinal Study on Aging)

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POI and Multimorbidity

- The Canadian Longitudinal Study on Aging (CLSA) collected cross-sectional data from 50,000 community-dwelling Canadians aged 45–85 years between 2010 and 2015.
  - Baseline data from the comprehensive and tracking cohorts of the CLSA were used
    - Self-reported menopausal status was the primary exposure, with menopause defined as cessation of menstrual periods for at least 1 year without restarting. Menopausal status was described retrospectively at time of baseline data collection.
- Primary exposure was POI (defined by onset of menopause at the age of<40 years)
  - Comparators included average age of menopause (age, 46–55 years), early menopause (40–45 years)
- The primary outcome was multimorbidity, which was defined as two or more chronic conditions
  - Secondary outcomes were severe multimorbidity (defined as 3 or more chronic conditions)
- Of 12,339 postmenopausal participants
  - **3.0% experienced POI (mean age 34.8)**
  - **11.3% experienced early menopause**
  - **Avg age of menopause in referent group was 51**

Kirubarajan A et al, Fertil Steril 2025;123:289-299

POI and Multimorbidity

- Prevalence of multimorbidity was 64.8% among those with POI and severe multimorbidity was reported by 39.2%
    - OR for multimorbidity in POI compared to avg age of menopause was 2.5 (95% CI, 2.0–3.1) → AOR 2.0 (95% CI, 1.5–2.5) and AOR for severe multimorbidity was 1.9 (95% CI 1.5-2.5)
    - There were significantly increased risks of ischemic heart disease (AOR, 2.8; 95% CI, 1.7–4.7; 5.9% vs 1.8%) and osteoporosis (aOR, 1.6; 95% CI, 1.2–2.1) in the POI group
- 53.5% of individuals with POI had ever been on HRT
  – Mean duration of use was 7.1 years
  – 80% of ever users had discontinued HRT before study initiation

Hormonal Management Risks and Benefits

Women's Health Initiative (WHI)

- Large, NIH-sponsored, randomized, multicenter study of conjugated equine estrogen (CEE) and combination CEE plus medroxyprogesterone acetate (MPA)[1]
- Purpose: Assess long-term risks and benefits of CEE and combination CEE/MPA in chronic disease prevention[1]
- Randomized 27,000 women aged 50 to 79 years (mean age, ~63 years) between 1993 and 1998; originally scheduled to conclude in 2005[1]
- Stopped CEE/MPA arm early after 5.2 of planned 8.5 years[2]

[1]The Women's Health Initiative Study Group. *Control Clin Trials.* 1998;19:61-109.
[2]Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-33.

WHI: CEE/MPA Arm of Clinical Trial

- Regimens: CEE 0.625 mg/d + MPA 2.5 mg/d (n = 8506) or placebo (n = 8102)
- Primary outcome: coronary heart disease (CHD) events (nonfatal myocardial infarction [MI] and CHD death)
- Primary adverse outcome: invasive breast cancer
- Global index: a summary measure of the effects of CEE/MPA on major disease outcomes recorded during the trial
  - Menopausal symptoms, quality of life, and cognitive function not included

WHI: Data and Safety Monitoring Board Recommendations on 5/31/02

Terminate CEE/MPA study

- Excess of breast cancer
  - Crossed pre-specified monitoring boundary
- Global index: trend towards greater risk than benefits

WHI Results

Absolute and Relative Risk or Benefit of CEE/MPA

Health Event	Overall Hazard Ratio	Confidence Interval		Increased Absolute Risk per 10,000 Women/Year	Increased Absolute Benefit per 10,000 Women/Year
		Nominal 95%	Adjusted 95%		
CHD	1.29	1.02–1.63	0.85–1.97	7	
Strokes	1.41	1.07–1.85	0.86–2.31	8	
Breast cancer	1.26	1.00–1.59	0.83–1.92	8	
VTED	2.11	1.58–2.82	1.26–3.55	18	
Colorectal cancer	0.63	0.43–0.92	0.32–1.24		6
Hip fractures	0.66	0.45–0.98	0.33–1.33		5
Total fractures	0.76	0.69–0.85	0.63–0.92		44

CHD = coronary heart disease; VTED = venous thromboembolic disease.

