Perimenopause management

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

Conflict of interest & Disclosure

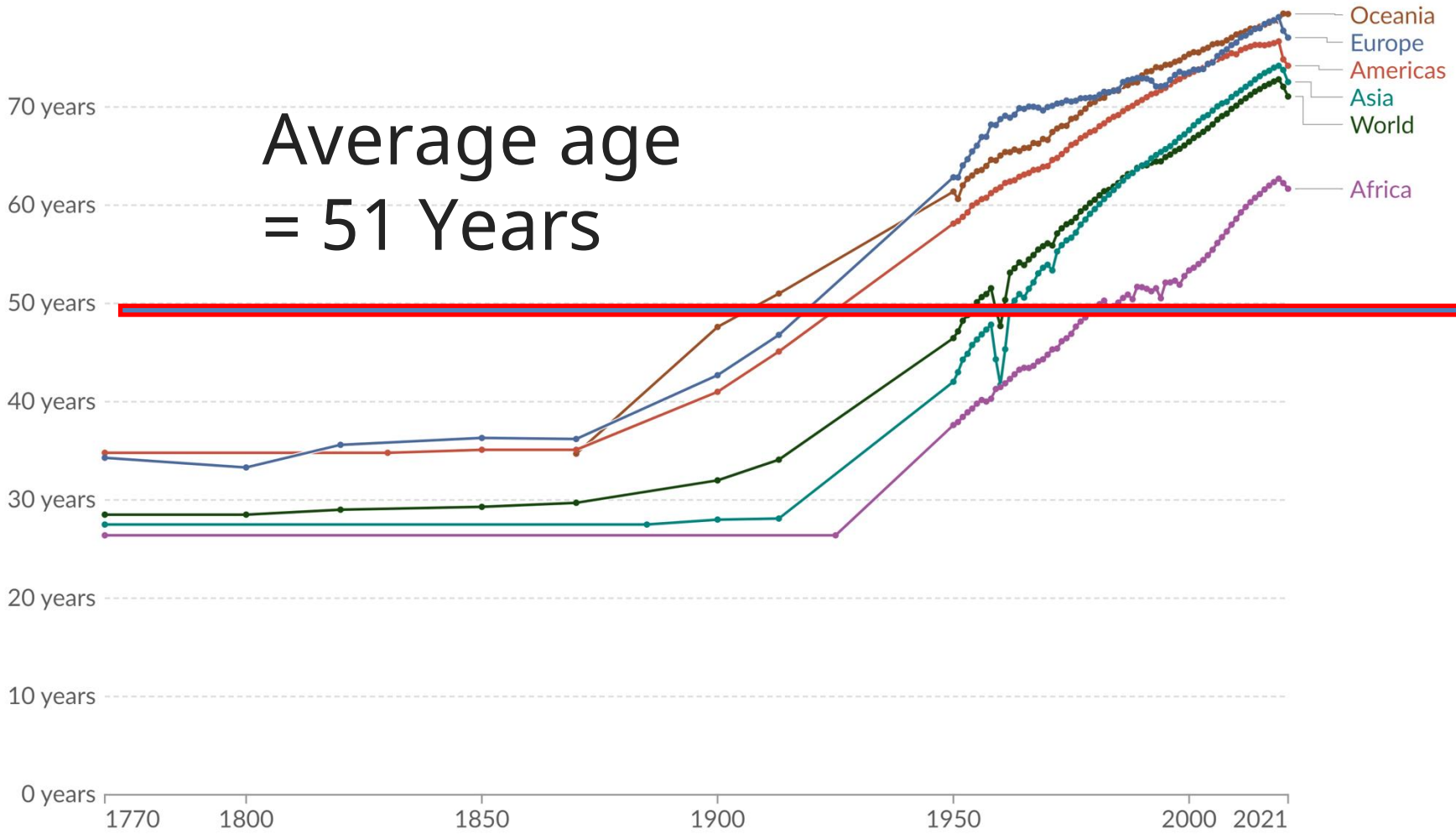
Conflict of interest: none

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

Life expectancy

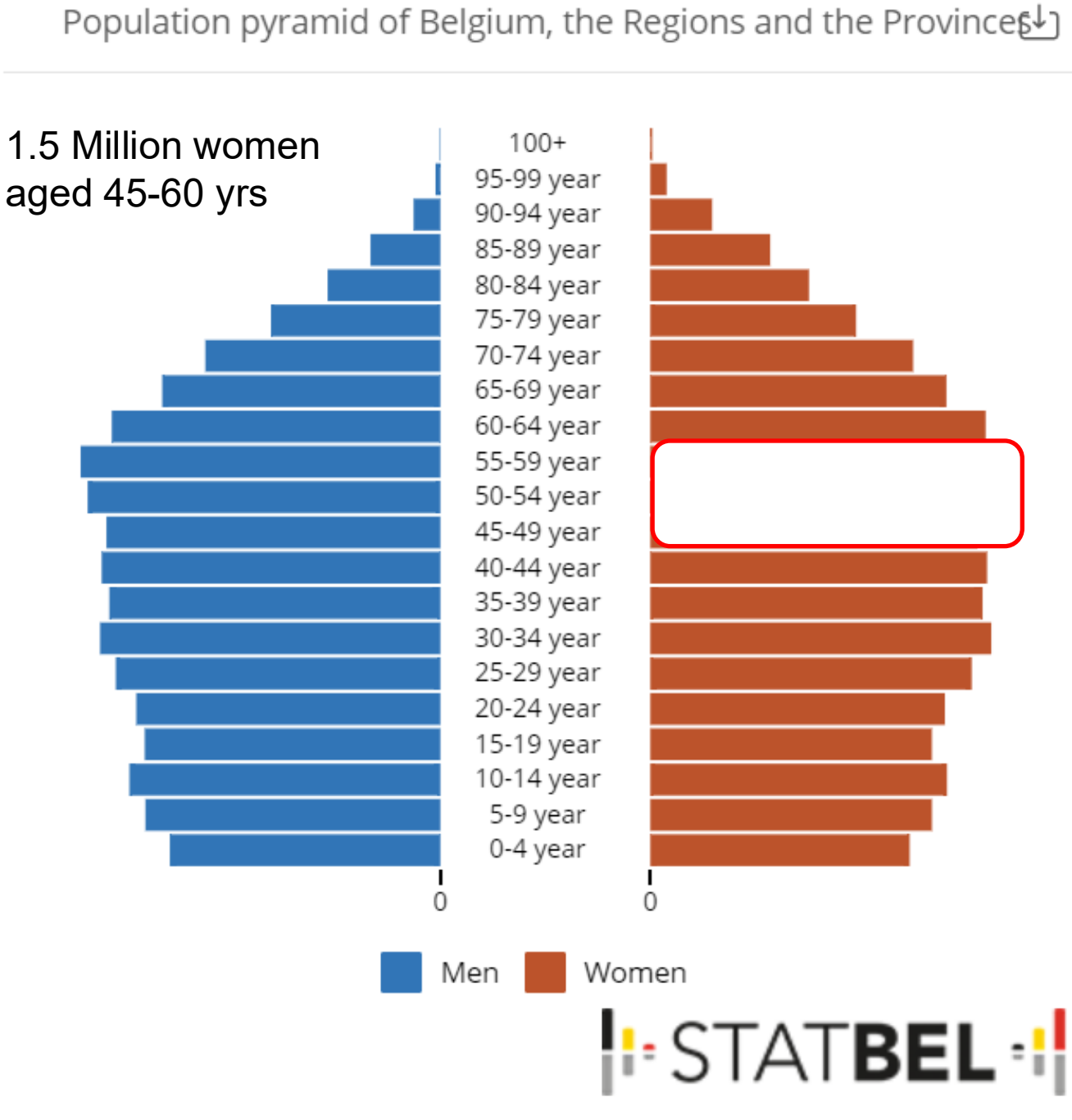
The period life expectancy[1] at birth, in a given year.



Data source: UN WPP (2022); HMD (2023); Zijdeman et al. (2015); Riley (2005)

OurWorldInData.org/life-expectancy | CC BY

1. Period life expectancy: Period life expectancy is a metric that summarizes death rates across all age groups in one particular year. For a given year, it represents the average lifespan for a hypothetical group of people, if they experienced the same age-specific death rates throughout their whole lives as the age-specific death rates seen in that particular year. Learn more in our article: "Life expectancy" – What does this actually mean?

