



Respect



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Innovation



Engagement

Perimenopause management

Too early for MHT? Or alternatives?

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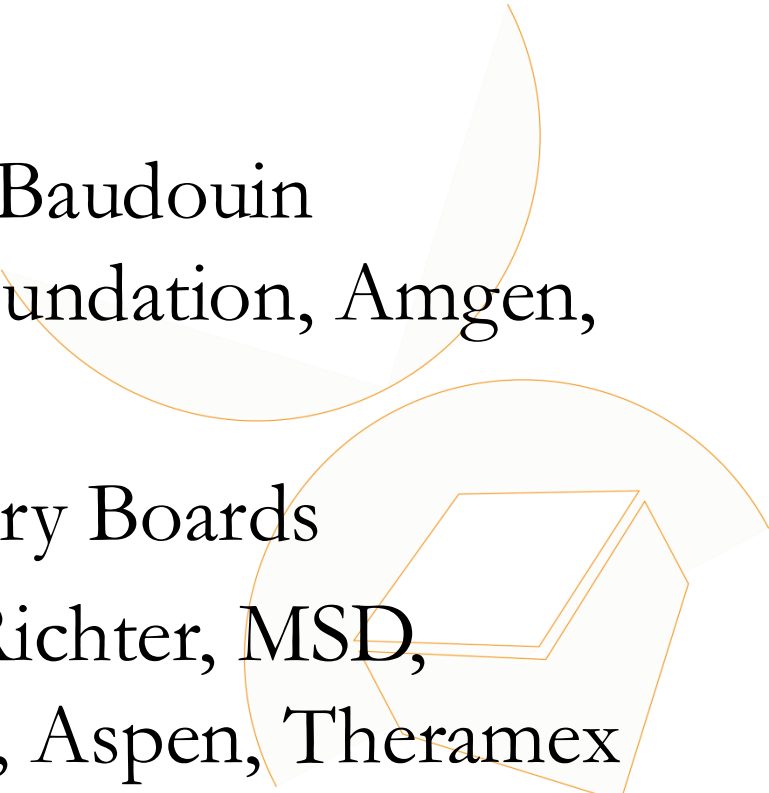
In the center of the city, in the center of life, with passion for care



Conflict of interest & Disclosure

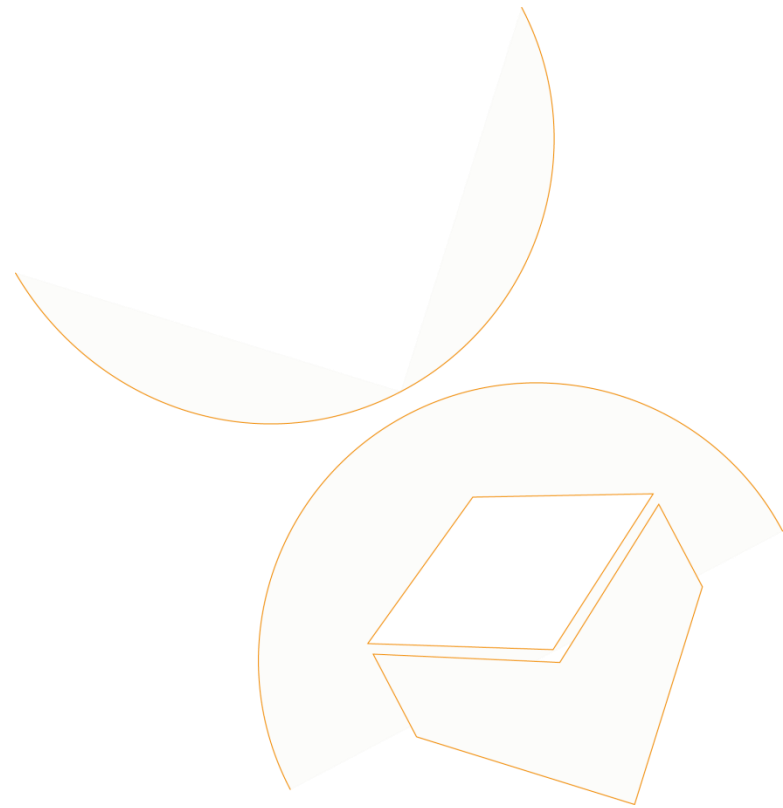
Conflict of interest: none

Disclosure SR

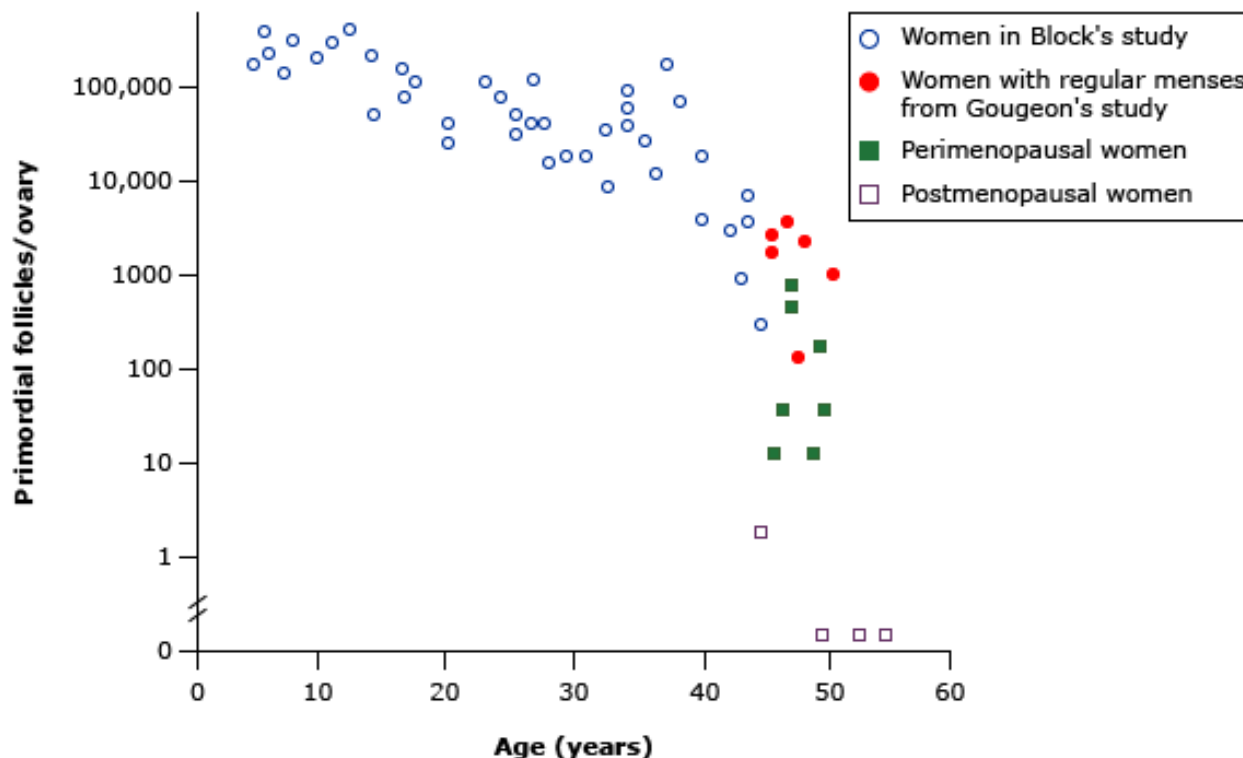
- Research funding IRIS- King Baudouin Fondation, Vesale research Foundation, Amgen, MSD
 - Speakers bureau &/or Advisory Boards
 - Abbot, Pfizer, Will, Gedeon Richter, MSD, Amgen, UCB, Astellas, Bayer , Aspen, Theramex
- 
- Decorative orange geometric shapes, including a large circle and a hexagon, are positioned on the right side of the slide.

