Centro Salute Donna
Azienda USL Ferrara

OSTETRICIA e GINECOLOGIA
2025

4 APRILE

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C.so della Giovecca, 47
Ferrara

Università degli Studi di Ferrara

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Endo-ERN

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Direttore: Prof. Maria Rosaria Ambrosio
U.O. di Endocrinologia e Malattie del Ricambio
Direttore: Prof. Maria Chiara Zatelli
Dipartimento di Scienze Mediche
Dipartimento di Eccellenza MUR 2023-2027

Insufficienza Ovarica Prematura: Cause, sintomi e trattamento

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Disclosure

- I have no conflicts of interest to disclose.

What does POI means?

Premature ovarian insufficiency (POI) is a condition defined by loss of ovarian activity **before the age of 40 years**.

Age of Menopause.

Cattaneo et al 2025

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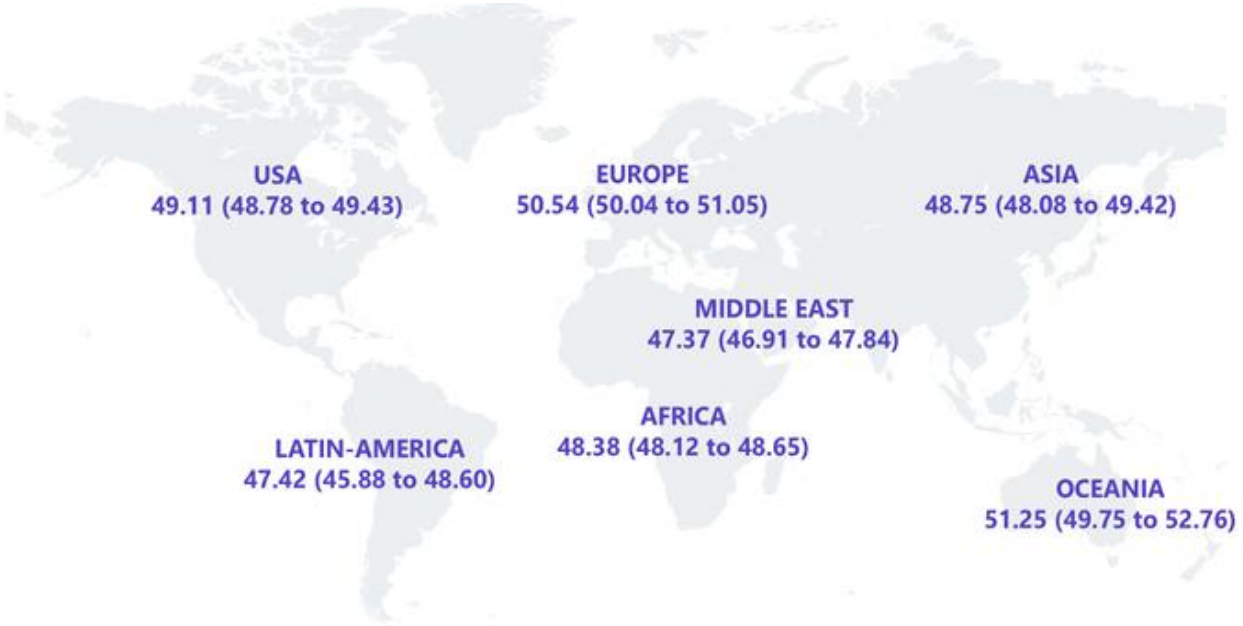
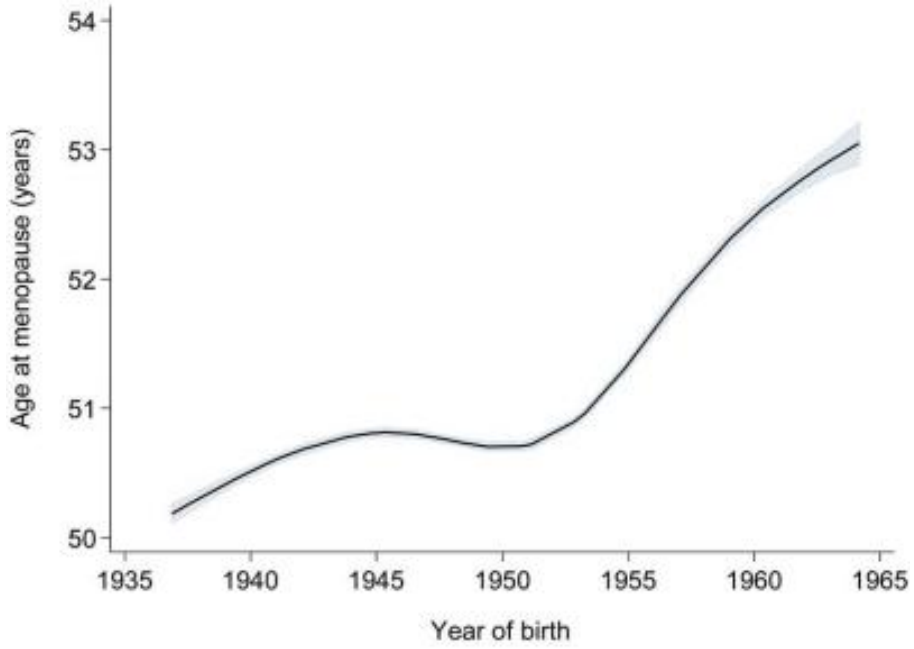
Menopause

The age limit of 40 is approximately **two SD below** the usual age of menopause (50 ± 4 years). Menopause occurring in the 40-44 age group is referred to as '**early menopause**'.



Schoenaker et al, 2014



Gottschalk MS, Hum Reprod. 2020

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Epidemiology and Prevalence

Previous studies indicate a prevalence of POI approximal of 1.0 %.

The global overall prevalence of POI among women was **3.5%,** with significant differences among ethnic groups.

This prevalence decreases in younger age groups:

- 1/1000 in women < 30 years old,
- 1/10000 in women < 20 years old.

Li et al, 2023; Golezar et al, 2019

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When Should It Be Suspected ?

POI is a clinical condition characterised by:

- **Amenorrhoea** or **oligomenorrhoea** for more than 4-6 months.
- Typical Symptoms of **Estrogen Deficiency**.
- **Infertility** *About 5-10% of women with POI can achieve a natural pregnancy due to sporadic episodes of ovarian activity.*

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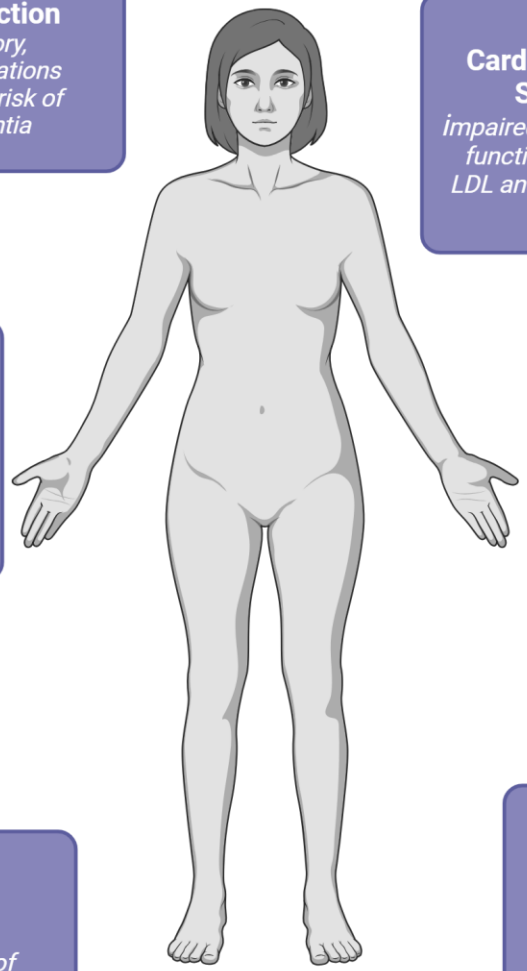
Clinical Presentation



Cognitive Dysfunction
memory, concentrations Increase risk of dementia

Cardiovascular System
impaired endothelium function, increase LDL and Triglycerids

Before the age of 25, reduced peak bone mass.

Bone
Osteopenia/ Osteoporosis/ fractures

Urogentinals Symptmos
vaginal dryness, vaginal irritation, itching and sexual disorders

Mortality
Increase risk of premature death

Vasomotor Symptmos
hot flushes and night sweats
Insomnia and Mood Disturbances

AUTOIMMUNE DISEASE ASSOCIATED
Autoimmune Thyroid Diseases *(30-40%)*
Addison's Disease, APS-1 *(4-10%)*
Type 1 Diabetes *(4-5%)*
Celiac Disease *(2-3%)*
Myasthenia Gravis, Systemic Lupus Erythematosus Rheumatoid Arthritis.

Podfigurna-Stopa A et al. Premature ovarian insufficiency: the context of long-term effects. J Endocrinol Invest. 2016 Betterle C, 2005; Hsieh Y-T, 2021; Coulam, 1983, Silva et al., 2014, Kirshenbaum and Orvieto, 2019, Grossmann et al., 2020 , Hsieh and Ho, 2021, Chaker et al., 2022.

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human reproduction ESHRE PAGES

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ESHRE Guideline: management of women with premature ovarian insufficiency†

Diagnosis of POI

The guideline group recommends the following 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.