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

Hormone Replacement – Ways to Give

- How long?
  - Until average age of menopause 50-51 years
- What dose and delivery system?
  - HRT vs OCPs
  - Oral vs transdermal
  - Continuous vs sequential

HRT

Benefits

- Potentially more physiologic dosing can be achieved
  - 100 ug of transdermal estradiol; 2 mg oral estradiol; 1.25 mg CEE
  - 0.045 mg / 0.015 mg (E/LNG)
  - 0.05/.14 mg or 0.05/.25 mg (E/NA)
- Multiple delivery routes
- Continuous or sequential
  - 5 mg of provera continuous
  - 10 mg of provera sequential
  - 100 mg Prometrium continuous
  - 200 mg prometrium sequential
- LNG IUD can be used for contraception but is not FDA approved for endometrial protection in HRT regimen

Risks

- General risks of any exogenous hormone therapy
  - Transdermal HRT may be associated with fewer VTE events
- No head to head trials of safety and efficacy of HRT compared to OCPs in this population; no studies demonstrating optimal dosing
- Breast Cancer
  - Limited epidemiologic data in POI
  - Short term HRT use in BRCA 1 and 2 carriers post RRBSO not associated with increased risk
  - Does POI reduce the risk of incident Breast Ca?
  - Does long-term HRT or COC use impact risk in this group?
  - No strong evidence supporting an association between HRT and increased risk of breast cancer in POI before the usual age of menopause compared to comparable age women without POI

Combination OCPs

Benefits

- Ethinyl Estradiol
  - 20-35 mcg/d
    - 5-10 mcg is comparable in effect with estrogen doses in common HRT preparations
- Better suppression of gonadotropins than HRT
  - Contraception
  - 5-10% lifetime odds of pregnancy
- Potentially less stigma
- Multiple delivery routes

Risks

- General risks of OCPs
  - VTE
  - Cardiovascular risk
- Individualized for patient history
- Limited data suggests HRT may be more favorable for bone health

Pitfalls and Troubleshooting

- Vaginal Bleeding
  - Concerns
    - Endometrial polyp or fibroid
    - Endometrial pathology (hyperplasia or cancer)
  - Ultrasound assessment
  - Management options
    - Modify delivery method
    - Modify progestin dose