Agenda

- Perimenopause
 - Physiology
 - Symptoms
 - Implications
 - Treatments
 - Special populations



Dedining follicle number with age

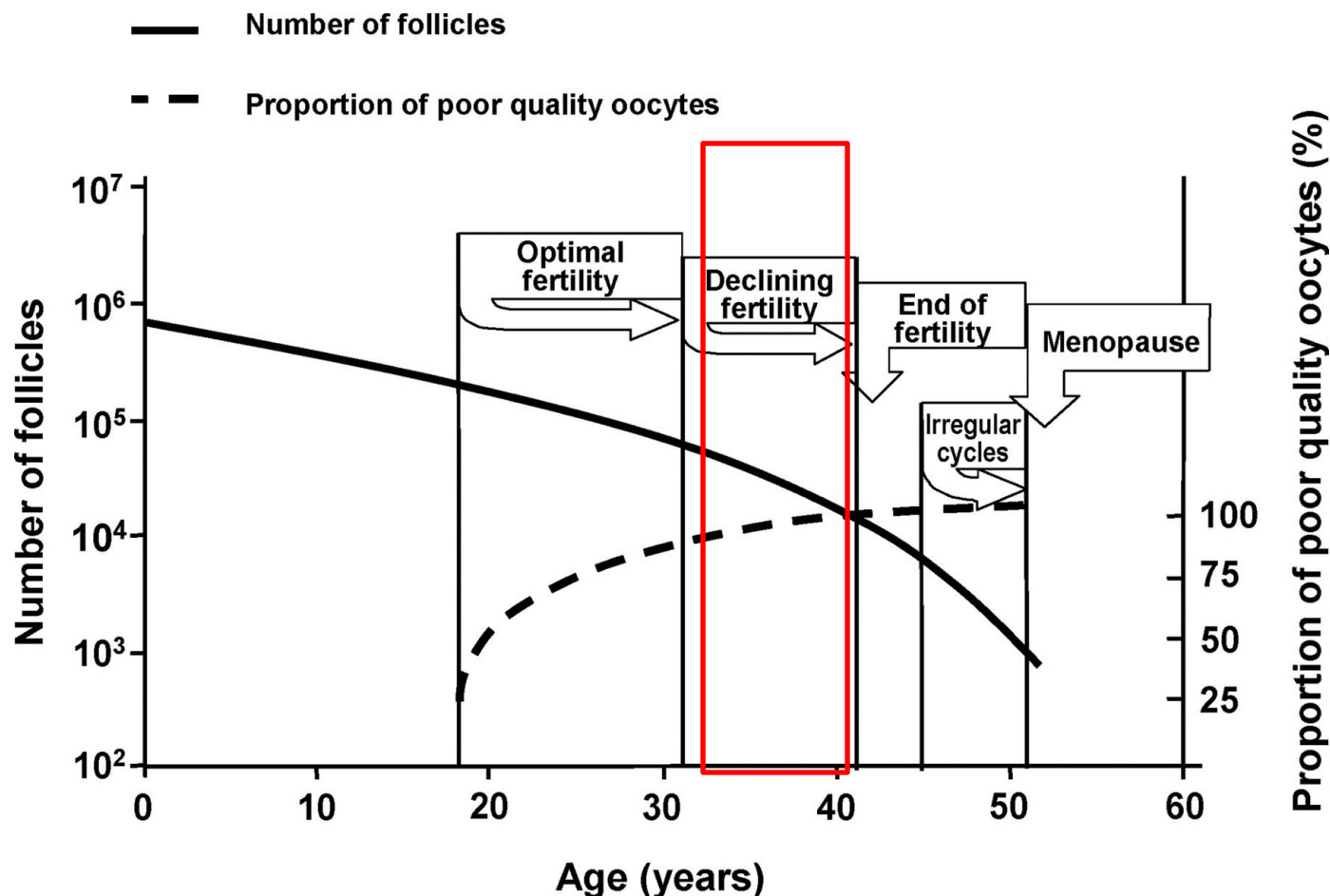


A comparison of the relationship between age and primordial follicle number in Block's study of 44 girls and women aged 7 to 44 years with that of Gougeon's study of women aged 45 to 55 years. Follicle depletion appears to accelerate in the decade preceding menopause.

Data from:

1. Block E. Quantitative morphological investigations of the follicular system in women; variations at different ages. *Acta Anat* 1952; 14:108.
2. Gougeon A. Caractères qualitatifs et quantitatifs de la population folliculaire dans l'ovaire humain adulte. *Contr Fert Sex* 1984; 12:527.

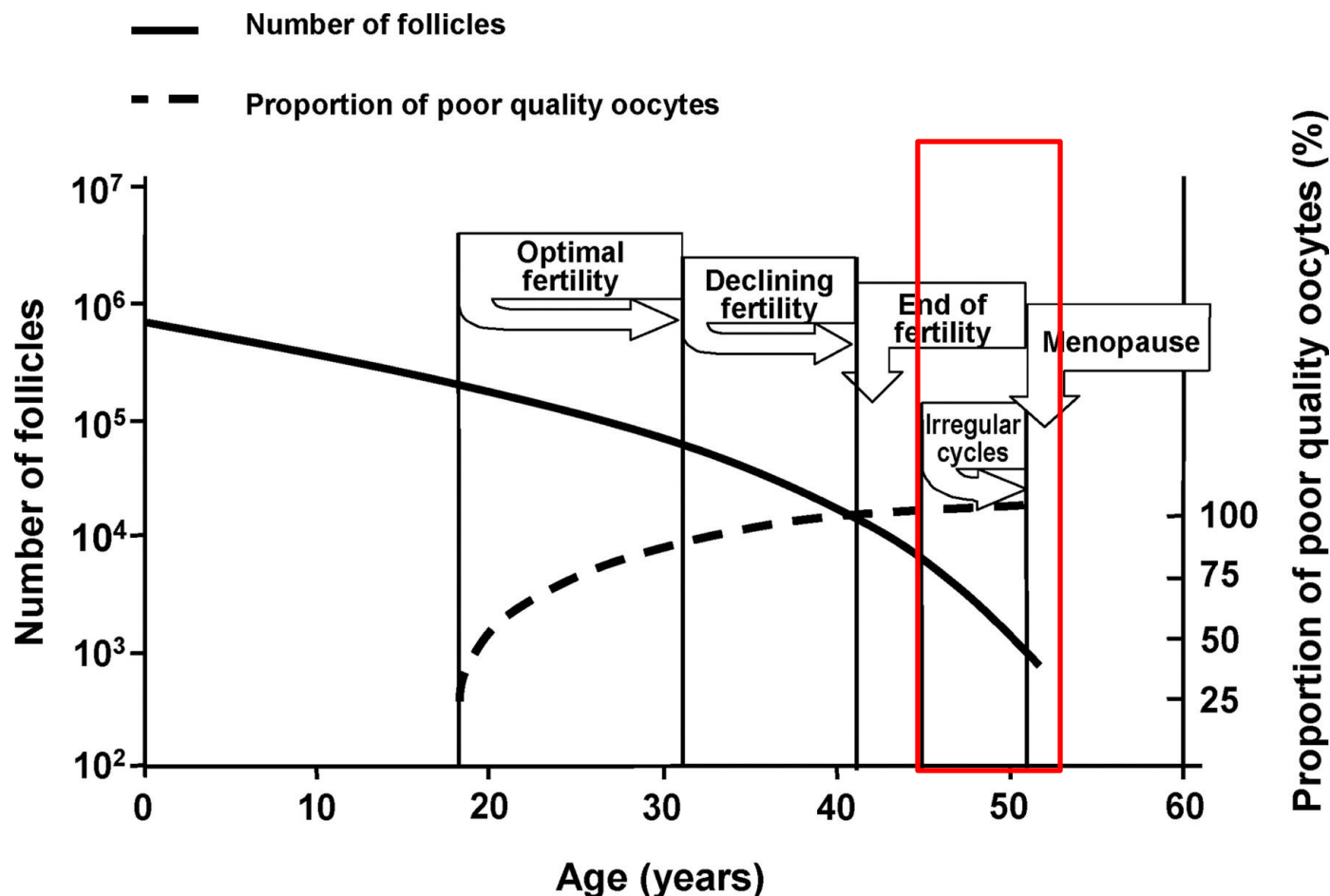
FIG. 1. Schematic representation of the number of primordial follicles present in the ovaries and the chromosomal quality of oocytes in relation to female age and corresponding reproductive events