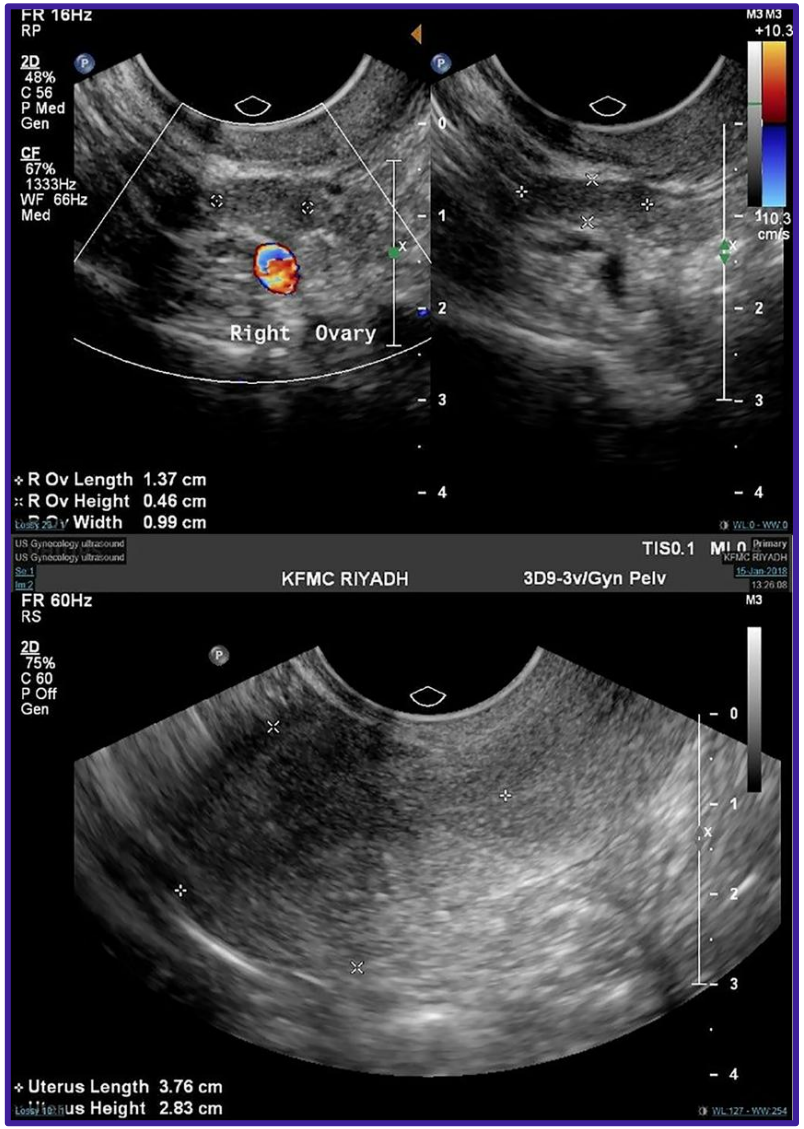
FSH assessment should be repeated after 4-6 weeks if there is diagnosti uncertainty. FSH testing for the diagnosis of POI does not have to be timed to a specific day of the menstrual cycle.

- ✓ Pregnancy should be excluded in women presenting with amenorrhea.
- ✓ Use of hormonal therapy (including oral, injectable, or long-acting contraceptives) potentially lower FSH concentrations; may need to be ceased before a diagnosis of POI can be confirmed.
- ✓ Women who had Bilateral Salpingo-Oophorectomy before age 40 have a diagnosis of POI and additional diagnostic testing is unnecessary.

US and Antral Follicule Count

Ultrasound with AFC in POI generally shows compact, reduced-size ovaries. In up to 50% cases, gonadal dysgenesis can be observed, with "streak ovaries".

In autoimmune forms the ovaries can be of normal size or enlarged, and follicles may have a cystic appearance.



Bannatyne et al., 1990, Welt et al., 2005, Nelson, 2009

AMH and POI

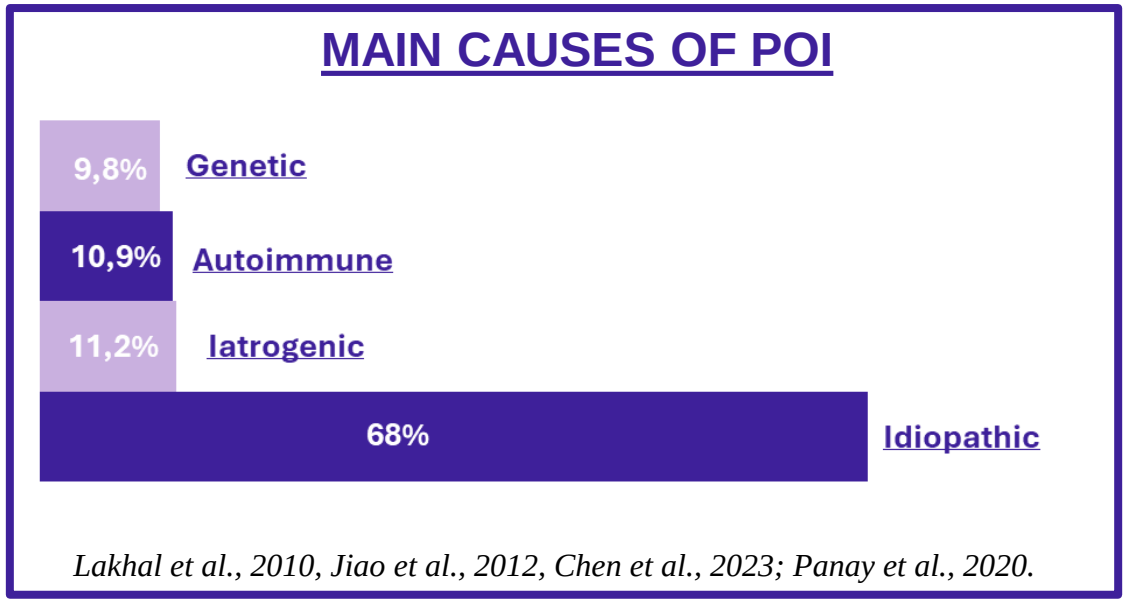
- AMH is predominat producted by **small antral follicles**.
- Useful marker for **ovarian response** to stimulation in IVF.
- **Significant reduced** in women with POI vs PCOS (high AMH) and hypothalamic amenorrhea (normal/mildly reduced AMH).
- The largest such study, including 410 women with clinical presentations including early and established POI, found that a diagnostic threshold of less than **0.25 ng/mL** (1.78 pmol/L) gave an optimum combination for the diagnosis of POI.

Anderson et al , 2017

The causes of POI

POI is a complex, multifactorial condition and its etiology remains poorly understood in many cases (**39-68% idiopathic**).

A combination of different factors such as genetics, recreational drug use, autoimmune diseases, pelvic surgery, or chemical exposures, may ultimately precipitate the disorder.



Lakhal et al., 2010, Jiao et al., 2012, Chen et al., 2023; Panay et al., 2020.

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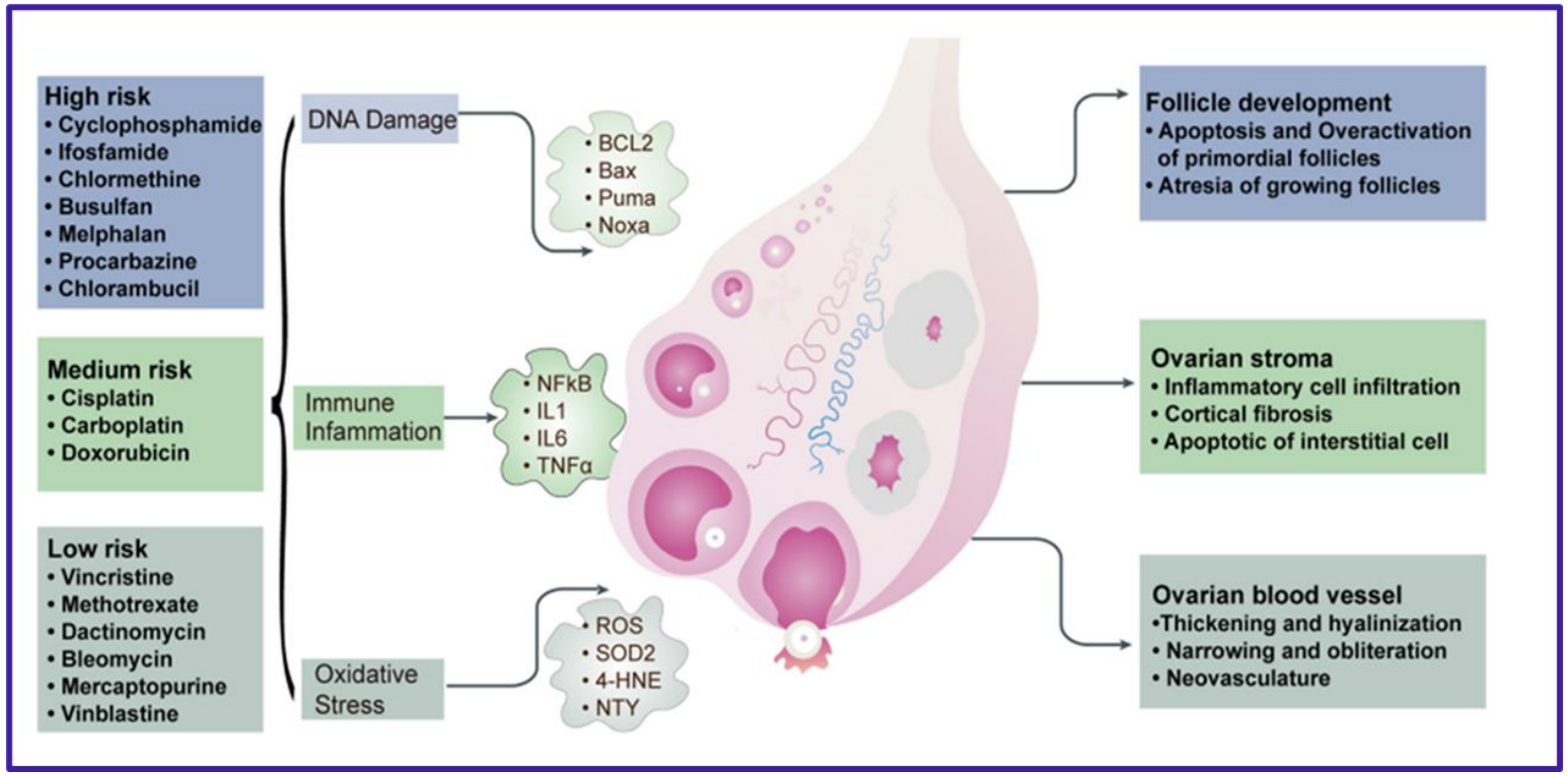
Iatrogenic

Chemotherapy;

Pelvic field **radiotherapy**;

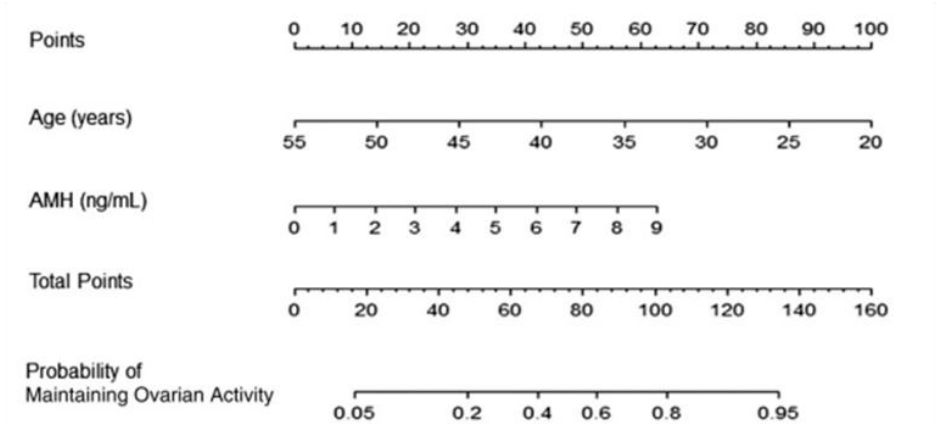
Linked to **ovarian pathology or pelvic surgery**, e.g. endometriosis surgery, ovarian torsion, or bilateral oophorectomy.