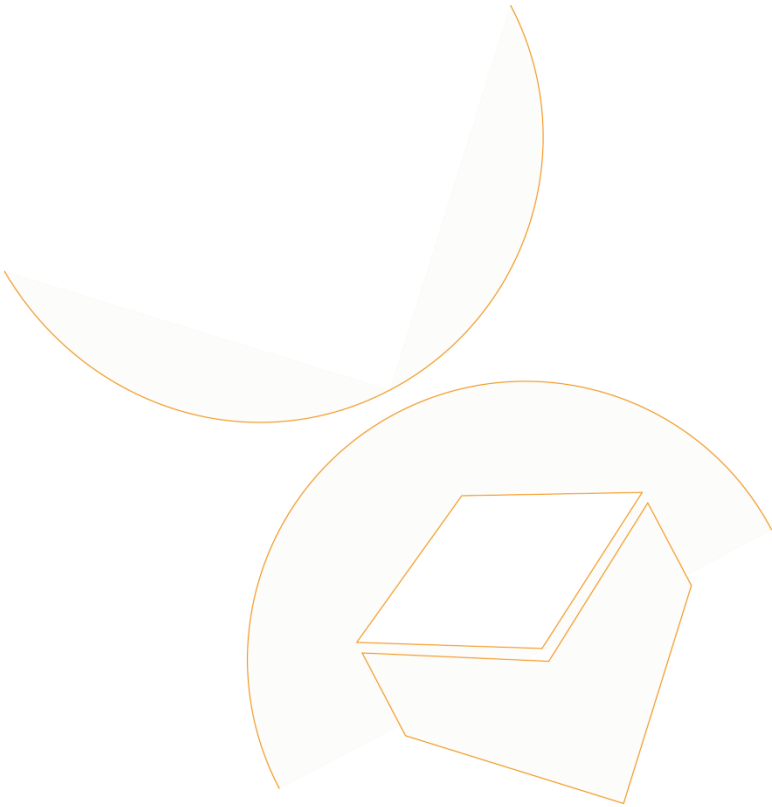


- 1.5 Million women aged 45-60 yrs

STATBEL

Agenda

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



Case 1
Perimenopausal woman

- Mrs A : 47 years
- G3 P2 A1 no particular history
- Symptoms: irregular menses, Menorrhagia , Mastodynia,
- FSH 50 UI/ L , E2 300 Pg/ml