Broekmans, F. J. et al. Endocr Rev 2009;30:465-493

ENDOCRINE
REVIEWS

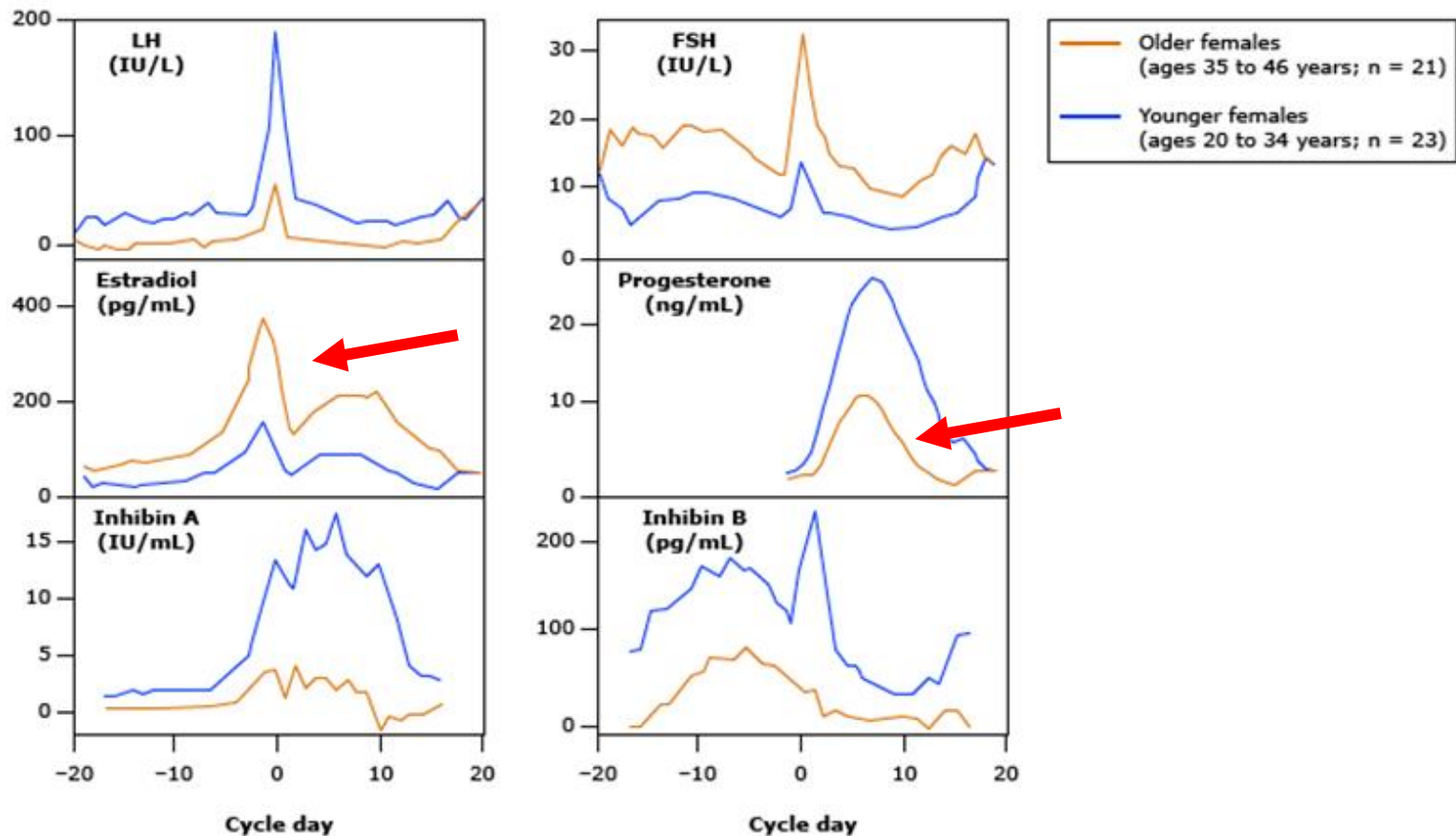
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Broekmans, F. J. et al. Endocr Rev 2009;30:465-493

ENDOCRINE
REVIEWS

Hormone levels: Older and younger reproductive age



Mean daily levels of gonadotropins, sex steroids, and inhibins in older (ages 35 to 46 years; n = 21), shown in orange, and younger females (ages 20 to 34 years; n = 23), shown in blue.

FSH: follicle-stimulating hormone; LH: luteinizing hormone.

Adapted from: Welt CK, McNicholl DJ, Taylor AE, Hall JE. Female reproductive aging is marked by decreased secretion of dimeric inhibin. *J Clin Endocrinol Metab* 1999; 84:105.

What are the issues ?

- Symptoms may vary
- Hormonal status varies : E2 may be normal, low or even very high !



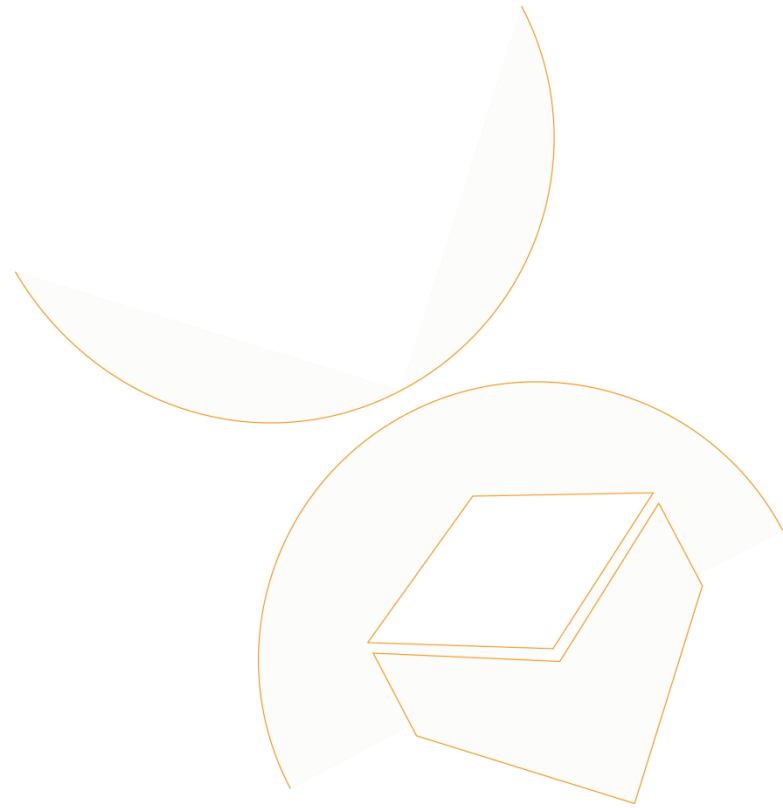
So how do you treat perimenopausal patients ?

- Abstinence ?
- Contraception ?
- Progestins ?
- Menopause Hormone Therapy (E-P-T) ?
- Others ? (NK-Antagonists) ?



MHT : RCT in perimenopause?

- Very few !



Long-term hormone therapy for perimenopausal and postmenopausal women

Included 22 studies n= 43,637 women.

Nearly 70% of the data from (HERS 1998; WHI 1998).

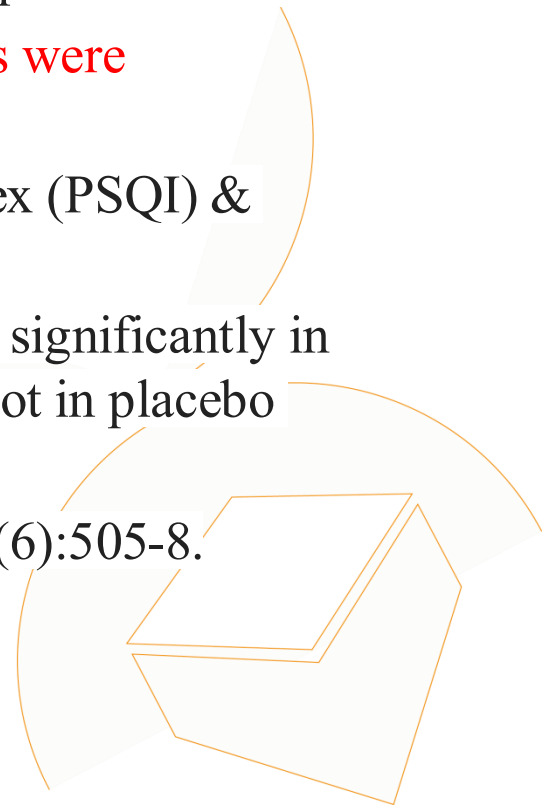
Most participants were postmenopausal American women with at least some degree of comorbidity, and mean participant age in most studies was over 60 years.

None of the studies focused on perimenopausal women.