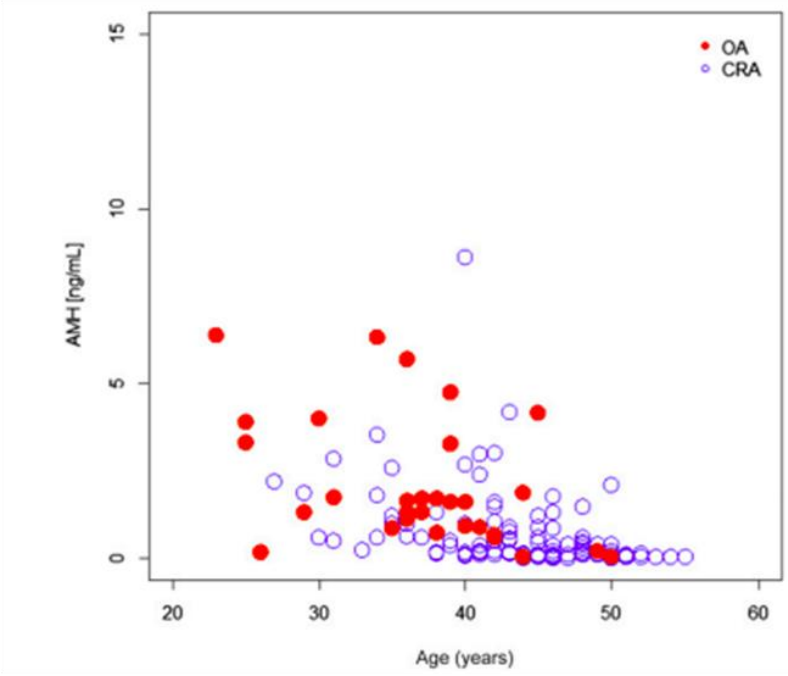
Xiong J et al,European Journal of Endocrinology.2021;184:R177

There are no consensus criteria for diagnosing menopause after cancer. The general diagnostic cannot be reliably used, as ovarian function may resume many years after treatment.
Hickey Met al Lancet 2024; 403: 984

Age and **AMH** levels are predective of POI.



Barnabei, Strigari, Marchetti et al



Although circulating AMH can indicate reduced ovarian reserve after chemotherapy, it does not reliably predict fertility, duration of reproductive life-span, or ovarian function.
Hickey Met al Lancet 2024; 403: 984

Menses resumption after cancer treatment–induced amenorrhea occurs early or not at all

Melanie H Jacobson [1], Ann C Mertens [2], Jessica B Spencer [3], Amita K Manatunga [4], Penelope P Howards [5]

A total of **1,043 women** diagnosed with their first cancer between the ages of 20 and 35, who were 22 to 45 years old at the time of the interview

- **Amenorrhea oc**
- **Risk factors fo**
  - **Chemotherapy**
  - **Older age at d** = 2.37, 95% confidence interval (CI): 1.3
  - **Nulliparity** (vs. ever pregnant: aOR = 1.50, 95% CI: 1.02–2.21)
- **Resumption of Menstruation**
  - Menstruation resumed in the majority (**70.0%**) of women.
  - 90.0% resumed menstruation within **two years** after treatment.
  - Women diagnosed at an **older age** were more likely to have longer delays in menstrual recovery and present irregular cycles when menstruation returned.

In women, an ovarian dose between 5 and 20 Gy is sufficient to cause permanent gonadal dysfunction, regardless of age.
At 30 Gy, 60% of women under 26 develop early menopause. *Karamitrou EK et al, Maturitas 2023*

Genetic causes of POI

Table 2. List of genetic defects associated with POI and their estimated frequencies

	Estimated frequency in POI	References
Sindromic Disease		
X chromosome defects		
Turner's syndrome and related defects	4–5%	(9, 55, 59, 60)
Triple X syndrome	1–4%	(62)
Fragile X syndrome (*FMR1* premutation)	3–15%	(119, 120, 122, 132)
DIAPH2 disruption (translocation)	Unknown	(18, 19)
BMP15 variants	1.5–12%	(143–149)
PGRMC1 variants	1.5%	(155)
Autosomal defects		
Complex diseases	Rare	
Galactosemia (*GALT*)		(94, 95, 98)
BPES (*FOXL2*)		(79, 88)
APECED (*AIRE*)		(65, 70, 71)
Mitochondrial diseases (*POLG*)		(102, 103)
Demirhan syndrome (*BMPR1B*)		(109)
PHP1a (*GNAS*)		(101)
Ovarioleucodystrophy (*EIF2B*)		(106)
Ataxia telangiectasia (*ATM*)		(108)
Perrault syndrome (*HSD17B4*, *HARS2*, *CLPP*, *LARS2*, *C10ORF2*)		[a]
Premature aging syndromes:		
Bloom syndrome (*BLM*)		(113, 114)
Werner syndrome (*WRN*)		(117)
GAPO disease (*ANTXR1*)		(118)
Isolated Disease		
Isolated disease		
FSH/LH resistance (*FSHR* and *LHCGR*)	0–1%	(42, 47, 134, 135)
INHA variants	0–11%	(138, 139)
GDF9 variants	1.4%	(32, 146, 150)
FOXL2 variants	Rare	(50, 92, 93)
FOXO3 variants	2.2%	(168, 169)
NOBOX variants	0–6%	(50, 175, 177–179, 182)
FIGLA variants	1–2%[b]	(183, 184)
NR5A1 variants	1.6%	(164, 165)
LHX8 variants	Rare	(50, 185, 186)
DNA replication/meiosis and DNA repair genes variants (*DMC1*, *MSH4*, *MSH5*, *SPO11*, *STAG3*, *SMC1β*, *REC8*, *POF1B*, *HFM1*, *MCM8*, *MCM9*, *SYCE1*, *PSMC3IP*, *NUP107*, *FANCA*, *FANCC*,*FANCG*)	Unknown	(35, 38–41, 45, 156–162)

Rossetti R et al, ClinGenet. 2017

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	⊕⊕◯◯

The evaluation of other candidate genes for POI can be performed using Next Generation Sequencing (NGS), increasingly recognized as the underlying cause of previously idiopathic forms of POI.

Identifying the genetic defect responsible for POI enables the prediction of POI risk in young female relatives, allowing them to plan pregnancy or oocyte cryopreservation.

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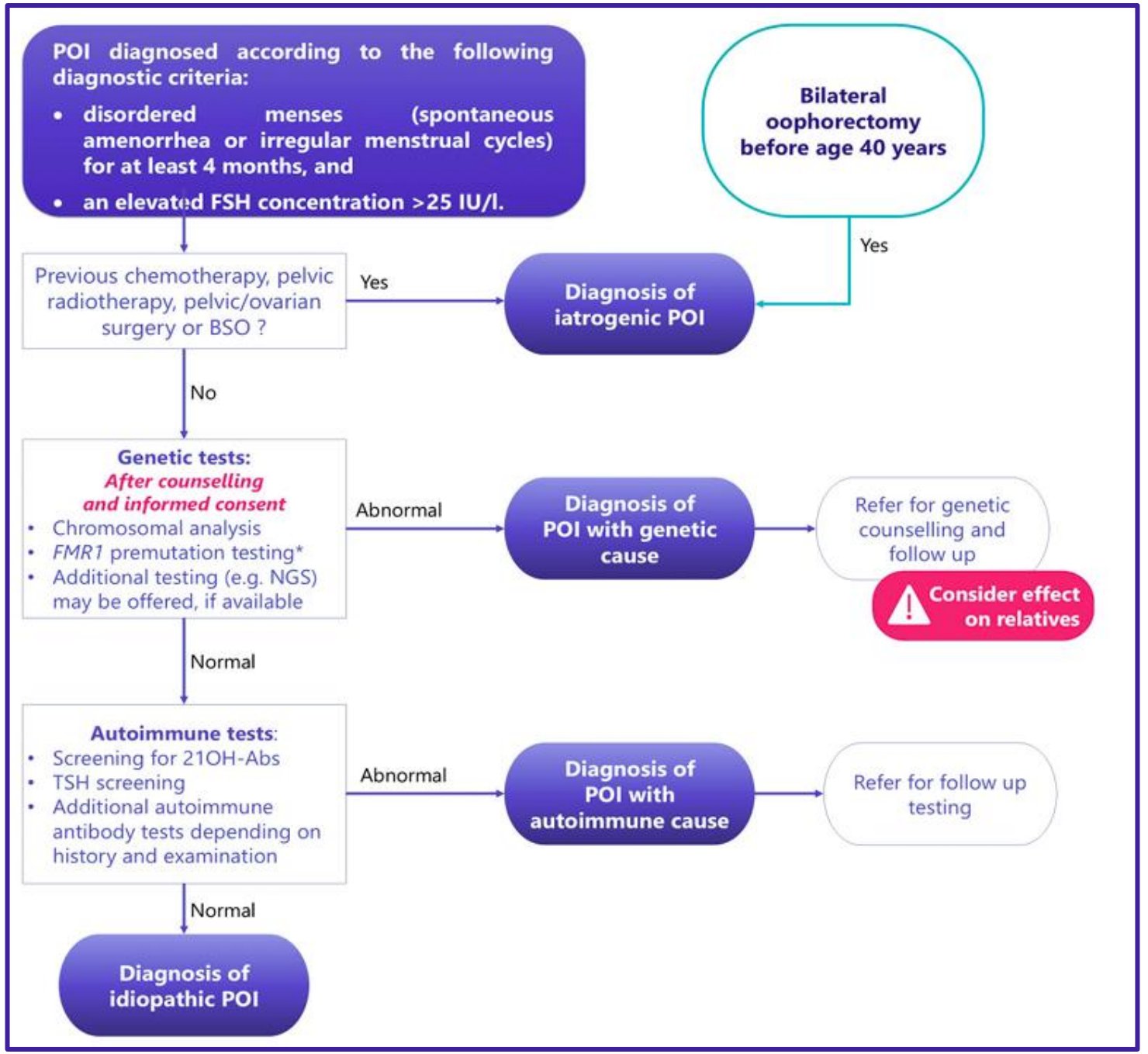
Autoimmune causes of POI

Autoimmune attacks can affect the ovaries leading to disruptions in both endocrine function and reproduction.