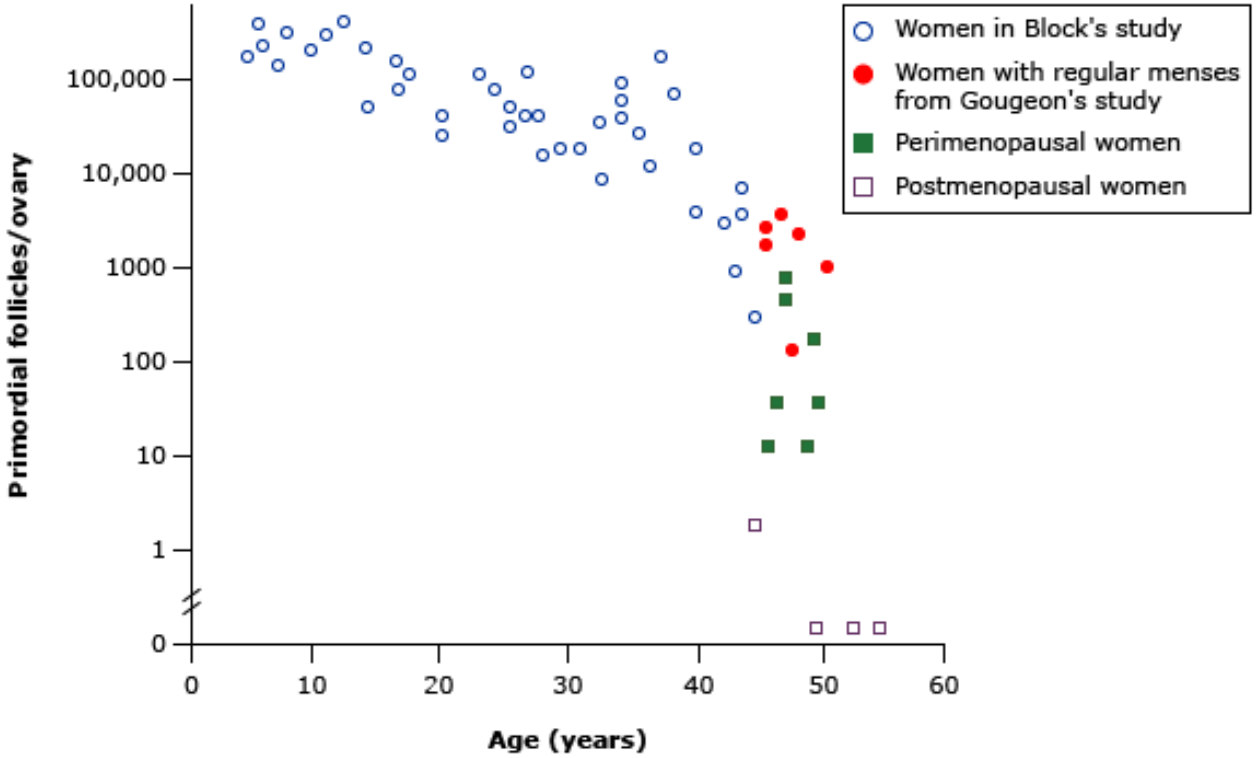
Case
Perimenopausal woman

- Mrs B : 49 years
- G3 P2 A1 no particular history
- Symptoms: irregular menses, Mood swings, Insomnia, Hot flushes
- FSH 50 UI/ L , E2 30 Pg/ml

Case
Perimenopausal woman

- Mrs C : 50 years
- G3 P2 A1 no particular history
- Symptoms: amenorrhea 6 months, Insomnia, Hot flushes , Arthralgia, Vaginal dryness
- FSH 80 UI/ L , E2 <30 Pg/ml