Bofill Rodriguez M, et al [Cochrane Database Syst Rev. 2026 Sep 4;9\(9\):CD004143.](#)

A randomized, controlled pilot trial of hormone therapy for perimenopausal insomnia

- N= 12 women (?)
- 28 days (?) 1 mg estradiol + 0.125 mg trimegestone/d vs placebo
- **Perimenopausal insomnia ? (Actually : no ! Most patients were postmenopausal !)**
- Outcomes : changes in The Pittsburgh Sleep Quality Index (PSQI) & polysomnography
- Sleep efficiency and median score of the PSQI improved significantly in MHT group ($p = 0.041$ and $p = 0.027$, respectively) and not in placebo group.
- Silva BH, et al Arch Womens Ment Health. 2011 Dec;14(6):505-8.



Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, RCT vs placebo

- Perimenopausal women (40-55 years, with irregular menstrual periods, FSH >25 IU/L),
- criteria for depressive disorder, DSM-IV,
- Transdermal patches E2 (100 µg) or placebo in a 12-week,
- Outcome measures: Montgomery-Asberg Depression Rating Scale and Blatt-Kupperman Menopausal Index scores.
- N=50 ; 26 met DSM-IV criteria for major depressive disorder, 11 for dysthymic disorder, and 13 for minor depressive disorder.
- Remission of depression in 17 (68%) women treated with E2 vs 5 (20%) in placebo (P =.001).
- Subjects responded similarly to E2, regardless of DSM-IV diagnosis.
- **Conclusion:** Transdermal E2 is an effective treatment of depression for perimenopausal women.
- Soares CN, et al Arch Gen Psychiatry. 2001 Jun;58(6):529-34.

Table 1. Subject Characteristics*

Characteristics	Estradiol Group (n = 25)	Placebo Group (n = 25)	Test Statistic†	P
Age, y	49.3 ± 3.8	50.3 ± 3.4	$t = 0.97$	.34†
Age at menarche, y	13.0 ± 1.7	12.5 ± 1.3	$t = -1.21$	.23†
Duration of amenorrhea, d	165.0 ± 123.0	137.0 ± 133.0	$t = -7.77$	.44†
Marital status				
Never married	2 (8)	2 (8)	$\chi^2 = 4.39$	.11
Married	10 (40)	17 (68)		
Divorced or widowed	13 (52)	6 (24)		
Education				
≤High school	21 (84)	16 (64)	$\chi^2 = 2.60$	.10
>High school	4 (16)	9 (36)		
Employed outside home	12 (48)	10 (40)	$\chi^2 = 0.32$	.87
History of successful pregnancies (≥1)	24 (96)	23 (92)	...	>.99‡
History of previous psychiatric symptoms	13 (52)	14 (56)	$\chi^2 = 0.81$	.78
History of puerperal mood changes	8 (32)	9 (36)	$\chi^2 = 0.09$	.76
Previous use of antidepressants, ever	4 (16)	3 (12)	...	>.99‡
Current depressive disorder				
Major depressive disorder	15 (60)	11 (44)	$\chi^2 = 1.51$	.47
Dysthymic disorder	4 (16)	7 (28)		
Minor depressive disorder	6 (24)	7 (28)		

*Data are given as mean ± SD or number (percentage) of subjects.

†Independent t test (2-sided) (df = 48); Pearson χ^2 test (df = 1, except for marital status [df = 2] and current depressive diagnoses [df = 2]).

‡Fisher exact test.

Estrogen replacement in perimenopause-related depression: a preliminary report

- **E2 or placebo for 3 weeks (cross-over)**. Subsequently, women receiving estradiol during the first 3 weeks continued receiving estradiol for an additional 3 weeks, whereas women who had received placebo crossed over to estradiol for 3 weeks.
- Outcome: standardized mood rating scales
- **N= 34; 16 received estradiol first and 18 received placebo first**. After 3 weeks of estradiol, standardized mood rating scale scores and visual analog scale symptom scores (eg, sadness, anhedonia, and social isolation) were significantly decreased compared with baseline scores ($P < .01$) and were significantly lower than scores in women receiving placebo ($P < .01$), who showed no significant improvement. Neither the presence of hot flashes nor the duration of treatment (3 weeks vs 6 weeks) influenced outcome. **A full or partial therapeutic response was seen in 80% of subjects receiving estradiol and 22% of those receiving placebo.**
- Schmidt PJ, et al Am J Obstet Gynecol. 2000 Aug;183(2):414-20.

Table II. Characteristics of subjects entering study

	<i>17β-estradiol (n = 16)</i>	<i>Placebo (n = 18)</i>
Age (y)		
Mean $\pm$ SD	48.3 $\pm$ 2.7	50.1 $\pm$ 3.1
Range	44-52	44-55
Parity (mean $\pm$ SD)	1.8 $\pm$ 1.3	1.8 $\pm$ 1.5
Marital status—Married (%)	63	72
No. of subjects without hot flushes	9	9
Time since onset of menstrual cycle irregularity (mo, mean $\pm$ SD)	22.6 $\pm$ 12.2	19.9 $\pm$ 9.3
Time since onset of mood syndrome (mo, mean $\pm$ SD)	13.8 $\pm$ 9.5	14.0 $\pm$ 5.6
Current Research Diagnostic Criteria for minor depression (No.)	13	13
Criterion symptoms met (No., mean $\pm$ SD)	10.3 $\pm$ 3.9	11.0 $\pm$ 2.8
Current <i>Diagnostic and Statistical Manual III Revised</i> criteria for major depression (No.)	3	5
Criterion symptoms met (No., mean $\pm$ SD)	5.6 $\pm$ 0.6	5.6 $\pm$ 0.5
History of affective disorder* (No.)		
Minor depression	6	6
Major depression	3	2

*One woman had both a past major and a past minor depression.

Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

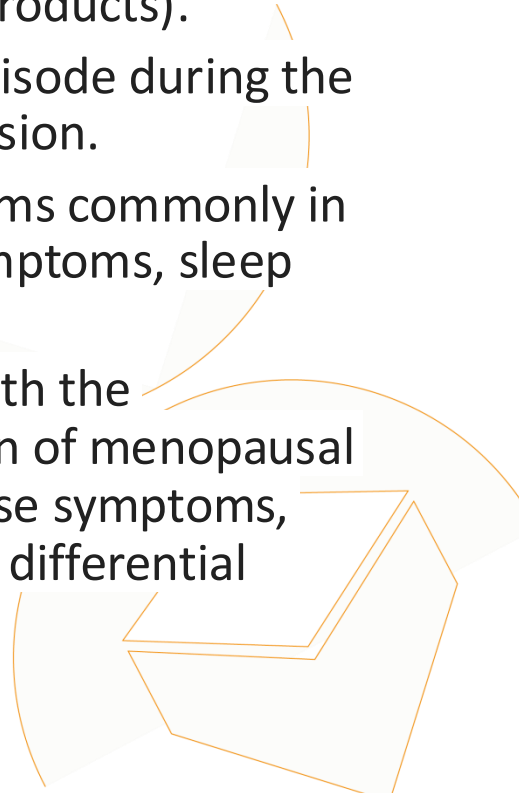
1) epidemiology; 2) clinical presentation; 3) therapeutic effects of antidepressants; 4) effects of hormone therapy; and 5) efficacy of other therapies (eg, psychotherapy, exercise, and natural health products).

Most midlife women who experience a major depressive episode during the perimenopause have experienced a prior episode of depression.

Midlife depression presents with classic depressive symptoms commonly in combination with menopause symptoms (ie, vasomotor symptoms, sleep disturbance), and psychosocial challenges.

Menopause symptoms complicate, co-occur, and overlap with the presentation of depression. Diagnosis involves identification of menopausal stage, assessment of co-occurring psychiatric and menopause symptoms, appreciation of the psychosocial factors common in midlife, differential diagnoses, and the use of validated screening instruments.

Maki PM, et al Menopause. 2018 Oct;25(10):1069-1085.