Clinically women present **higher** serum **inhibin B** and **AMH** levels compared to women with other causes of POI, reflecting the presence of functional intact granulosa cells.

Several years of **fluctuating ovarian function** may precede complete ovarian failure.

- Diagnostic biopsies of the ovaries are not recommended as a routine investigation.
- Autoantibodies against ovarian antigens, including **anti-ovarian autoantibodies** (AOA), **21-OH-Abs** and **steroid-cell autoantibodies** (SCA).
- Women with POI and positive 21OH-Abs should be referred to an endocrinologist for testing of **adrenal function.**
- Basal determination of morning **cortisol** and **ACTH** hormone levels. Additionally, an ACTH stimulation test should be considered if adrenal insufficiency is suspected.
- Thyroid function should be assessed by measuring **TSH** and **TPO-ab** at POI diagnosis.
- If 21OH-Abs are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of **adrenal insufficiency** develop.



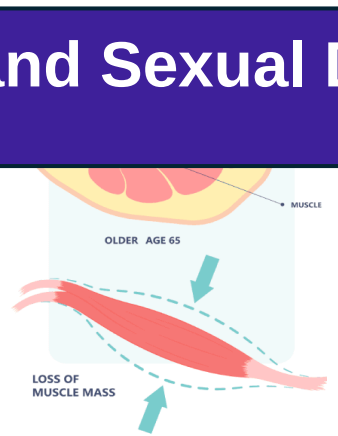
POI

Coronary disease HR : 1.85 (CI 1.48-2.1)
Stroke HR: 1.93 (CI 1.48-2.52)
Heart failure HR: 1.39 (CI 1.31-1.47)

Obesity (altered body mass distribution)
Insulin Resistance
T2 DM RR 1.32 (CI 1.08-1.62)
Dyslipidemia (↑ TG and LDL, ↓ HDL) RR 1.21 (CI 1.05-1.39)

Physical, Psychological, Social, and Sexual Distress.

Osteoporosis RR 2.54

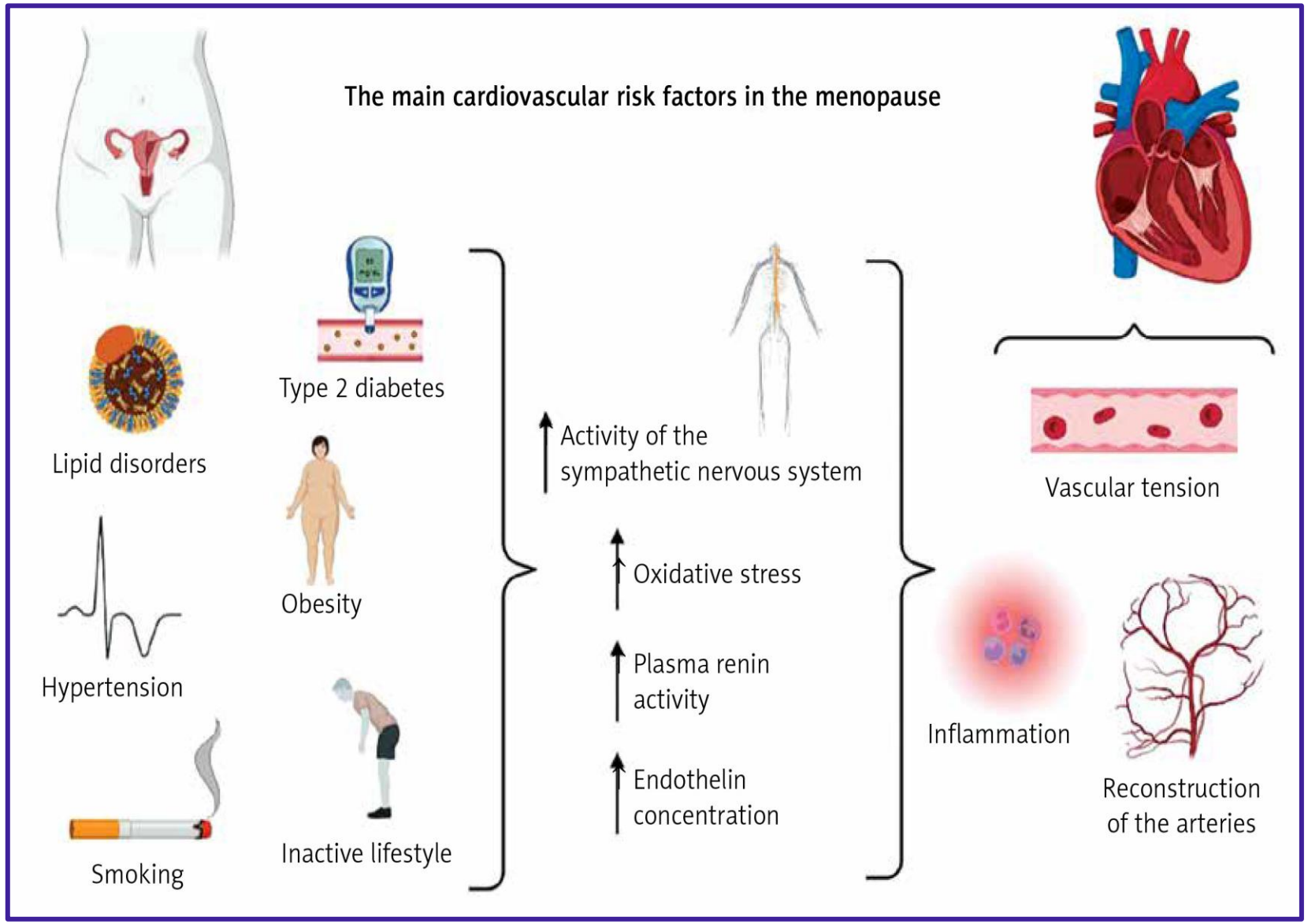


↓ Muscle Mass, Strength and Performance

Anxiety OR 4.89 (CI 3.28-7.30)
Depression OR 3.33 (CI 2.31-4.81)

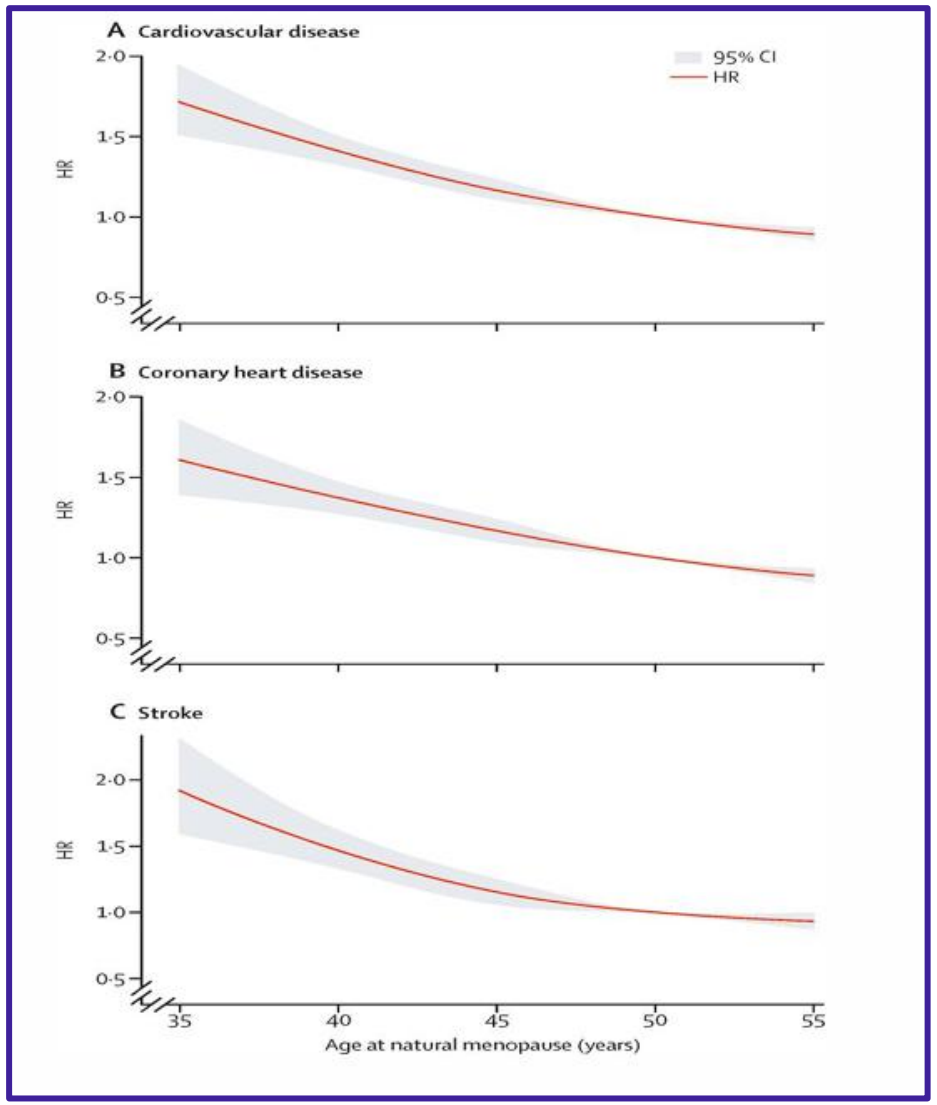
Cognitive Dysfunction
Alzheimer's Disease
Dementia OR 1.47

Zhang W et al, Am J Reprod Immunol 2023; Karamitrou EK et al, Maturitas 2023; Sochocka M et al, Int J Mol Sci 2023; Xi D et al, Arch Womens Ment Health 2023; Moukhah S et al, J Reprod Infertil 2023; Hammond J e Marczak M, Psychol Health 2023; Bermingham KM et al, EBioMedicine 2022; Leite G et al, Menopause 2022.