Declining follicle number with age

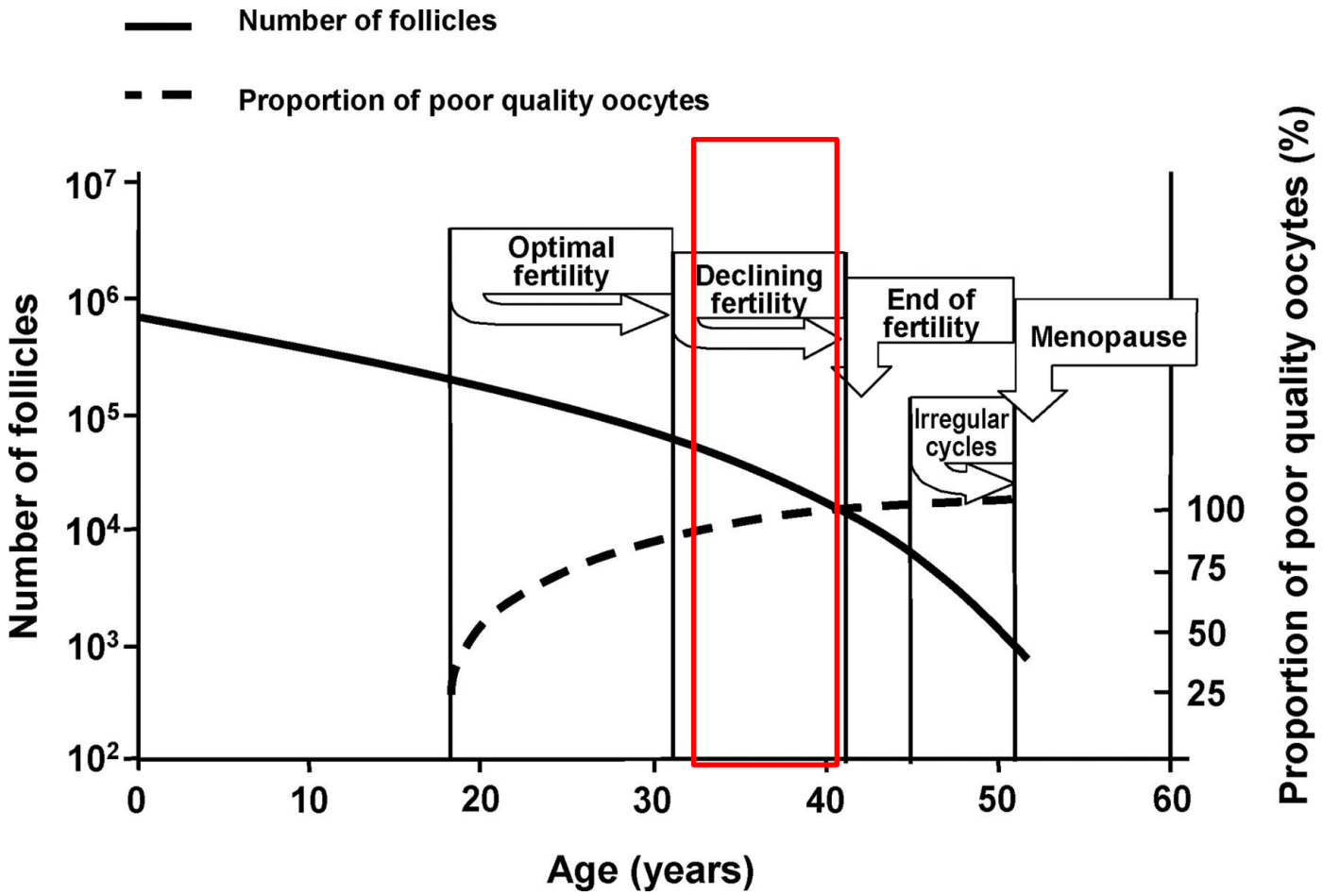


A comparison of the relationship between age and primordial follicle number in Block's study of 44 girls and women aged 7 to 44 years with that of Gougeon's study of women aged 45 to 55 years. Follicle depletion appears to accelerate in the decade preceding menopause.

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 lóvaire 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



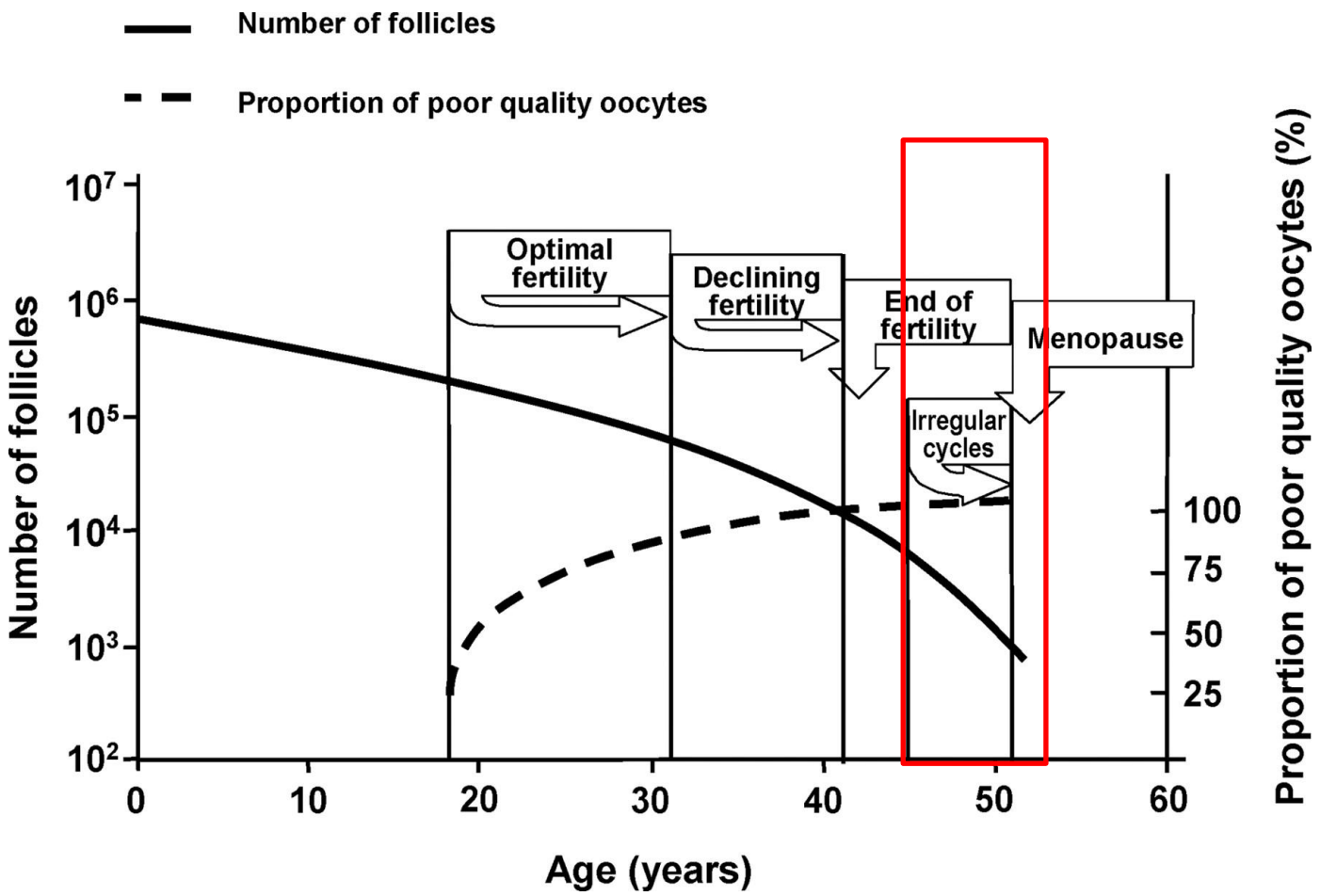
Broekmans, F. J. et al. Endocr Rev 2009;30:465-493