Pitfalls and Troubleshooting

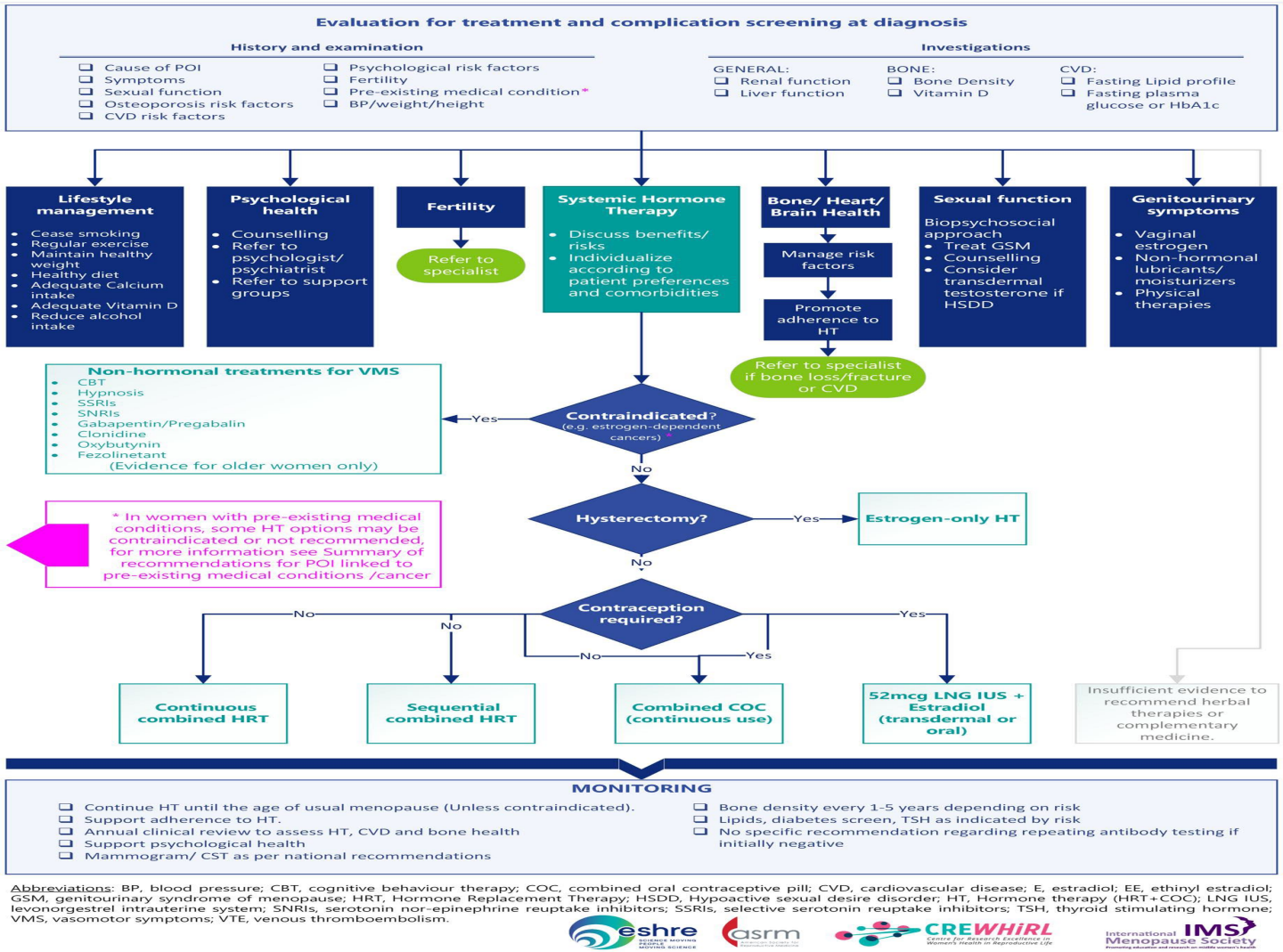
- Persistent Symptoms
  - Check for patch adherence with transdermal preparations
  - Depending on dose of estrogen there may be room to increase
  - Limited value in measuring serum estradiol in general or with persistent symptoms
    - OCPs and Conjugated Equine Estrogens
  - Consider non-hormonal approaches
    - SSRIs/SNRIs
    - NK3 receptor antagonists
  - Smoking cessation

Osteoporosis Screening and Prevention

- Baseline Dexa Scan at Diagnosis
  - Many patients have been hypoestrogenic for prolonged durations by the time they seek evaluation
- How often to repeat?
  - No formal guidelines or consensus for POI women
  - If normal and on HRT limited value in repeating sooner than 5 years
  - HT is first line and preferable compared to bisphosphonates in women who may spontaneously conceive or use donor egg IVF

ACOG Committee Opinion 698, "Hormone Therapy in Primary Ovarian Insufficiency" Obstet Gynecol 2017;129:e134–41
Evidence-based guideline: Premature Ovarian Insufficiency, Human Reproduction Open, 2024, 2024(4) 1-14

Management algorithm for premature ovarian insufficiency (POI)



Abbreviations: BP, blood pressure; CBT, cognitive behaviour therapy; COC, combined oral contraceptive pill; CVD, cardiovascular disease; E, estradiol; EE, ethinyl estradiol; GSM, genitourinary syndrome of menopause; HRT, Hormone Replacement Therapy; HSDD, Hypoactive sexual desire disorder; HT, Hormone therapy (HRT+COC); LNG IUS, levonorgestrel intrauterine system; SNRIs, serotonin nor-epinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TSH, thyroid stimulating hormone; VMS, vasomotor symptoms; VTE, venous thromboembolism.

Conclusions

- Evaluation for oligomenorrhea and amenorrhea (with or without vasomotor symptoms) should include a comprehensive endocrinologic evaluation
- **Recent estimates suggest higher prevalence of POI**
- HRT for young women with POI is physiological replacement
  - Reduction in cardiovascular risk, osteoporosis risk, improvement in quality of life
  - Risks from WHI should not be extrapolated to this population
- Risk mitigation where possible
  - Cardiovascular risk reducation
  - Smoking cessation
- Bone health/fracture risk reduction
  - Balanced diet
  - Exercise
  - Medical management
- Genetic counseling where possible
  - Family pedigree and screening where possible

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THANK YOU