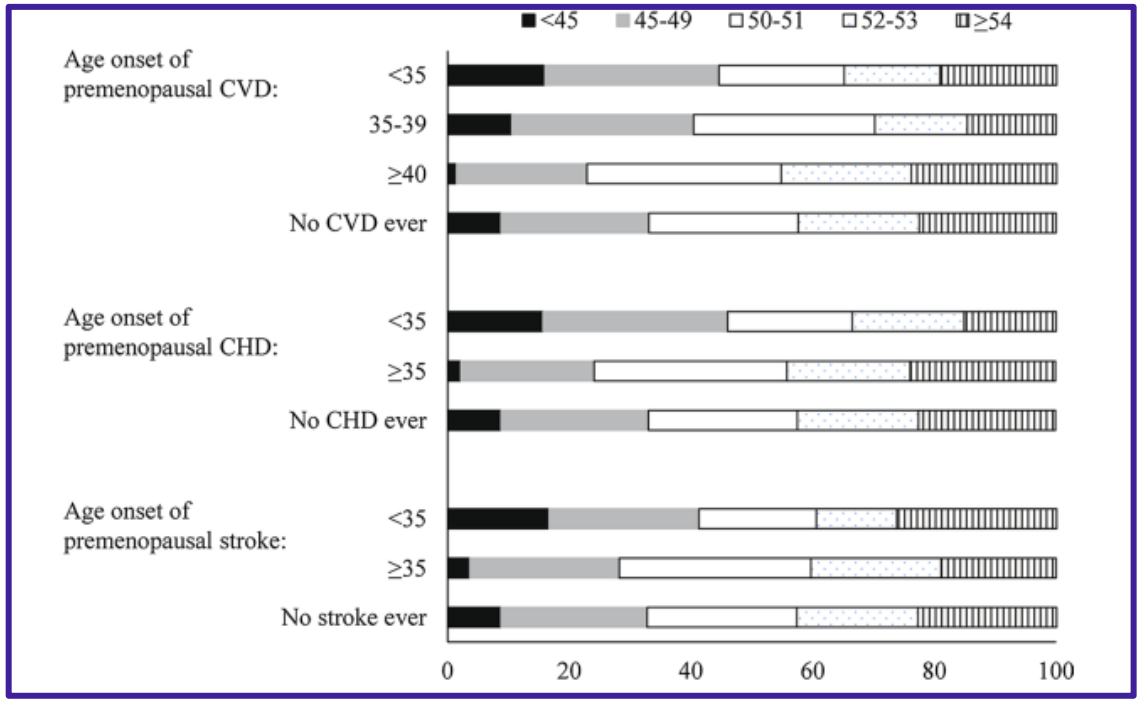


Ryczkowa et al, 2023

Cardiovascular Diseases and POI



The Lancet, 2019



Zhu et al, 2019

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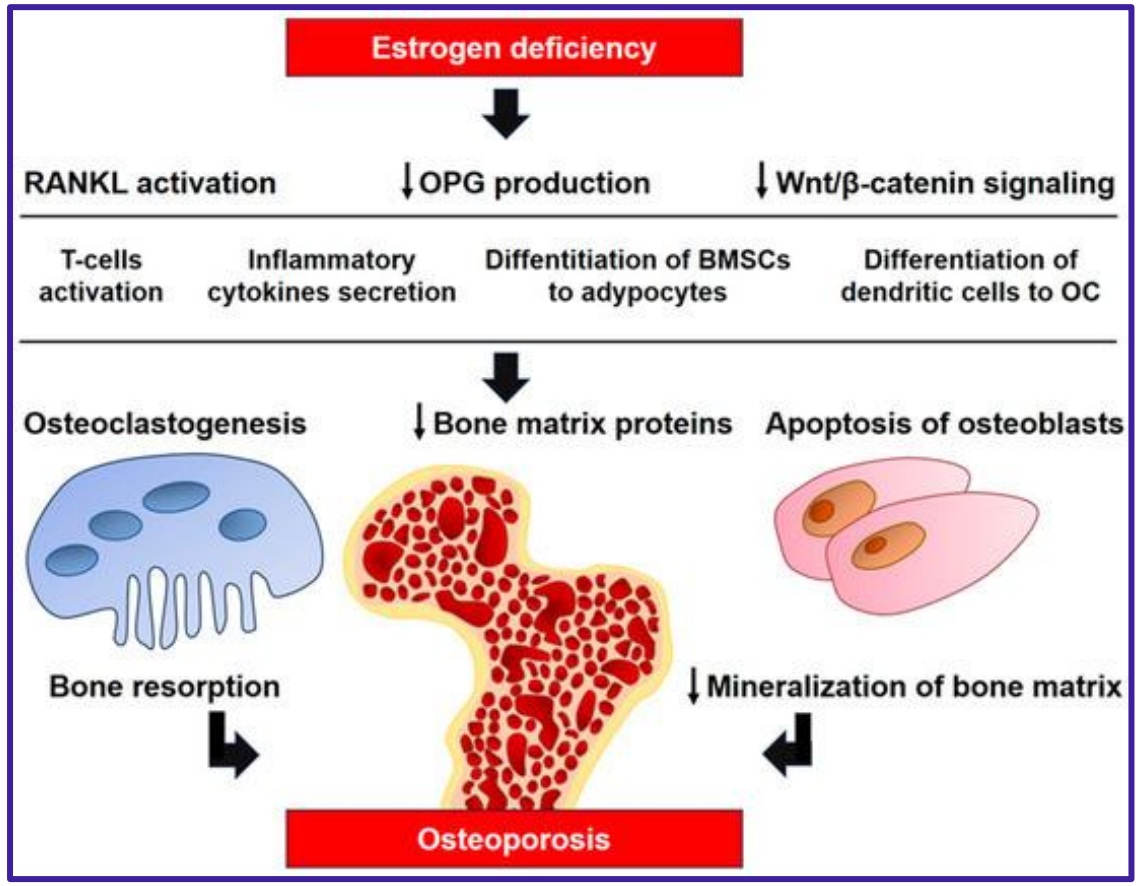
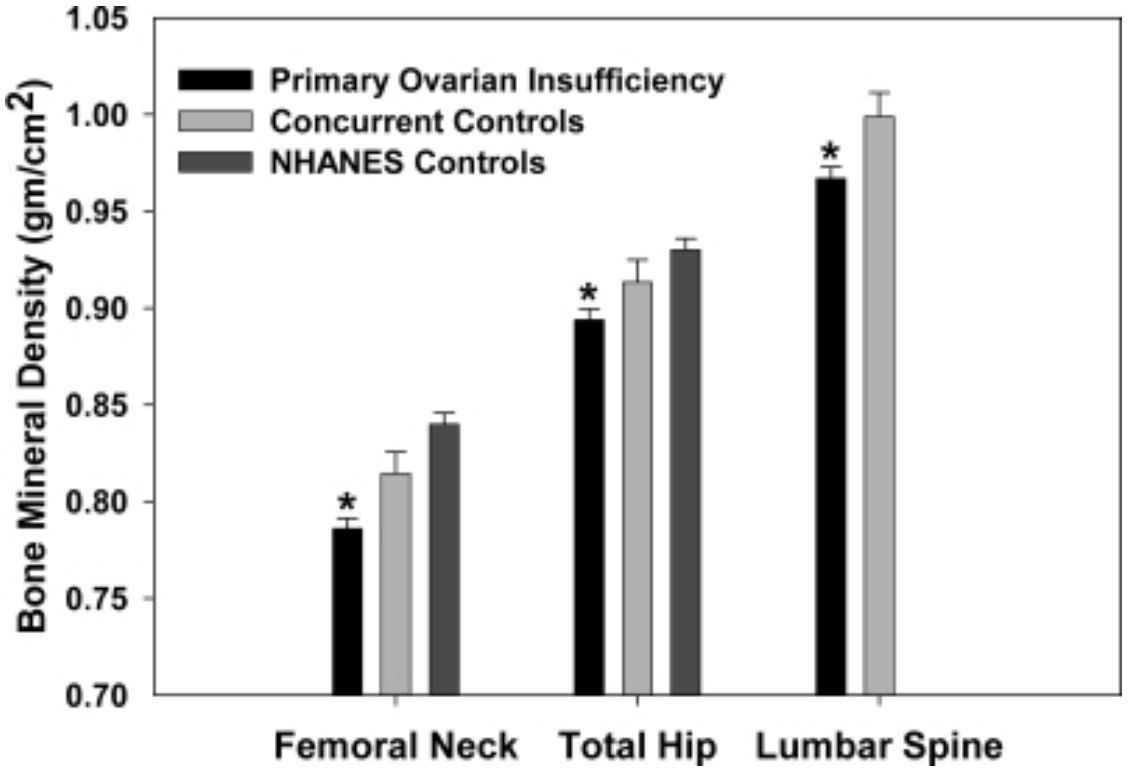
Bone Health and POI



Kirk et al. Compston JE. Clin Endo



Vaishali B et al Bone Mineral Density in Estrogen-Deficient Young Women. J Clin Endocrinol Metab, 2009