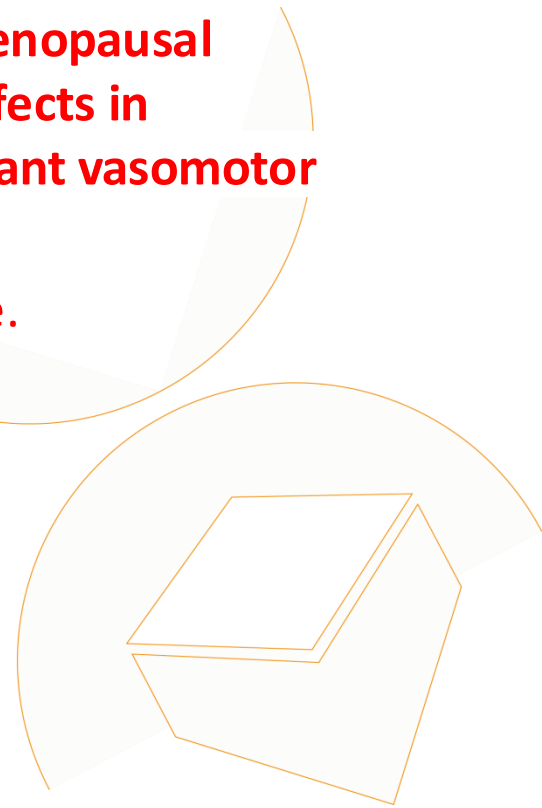
Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

Proven therapeutic options for depression (ie, **antidepressants, psychotherapy**) are the front-line treatments for perimenopausal depression.

Although estrogen therapy is not approved to treat perimenopausal depression, there is evidence that it has antidepressant effects in perimenopausal women, particularly those with concomitant vasomotor symptoms.

Data on estrogen plus progestin are sparse and inconclusive.

Maki PM, et al Menopause. 2018 Oct;25(10):1069-1085.



Comparison of low dose versus ultra-low dose hormone therapy in menopausal symptoms and quality of life in perimenopause women

- Retrospective analysis of perimenopause patients prescribed for 25 weeks HT
- N=132 perimenopause women
- Low dose HT (LD-HT) (E2V 1 mg + 10mg dydrogesterone seq) vs ultra-low dose HT (ULD-HT)(0.5 mg E2V +10mg dydrogesterone seq)
- Song Y, et al Gynecol Endocrinol. 2020 Mar;36(3):252-256.

Comparison of low dose versus ultra-low dose hormone therapy in menopausal symptoms and quality of life in perimenopause women

Table 1. Characteristics of the participants and changes in serum index.

Characteristics	All (n = 132)	LD-HT group (n = 63)	ULD-HT group (n = 69)	p ^a
Age (years)	46.21 ± 4.02	45.72 ± 4.17	46.29 ± 4.09	NS
Duration of amenorrhea (months)	4.68 ± 3.53	4.20 ± 3.39	5.03 ± 3.35	NS
Weight at baseline (kg)	55.47 ± 6.76	55.34 ± 5.67	56.20 ± 6.88	NS
Weight at 25th week (kg)	55.56 ± 6.39	55.26 ± 5.74	55.71 ± 6.80	NS
BMI at baseline (kg/m ²)	21.83 ± 2.33	21.80 ± 2.19	21.82 ± 2.28	NS
BMI at 25th week (kg/m ²)	21.72 ± 2.25	21.70 ± 2.29	21.38 ± 2.20	NS
FSH at baseline (IU/L)	74.33 ± 27.27	71.08 ± 27.89	76.98 ± 26.57	NS
FSH at 25th week (IU/L)	47.32 ± 26.31	42.08 ± 20.59 ^b	51.41 ± 29.37 ^b	NS
Estradiol at baseline (pmol/L)	92.70 ± 124.73	124.50 ± 161.67	68.28 ± 120.79	<0.05
Estradiol at 25th week (pmol/L)	269.79 ± 251.73	273.56 ± 202.31 ^b	264.48 ± 287.07 ^b	NS

Data are presented as mean ± standard deviation (SD). BMI: body mass index; FSH: follicle-stimulating hormone; NS: no statistical significance.

^aComparison between LD-HT and ULD-HT groups.

^bIndicates that the treatment changes compared with baseline was statistically significant ($p < .05$).

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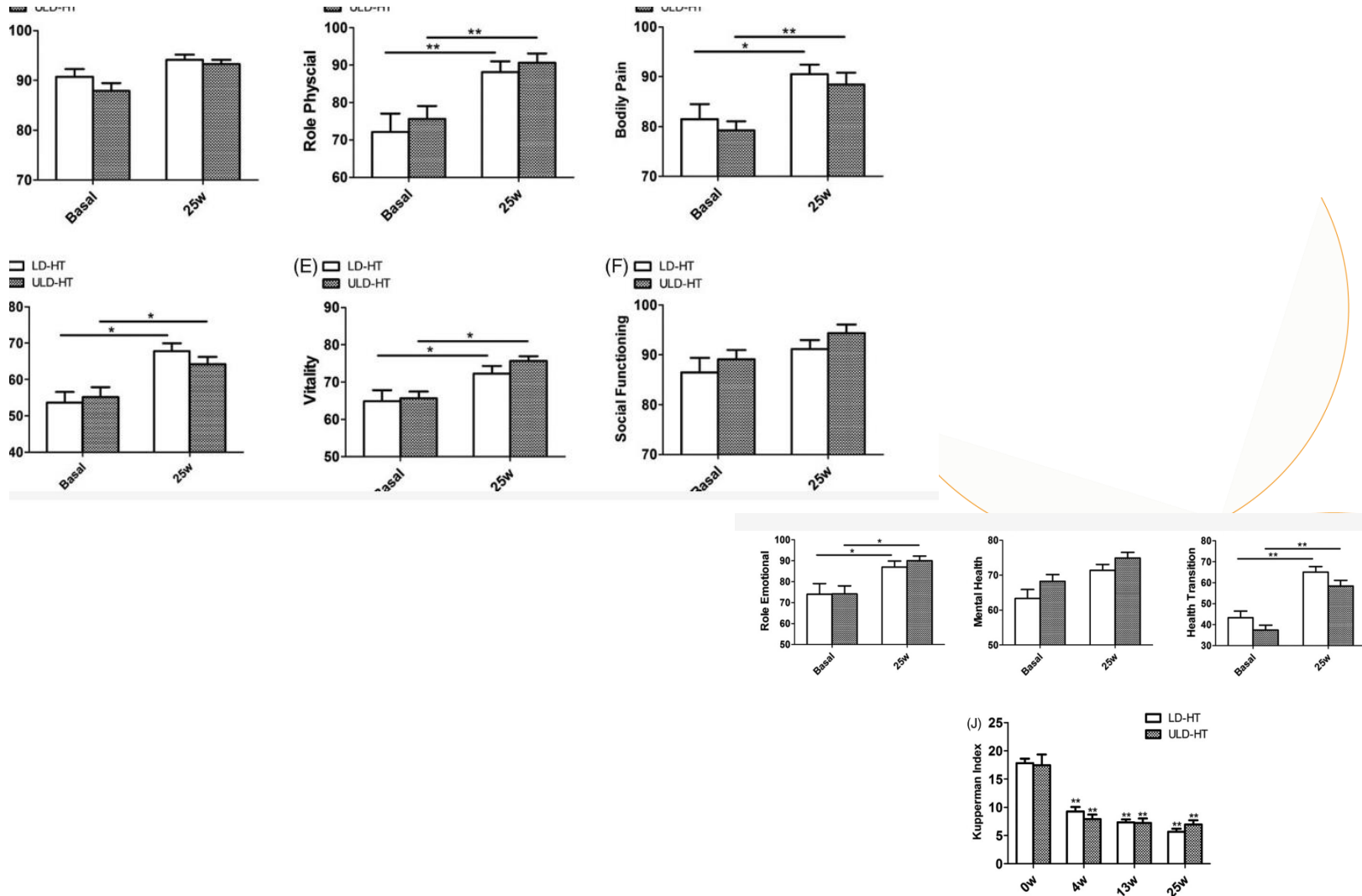
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Comparison of low dose versus ultra-low dose hormone therapy in menopausal symptoms and quality of life in perimenopause women



- Song Y, et al Gynecol Endocrinol. 2020 Mar;36(3):252-256.

Comparison of low dose versus ultra-low dose hormone therapy in menopausal symptoms and quality of life in perimenopause women

Table 2. Incidence of adverse events and increasing of endometrial thickness.

Variables	All (<i>n</i> = 132)	LD-HT (<i>n</i> = 63)	ULD-HT (<i>n</i> = 69)	<i>p</i> ^a
Mastodynia	37 (28.03%)	23 (36.51%)	14 (20.29%)	<.05
Abnormal uterine bleeding	3 (2.27%)	2 (3.17%)	1 (1.45%)	NS
Endometrial thickness at baseline (mm)	1.98 ± 0.85	1.98 ± 0.83	1.97 ± 0.88	NS
Endometrial thickness at 25th week (mm)	2.17 ± 0.96	2.32 ± 0.12 ^b	2.07 ± 0.78	NS

Values of adverse events are presented as *n* (%). Values of endometrial thickness are presented as the mean ± standard deviation (SD).