ENDOCRINE REVIEWS

Menopausal transition (perimenopause)

- ± 4 years (47 years) before the LMP
- Irregular menstrual cycles & marked hormonal fluctuations,
- HF, sleep disturbances, and mood symptoms
- Lipid changes and bone loss .
- "perimenopause" includes the menopausal transition years as well as the first year after the LMP.

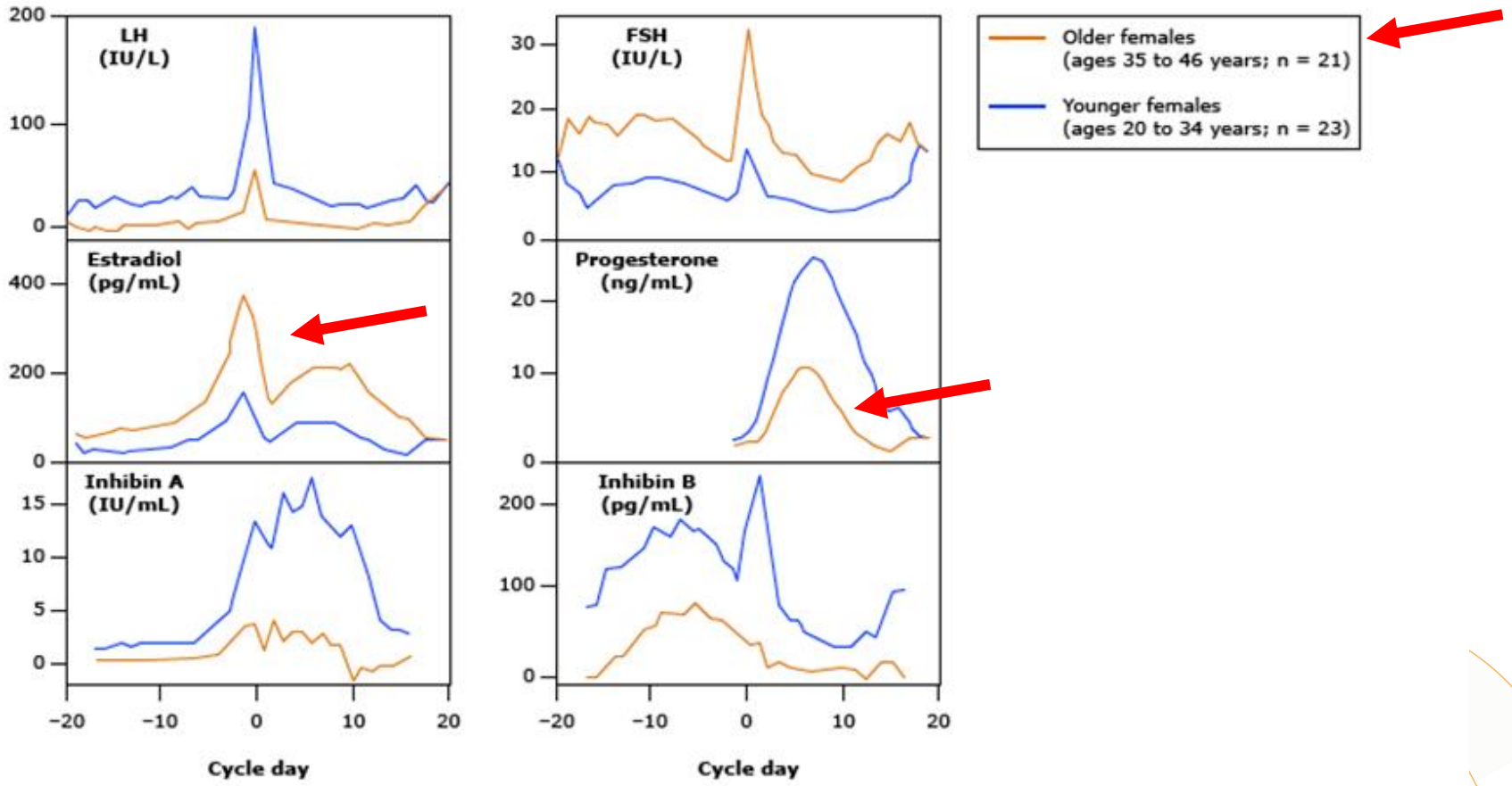
FIG. 1. Schematic representation of the number of primordial follicles present in the ovaries and the chromosomal quality of oocytes in relation to female age and corresponding reproductive events