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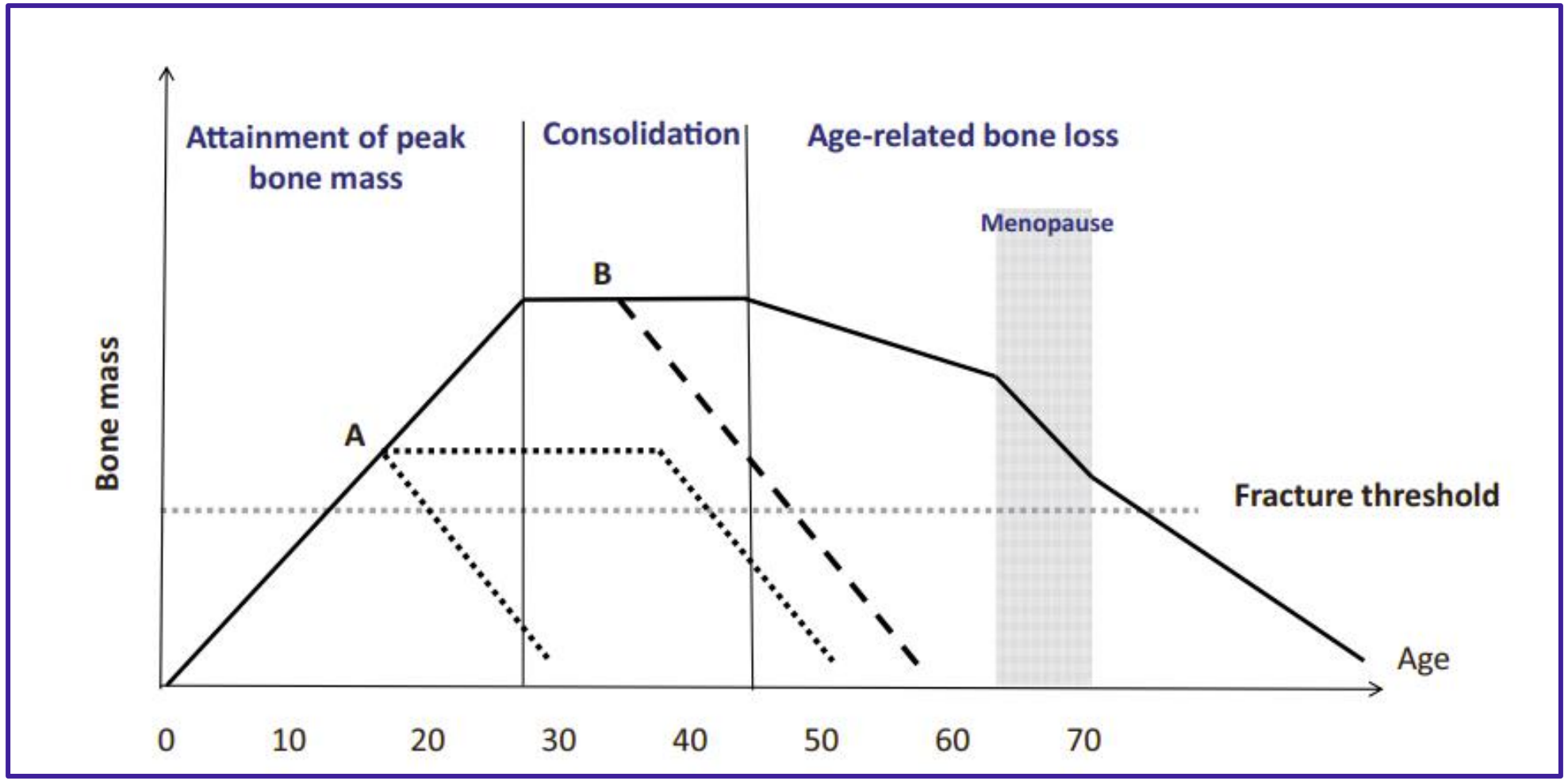
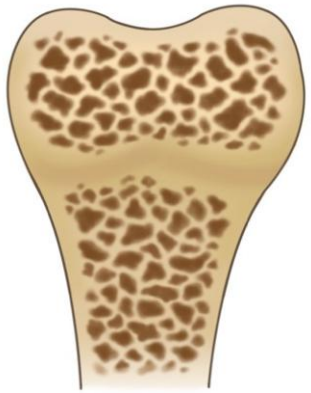


Compston JE. Clin Endo, 1990:33(5):653-82



EVALUTION OF BONE HEALTH IN WOMEN WITH POI

RF for low BMD in POI

- Primary Ame
- Longer durati
- >1yr delay in
- Chilhood can
  with hypogon

General RF for low BMD

Disease associated th low BMD

hyroidism
arathyroidism
nd DM
Disease
e Myeloma

nosis)

Calculation Tool

FRAX® Fracture Risk Assessment Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Italy Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 year
   Age: 38 Date of Bi Y:
2. Sex
3. Weight (kg)
4. Height (cm)
5. Previous Fracture
6. Parent Fractured Hip
7. Current Smoking — Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Second …rosis — No / Yes
11. A… /day — No / Yes

-3.0

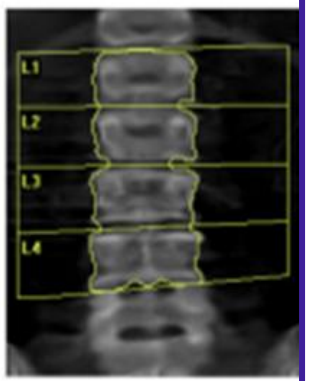
Clear Calculate

…cture (%)

Major … 8.5

Hip Fracture 6.3

If you have a TBS value, click here: Adjust with TBS



BS	TBS T-score	TBS Z-score	BMD
207	---	---	0.587
404	---	---	0.572
081	---	---	0.589
051	---	---	0.615
186	-3.0	-2.1	0.591

DXA

TBS

T-score or Z-score?

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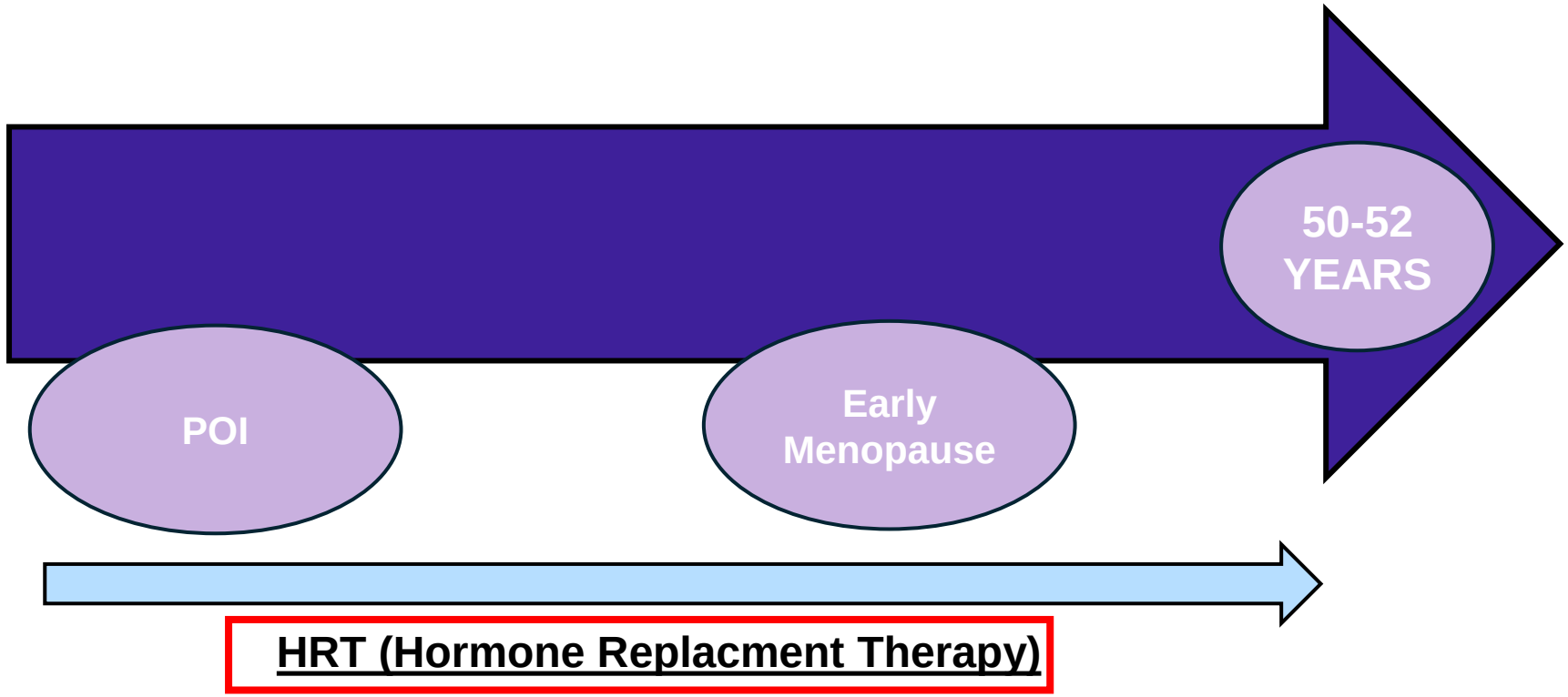
Management of POI



HRT (Hormone Replacment Therapy)

Healthy lifestyle, regular physical activity, no smoking and alcohol abuse.

Psychological Health

Fertility

Sexual Function

Management of Complications

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There are no consensus on the optimal HRT dosage.

HRT should be administered at **physiological hormonal doses** *(monitoring E2 levels during treatment is not recommended).*

Progesterone in women with a uterus to prevent endometrial hyperplasia and minimize irregular bleeding.

A **sequential regimen** is preferable when a woman is planning pregnancy or considering fertility treatment with oocyte donation.

In combination with estrogen therapy, **IUD** can be used when **contraception is needed** or in cases of **irregular vaginal bleeding**.

Higher estrogen doses, the progestin dosage may need to be adjusted based on clinical response.

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**

The **transdermal** administration is preferred, avoiding the first-pass metabolism in the liver, reducing the risk of thromboembolic events and ensuring more stable hormone levels. Formulations containing **synthetic estrogens** should be avoided whenever possible.

COC may be considered when a patient has residual ovarian reserve and desires contraception, data suggests a less favorable impact on **bone health and cardiovascular function.**

Micronized natural progesterone is preferred over synthetic progestins because it has a safer cardiovascular profile, a lower risk of thromboembolic events.

Women discontinuing treatment should be advised on the possible risk of relapse of menopausal symptoms and the **increased risk of bone loss**.

Parametro	HRT per os	HRT transdermica
D-dimero	↑	⟺
Prot S coagul	↓	⟺
Prot C coagul	↓	⟺
AT III	↓	⟺
APC ratio	↓	⟺
Fattore VII	↑	⟺
Produzione trombina	↑	⟺

Physiological actions of Estrogens

↑HDL cholesterol and Apolipoprotein A1
↓ total cholesterol, triglycerides (TG), and LDL cholesterol
↑ NOS
↓ endothelin-1
Regulate blood pressure (SBP), platelet function.