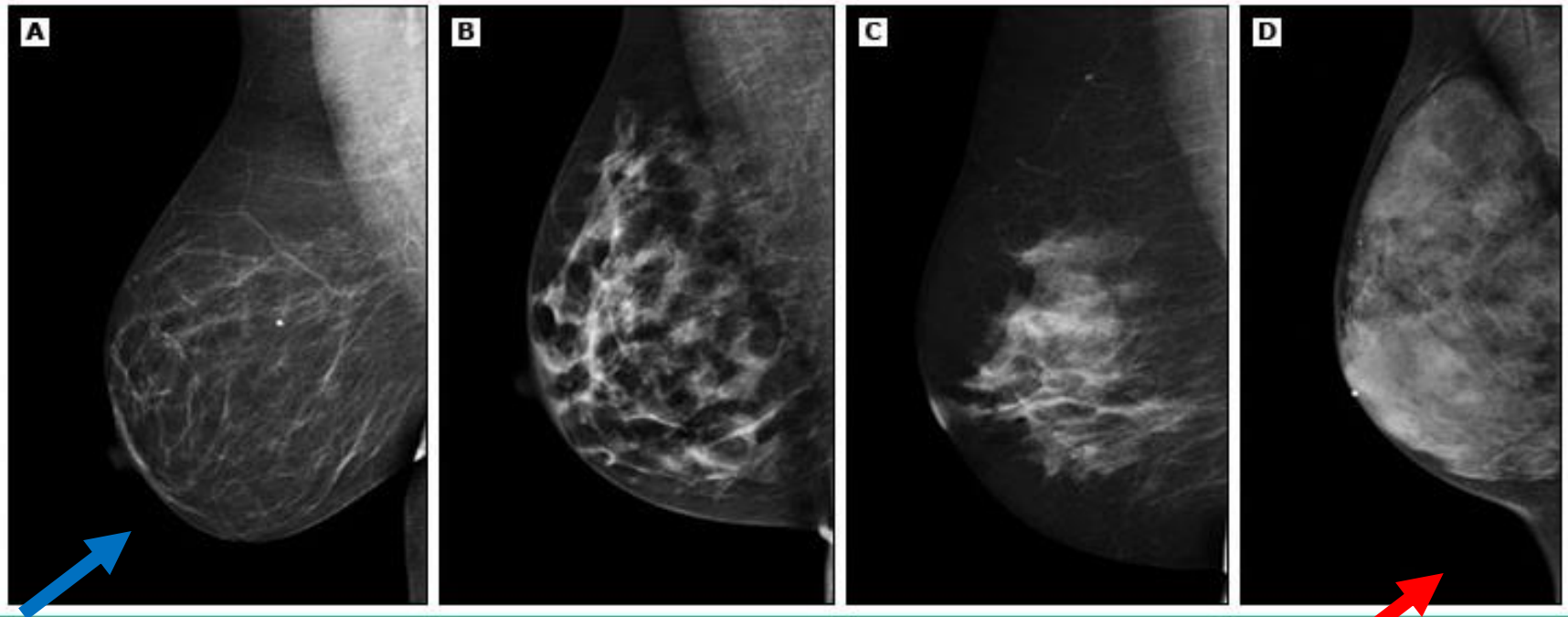
NS: no statistical significance.

^aComparison between LD-HT and ULD-HT groups.

^bIndicates that the treatment change compared with baseline was statistically significant (*p* < .05).

- **Both groups have negligible differences** in incidence of adverse effects. Ultra-low dose treatment may have a better advantage on safety and tolerance.
- Song Y, et al Gynecol Endocrinol. 2020 Mar;36(3):252-256.

Categories of breast density on mammography



(A) Almost entirely fatty.

(B) Scattered areas of fibroglandular tissue.

(C) Heterogeneously dense.

(D) Extremely dense.

These categories correspond to the four-point scale as defined by the Breast Imaging Reporting and Data System, 5th edition (BI-RADS).

Courtesy of Phoebe Freer, MD and Priscilla Slanetz, MD, MPH, FACR.

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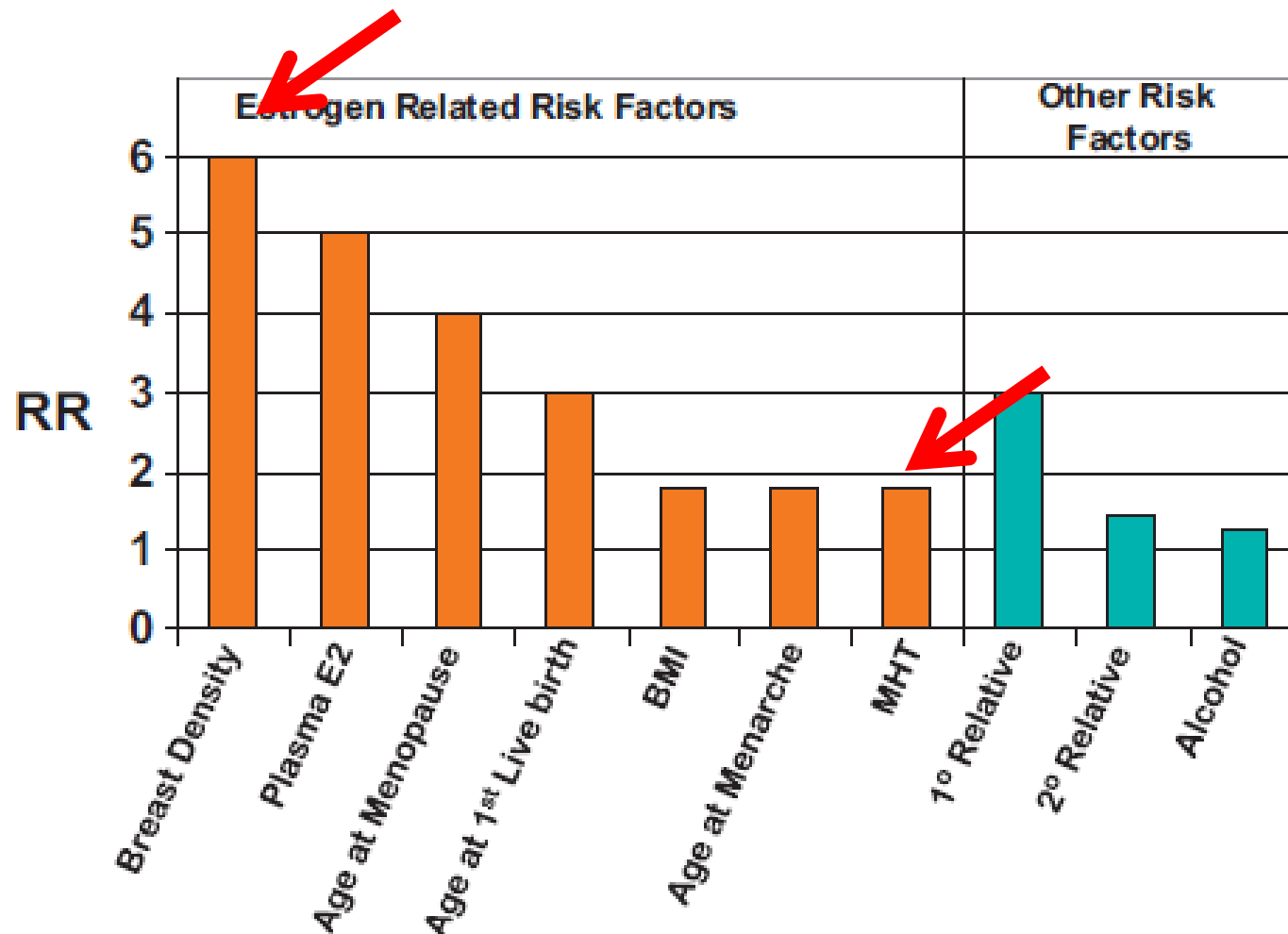


Fig. 1. Estrogen related risk factors for breast cancer. Risk factors for breast cancer related to clinical aspects that are associated with an increased chronic exposure to estradiol and expressed as relative risks (RR).