Liver-Mediated Actions of Estrogens

↑ HDL cholesterol, VLDL, TG
Increased angiotensinogen
Changes in coagulation and fibrinolytic factors
Stronger effect (EtE)
Weaker effect with CEE
No effect with transdermal E2

Women with a Factor V Leiden or Factor II mutation have a significantly increased risk of VTE (OR 3.4 and 4.8, respectively). This risk quadruples with oral HRT but remains unchanged with transdermal E2 combined with natural progesterone.

Rott H, Int J General Med 2014, mod; Eisenberger A e Westhoff C, J Steroid Biochem Mol Biol 2014; L'Hermite, Climacteric 2013

TIMELY START OF HRT

(amenorrhea is not a prerequisite for starting treatment)

Hypertension, migraine with aura, and obesity **are NOT contraindications to HRT**

Thrombosis risk screening should be performed only in patients with a **personal or family history of thromboembolic disease**.

A personal history of **breast cancer is a contraindication** to HRT.

Long-term estrogen-progestin therapy in POI **does not appear to increase breast cancer risk** beyond that of the age-matched general population.

Women with a history of thrombosis or thrombophilic disorders should be evaluated by a **hematologist before initiating HRT.**

Hormone-dependent tumors (e.g., *meningioma or ER+/PR+ gastric cancer, craniopharyngioma*), HRT may be **potentially harmful**

An **increased thrombotic risk is not an absolute contraindication** to estrogen therapy but requires careful monitoring.

Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Susan R. Davis, MBBS, PhD[1,A], Rodney Baber, B.Pharm, MBBS, FRANZCOG[2,A,B], Nicholas Panay, BSc, FRCOG, MFSRH[3,A], Johannes Bitzer, MD[4,C], Sonia Cerdas Perez, MD[5,D], Rakibul M. Islam, MPH, PhD[1,A], Andrew M. Kaunitz, MD[6,E], Sheryl A. Kingsberg, PhD[7,F], Irene Lambrinoudaki, MD, PhD[8,G], James Liu, MD[9,E], Sharon J. Parish, MD[10,H], JoAnn Pinkerton, MD[11,F], Janice Rymer, MBBS[12,I], James A. Simon, MD[13,H], Linda Vignozzi, MD[14,C] and Margaret E. Wierman, MD[15,J]

ow-up on treatment: after 2-3 months

ıce, symptom relief, possible side ge adjustments), then **annually**.

Discontinuation of HRT for ≥1 year leads to significant bone mass loss.

HRT should continue at least until the average age of menopause (51-52 years).

Gradual dose reduction is preferred to avoid sudden symptom recurrence.

Meczekalski B et al, J Clin Med 2023; Chen M et al, Medicine (Baltimore) 2023; Gonçalves CR et al, Reprod Biomed Online 2022; Armeni E et al, Best Pract Res Clin Endocrinol Metab, 2021; Rahman R e Panay N, Best Pract Res Clin Endocrinol Metab, 2021; Upton CE et al, Climacteric 2021; Karska P et al, Ginekol Pol 2021

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BONE PROTECTION AND IMPROVMENT

Healthy Lifestyles

- Stop Smoking,
- Physical Exercise,
- Weight control,
- >1yr delay in diagnosis,
- Intake of Vitamine D (800-1200 UI/die) and calcium (1 g/die).

Hormone Replecement Therapy (HRT)

Bisphosphonates may be necessary if HRT is contraindicated or if BMD does not improve despite optimal hormonal therapy.

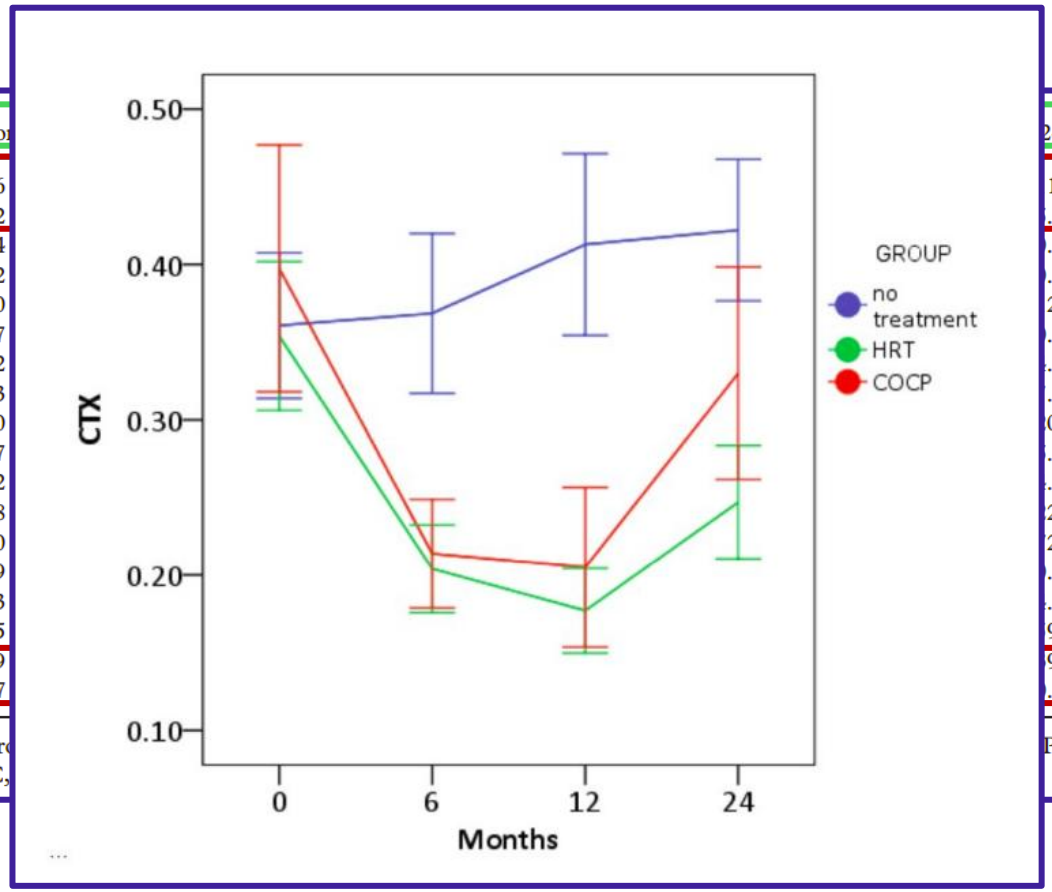
If a baseline DXA is performed, BMD is within the normal range and women are receiving adequate estrogen replacement, it is unclear when BMD measurement should be rechecked.
DXA→ Every 2 years.

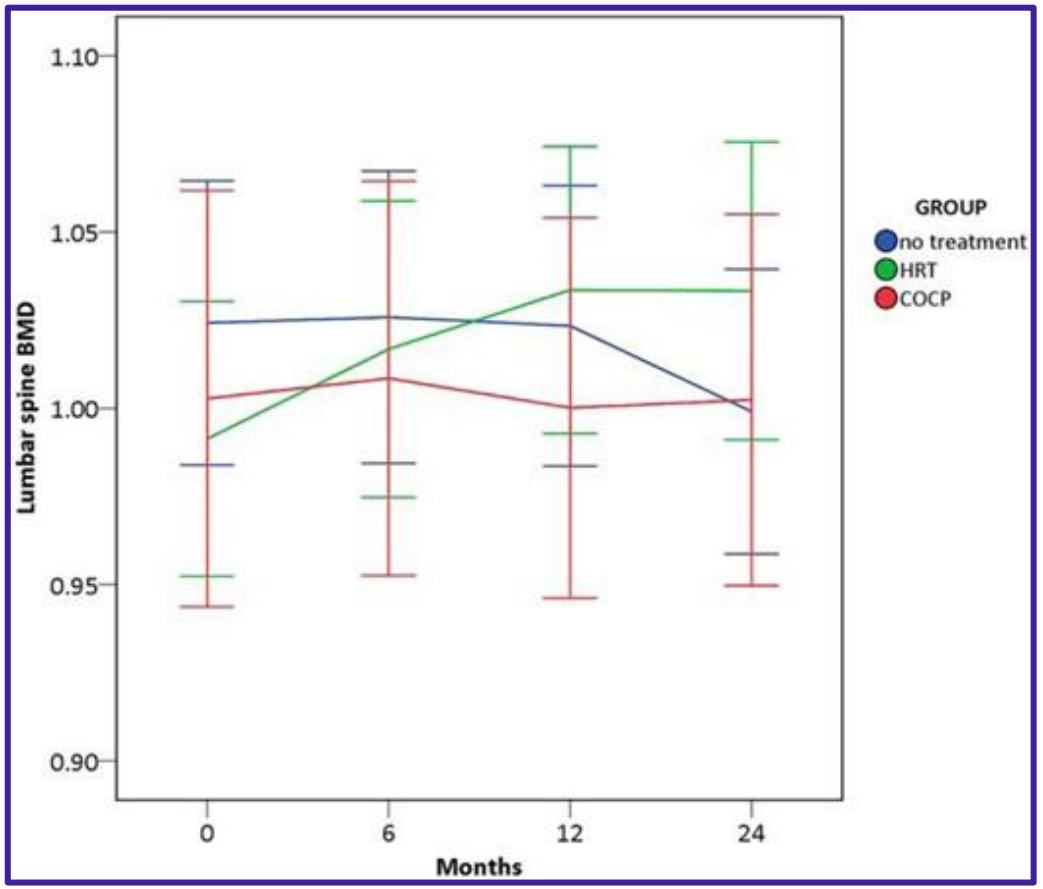
Bisphosphonates remain incorporated in bone for a long time, concern over use in young women in relation to future pregnancy.
Prudent to withdraw oral bisphosphonate therapy prior to pregnancy, a pragmatic recommendation is stopped biphosponates **3-6 months in advance of pregnancy**. *Stathopoulos et al. 2011, Schreiber et al., 2023*

Bone and HRT

	Mo	24
E2 (pg/ml)	11.56	1.68
PG (ng/ml)	2.02	.55
Free T (ng/dl)	0.14	.06
Δ4-A (ng/ml)	0.82	.28
DHEAS (ng/ml)	2040.00	246.49
17OHPG (ng/ml)	0.67	.28
PRL (ng/ml)	13.32	.17
GLUC (mg/dl)	86.33	.89
CHOL (mg/dl)	155.00	0.98
LDL (mg/dl)	137.67	.97
HDL (mg/dl)	57.22	.76
TG (mg/dl)	95.78	2.74
PLT	264666.70	2581.75
PT	11.79	.68
APTT	37.43	.38
FIBR (mg/dl)	342.55	9.95
BD (mg/cm^2)	950.89	9.25
Z-score	−0.07	.33