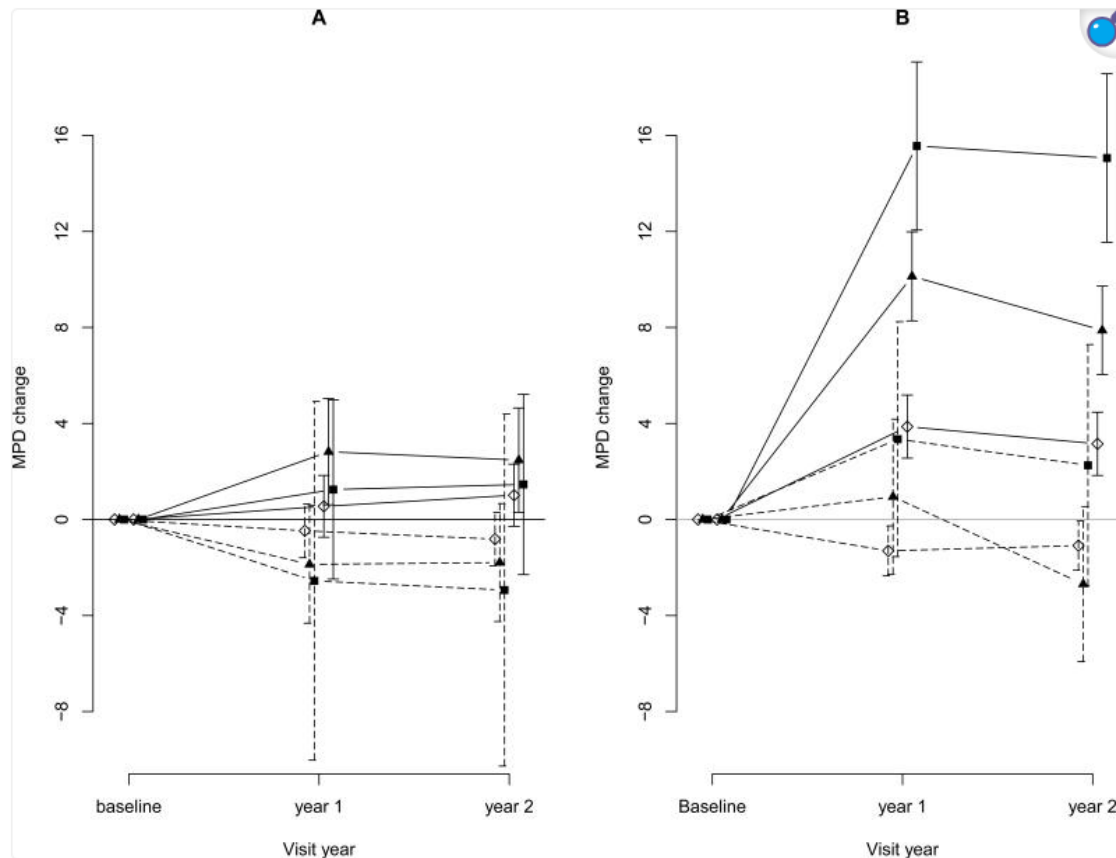
Figure adapted from the review of E. Amir et al. [83] and published in the article by Yager et al. [16]. Reproduced with the permission of the Endocrine Society.

Breast Tenderness after Initiation of Conjugated Equine Estrogens and Mammographic Density Change

- Baseline, year 1, and year 2 data from 695 participants of the WHI-EP (daily CEE 0.625 mg + MPA 2.5 mg or placebo) and Estrogen-Alone (CEE 0.625 mg or placebo) trials who participated in the Mammogram Density Ancillary Study.
- Active therapy increased the odds of new-onset breast tenderness (CEE + MPA vs. placebo risk ratio [RR] 3.01, [95% CI] 1.96-4.62; CEE vs. placebo RR 1.70, 95% CI 1.14-2.53).
- Among women assigned to CEE + MPA, mean increase in mammographic density was greater among participants reporting new-onset of breast tenderness than among participants without new-onset breast tenderness (11.3% vs. 3.9% at year 1, 9.4% vs. 3.2% at year 2, $P < 0.001$).
- Among women assigned to CEE alone, increase in mammographic density at year 1 follow-up was not significantly different in women with new-onset breast tenderness compared to women without new-onset breast tenderness (2.4% vs. 0.6% at year 1, 2.2% vs. 1.0% at year 2, $P = 0.30$).
- The new-onset of breast tenderness after initiation of CEE + MPA, but not CEE alone, is associated with greater increases in mammographic density.
- Crandall CJ, et al Breast Cancer Res Treat. 2012 Feb;131(3):969-79.

Breast Tenderness after Initiation of Conjugated Equine Estrogens and Mammographic Density Change

Figure 2. Associations between new-onset breast tenderness (NOBT) and change in mammographic density (MPD) from baseline, according to treatment assignment and severity of NOBT, and adjusted for age, ethnicity, BMD, and Gail risk score.



Panel A CEE trial (solid line) vs placebo (dashed line) by moderate or severe NOBT (solid square), mild NOBT (solid triangle), or absence of NOBT (open square).
Panel B CEE + MPA trial (solid line) vs placebo (dashed line) by moderate or severe NOBT (solid square), mild NOBT (solid triangle), or absence of NOBT (open square).

- Crandall CJ, et al Breast Cancer Res Treat. 2012 Feb;131(3):969-79.

My conclusions about MHT (E-PT) in perimenopause ?

- Not a first choice therapy
- Not in the first Straw stage of perimenopause, but rather the last stage.
- Favour low-dose or ultra-low dose E2
- Warn about possible side effects (mastodynia)



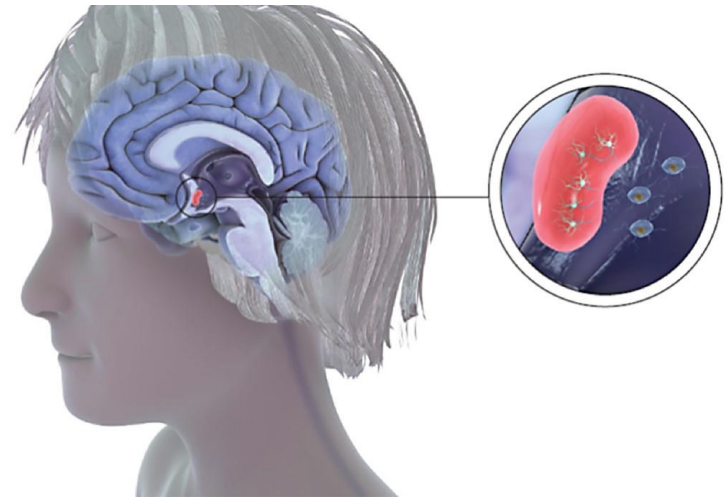
Alternatives ?

- Vaginal therapy : GUSM
 - Probably less or no side effects ?
 - No data
- SSRI for depression
- NK Antagonists for VSM symptoms ?
 - No study in perimenopause published
 - Likely to work



KNDy neurons and thermoregulation

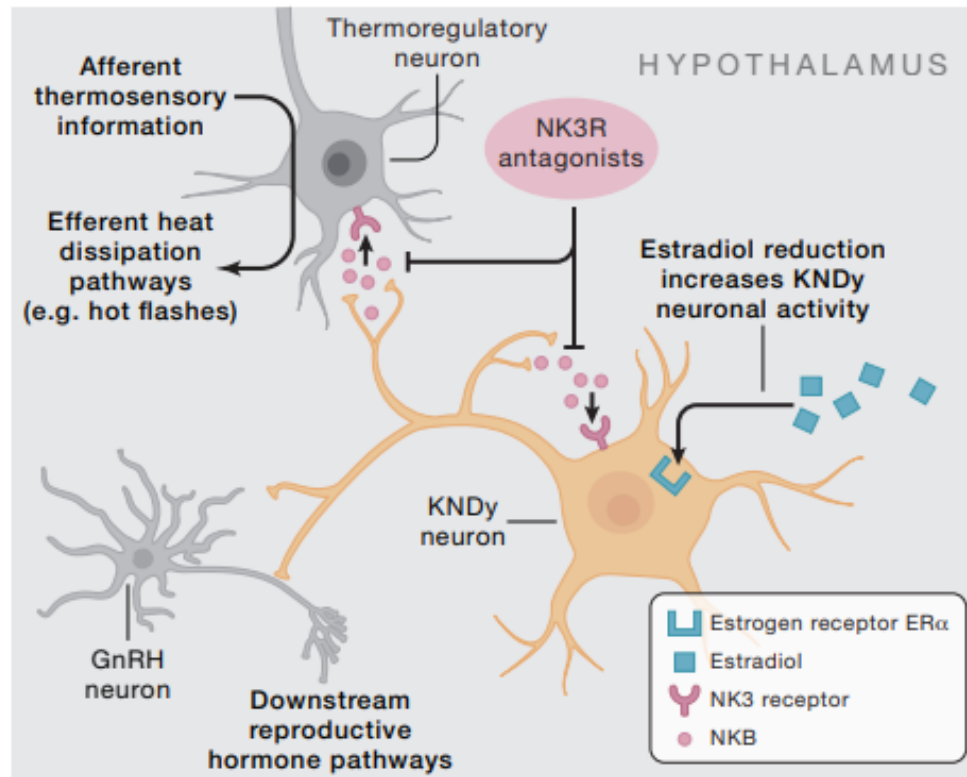
The thermoregulatory center is innervated by KNDy neurons that coordinate various functions, including thermoregulation^{1,2}



KNDy, kisspeptin-neurokinin B-dynorphin.

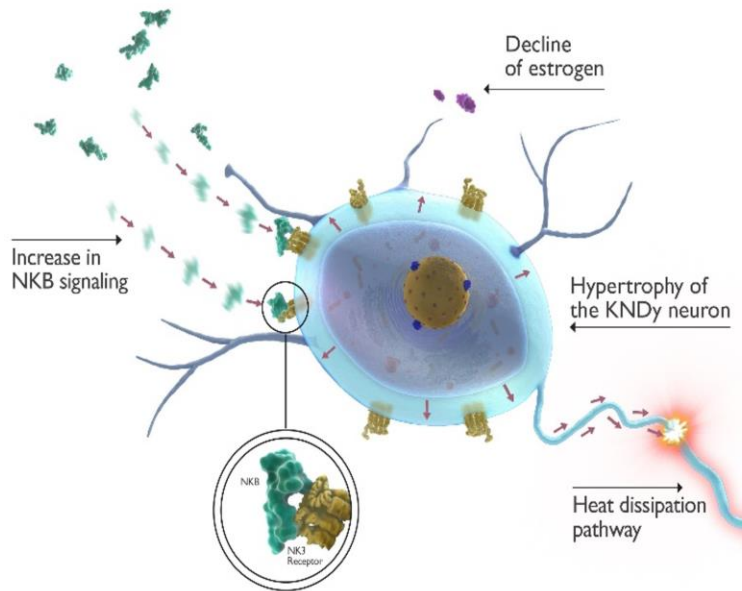
1. Rance NE et al. *Front Neuroendocrinol* 2013;34:211–227. 2. Mittelman-Smith MA et al. *Proc Natl Acad Sci U S A* 2012;109(48):19846–19851.

Neurokinin 3 receptor antagonism for menopausal hot flashes



NKB is released by KNDy neurons in greater amounts in hypoestrogenic states (menopause). KNDy neurons communicate with themselves/each other via NK3 receptors to control pulses of GnRH and project to thermoregulatory neurons expressing NK3Rs in the median preoptic nucleus. NK3R antagonism thereby inhibits thermoregulatory heat dissipation pathways at two sites.

Overstimulation of the thermoregulatory center



During menopause, estrogen levels decline and signaling from NKB increases^{1–4}

- No longer counterbalanced by estrogen, the increased NKB signaling overstimulates KNDy neurons to increase activity on the thermoregulatory center (median preoptic nucleus)
- The thermoregulatory center becomes hypersensitive to heat-sensitive peripheral sensors, activating heat dissipation effectors, including sweating and vasodilation, experienced as hot flashes

KNDy, kisspeptin-neurokinin B-dynorphin; NKB, neurokinin B.

1. Rance NE et al. *Front Neuroendocrinol* 2013;34:211–227. 2. Mittelman-Smith MA et al. *Proc Natl Acad Sci U S A* 2012;109(48):19846–19851. 3. Padilla SL et al. *Cell Rep* 2018;24(2):271–277. 4. Jayasena CN et al. *Sci Rep* 2015;5:8466.

Original Research

Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause

A Randomized Controlled Trial

Genevieve Neal-Perry, MD, PhD, Antonio Cano, MD, Samuel Lederman, MD, Rossella E. Nappi, MD, PhD, Nanette Santoro, MD, Wendy Wolfman, MD, Marci English, MPH, Catherine Franklin, BS, Udaya Valluri, MS, and Faith D. Ottery, MD, PhD

OBJECTIVE: To evaluate the safety, tolerability, and effect of fezolinetant on endometrial health over 52 weeks.

METHODS: We conducted a phase 3, randomized, double-blind, 52-week safety study (SKYLIGHT 4 [Study to Find Out How Safe Long-term Treatment With Fezolinetant is in Women With Hot Flashes Going Through Menopause]) of placebo, fezolinetant 30 mg, and fezolinetant 45 mg once daily (1:1:1). Participants were postmenopausal and seeking treatment for vasomotor symptoms associated with menopause. Primary endpoints were treatment-emergent adverse events,

percentage of participants with endometrial hyperplasia, and percentage with endometrial malignancy. Endometrial hyperplasia or malignancy was evaluated according to U.S. Food and Drug Administration guidance (point estimate of 1% or less with an upper bound of one-sided 95% CI of 4% or less). Secondary endpoints included change in bone mineral density (BMD) and trabecular bone score. A sample size of 1,740 was calculated to enable observation of one or more events ($\approx 80\%$ probability for events with background rate of less than 1%).

RESULTS: A total of 1,830 participants were randomized and took one or more medication dose (July 2019–

Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause

A Phase 3 Randomized Clinical Trial

Nick Panay, MBBS, BSc; Hadine Joffe, MD, MSc; Pauline M. Maki, PhD; Rossella E. Nappi, MD, PhD; JoAnn V. Pinkerton, MD, MSCP; Jai Claudio N. Soares, MD, PhD, MBA; Rebecca C. Thurston, PhD; Maja Francuski, MD; Cecilia Caetano, MD; Kelly Genga, MD, PhD; Claudia Nazanin Haseli Mashhadi, MSc; Kaisa Laapas, MSc; Susanne Parke, MD; Christian Seitz, MD, PhD, MSc; Judith Schwarz, PhD; Lineke Z

IMPORTANCE There is an unmet need for long-term, safe, effective, and hormone-free treatments for menopausal symptoms, including vasomotor symptoms (VMS) and sleep disturbances.

OBJECTIVE To evaluate the 52-week efficacy and safety of elinzanetant, a dual neurokinin-targeted therapy, for treating moderate to severe VMS associated with menopause.

DESIGN, SETTING, AND PARTICIPANTS OASIS-3 was a double-blind, placebo-controlled, randomized phase 3 clinical trial that was conducted at 83 sites in North America and Europe from August 27, 2021, to February 12, 2024, and included postmenopausal women aged 40 to 65 years who were seeking treatment for moderate to severe VMS (no requirement for a minimum number of VMS events per week). The data were analyzed on March 11, 2024.

INTERVENTION Once-daily oral elinzanetant, 120 mg, or matching placebo for 52 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was mean change from baseline to week 12 in the frequency of daily moderate to severe VMS, which was analyzed using a mixed model with repeated measures. Secondary end points included changes over 52 weeks in measures evaluating sleep disturbance and the effect on menopause-related quality of life. Exploratory end points included mean changes over 50 weeks in frequency and severity of daily moderate to severe VMS. Exploratory and secondary end points were analyzed using descriptive statistics. Safety was also assessed.

RESULTS Overall, 313 women (mean [SD] age, 54.6 [4.7] years; 51 [16.3%] were Black or African American, and 240 [76.7%] were White individuals; 34 [10.9%] were Hispanic or Latina) were randomized to receive elinzanetant and 315 (mean [SD] age, 54.9 [5.0] years; 44 [14.0%] Black or African American, 34 [10.8%] Hispanic or Latina, and 253 [80.3%] White individuals) to receive placebo. At week 12, the mean change from baseline in daily moderate

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Conclusions

- Perimenopause is a challenging period
- Changes in hormones result in different symptoms
- Going from high E and low P
 - Mastodynia Heavy bleeding
 - Prog/ LNG IUD/ OC / ...
- To low E and low P
 - HF and Insomnia, VVA
 - MHT
- Treatment need to be adapted to patient and their symptomatology