E2, estradiol; PG, progester… PG, 17-hydroxyprogesterone; GLUC,…





Cartwright, *The Journal of Clinical Endocrinology & Metabolism*, 2016

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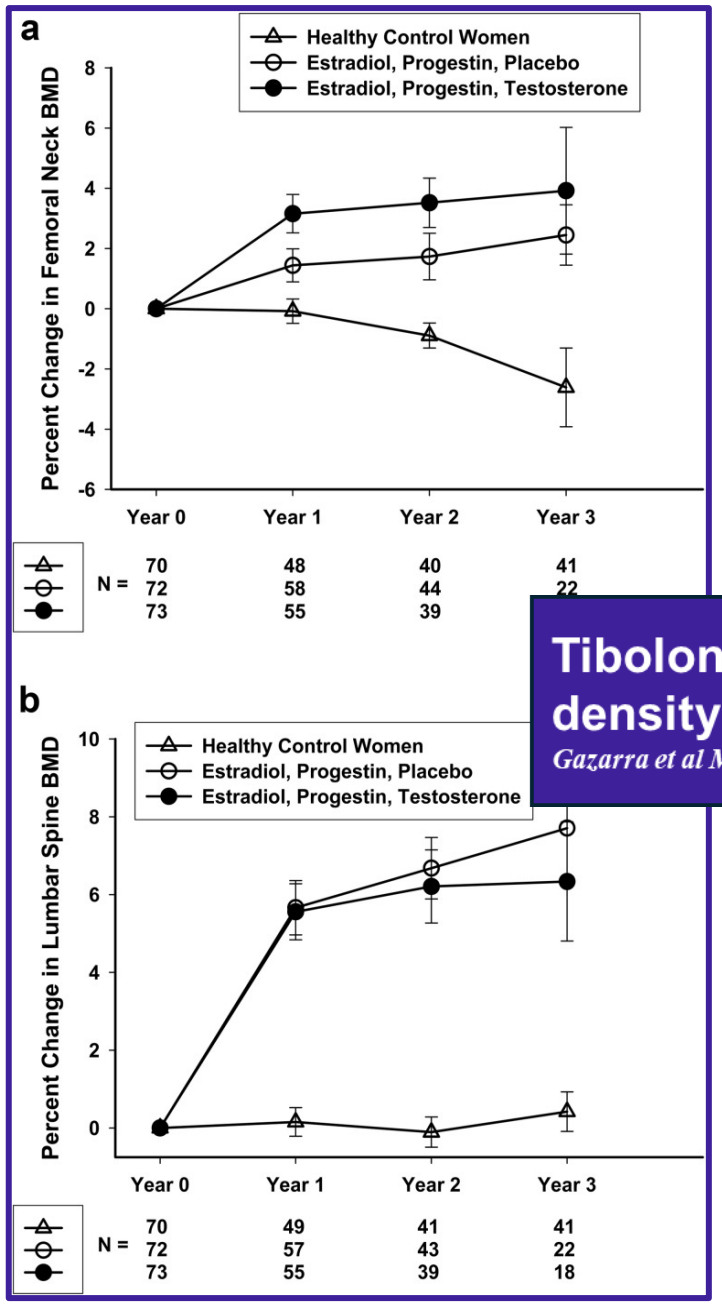
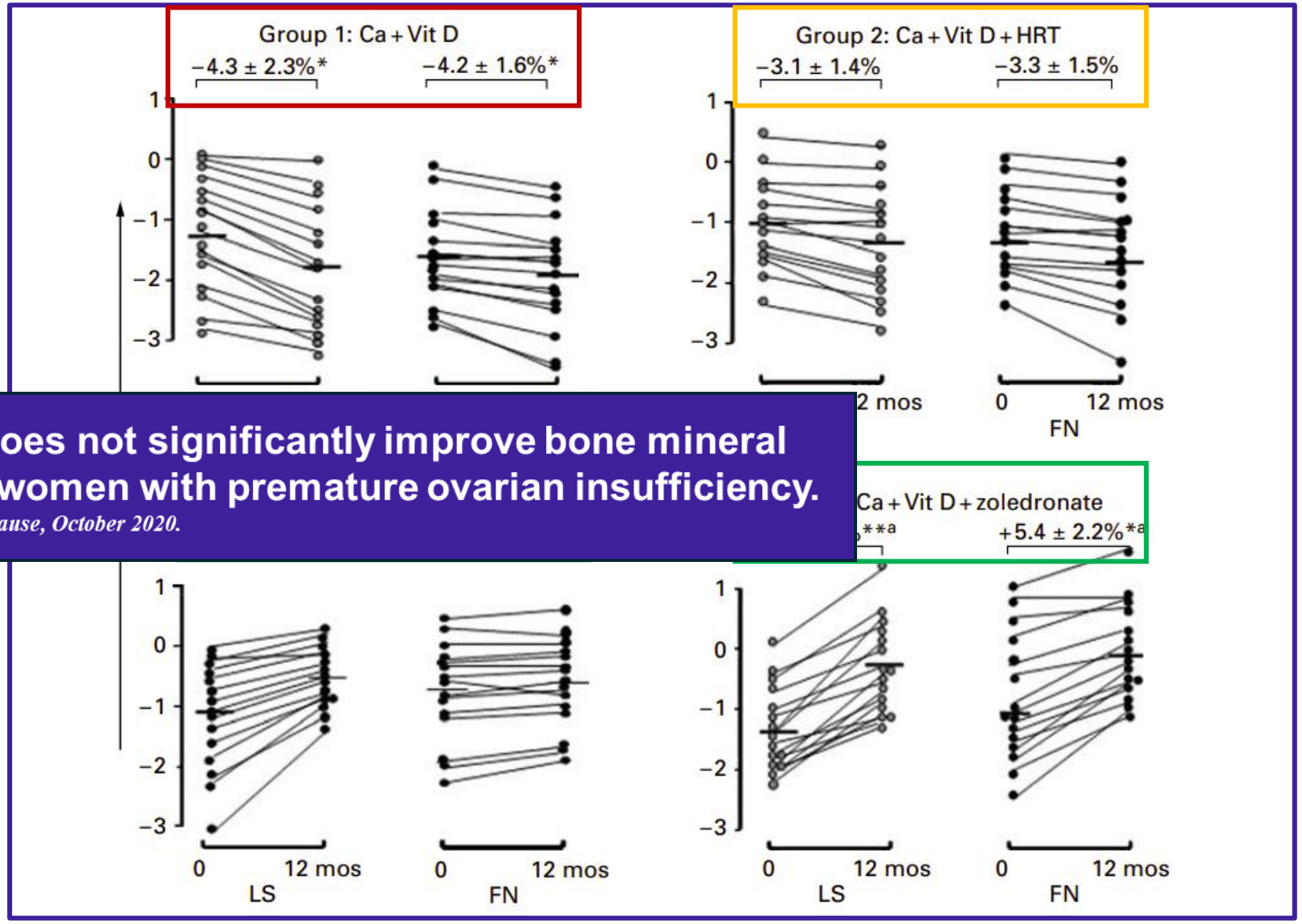


Tibolone does not significantly improve bone mineral density in women with premature ovarian insufficiency.

Gazarra et al Menopause, October 2020.



L Tauchmanova et al. Effects of various antireabsorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation.

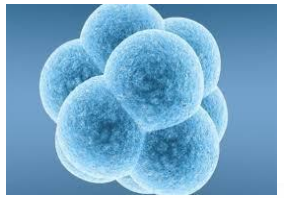
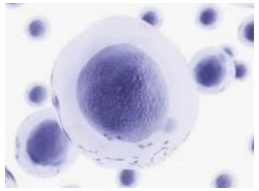
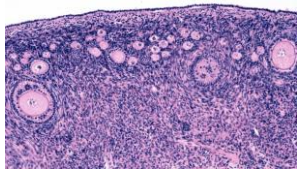
Fertility Preservation in POI

Recommendations		
Women with POI should be informed that POI substantially reduces the chances of natural conception.	STRONG	⊕◯◯◯
Women with non-surgical POI should be informed that ovarian activity may occur. This is associated with a chance of natural conception.	STRONG	⊕◯◯◯

POI intermittent and unpredictable ovarian function (*spontaneous pregnancy occurs in 5-10%).*

Intermittent ovarian function recovery **correlates with FSH levels at diagnosis**, but also with low-to-moderate intensity exercise (≥1.5h/week) and non-smoking.
HRT may increase spontaneous pregnancy during the transitional phase by reducing circulating FSH levels, leading to increased FSH receptor expression in granulosa cells and improved ovarian response to FSH.

Oocyte/embry stimulation (IVF)
Ovarian ti bsequent IVF)
Genetic Counseling

Pellicer N et al, RBMO 2023: Ding X et al, Reprod Sci 2023; Alesi LR et al, Reprod Ferttil 2023; Umer A et al, Stem cell Rev Rep 2023; Du J et al, RBMO 2022; Alur-Gupta S et al, Semin reprod med 2022; La Marca A e Mastellari E, J Assist Reprod Genet, 2021.

GnRH agonist for ovarian protection

Suppression of gonadotropin secretion, which induces a temporary prepubertal hormonal state and reduces the metabolic activity of gonadal cells, potentially making them less susceptible to the cytotoxic effects of chemotherapy.

GnRH agonists during chemotherapy should be offered as an option for ovarian function protection in premenopausal breast cancer patients receiving chemotherapy; however, limited evidence exists on their protective effect on the ovarian reserve and the potential for future pregnancies (Lambertini et al., 2015, 2018c)	**STRONG** ⊗⊗⊗⊗
In women with breast cancer, GnRH agonists during chemotherapy should not be considered instead of cryopreservation techniques (Lambertini et al., 2015)	**STRONG** ⊗⊗⊗○
In malignancies other than breast cancer, GnRH agonists should not be routinely offered as an option for ovarian function protection without discussion of the uncertainty about its benefit (Gilani et al., 2007; Senra et al., 2018)	**STRONG** ⊗○○○
GNRH agonists should not be considered an equivalent or alternative option but can be offered after cryopreservation techniques or when they are not possible.	**Good practice points**

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Grazie per l’attenzione!