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

ENDOCRINE REVIEWS

Hormone levels: Older and younger reproductive age

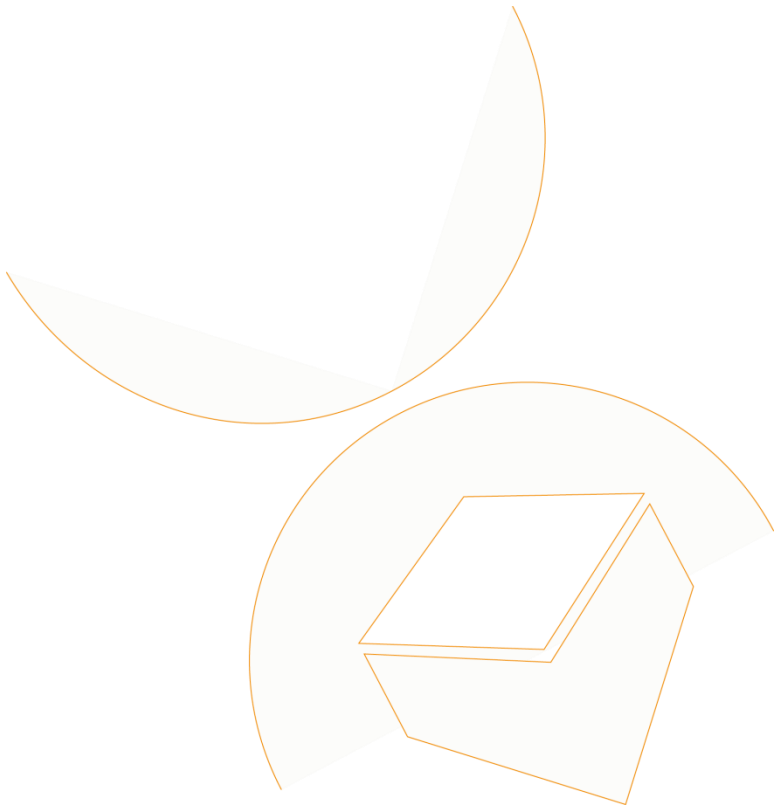


Mean daily levels of gonadotropins, sex steroids, and inhibins in older (ages 35 to 46 years; n = 21), shown in orange, and younger females (ages 20 to 34 years; n = 23), shown in blue.

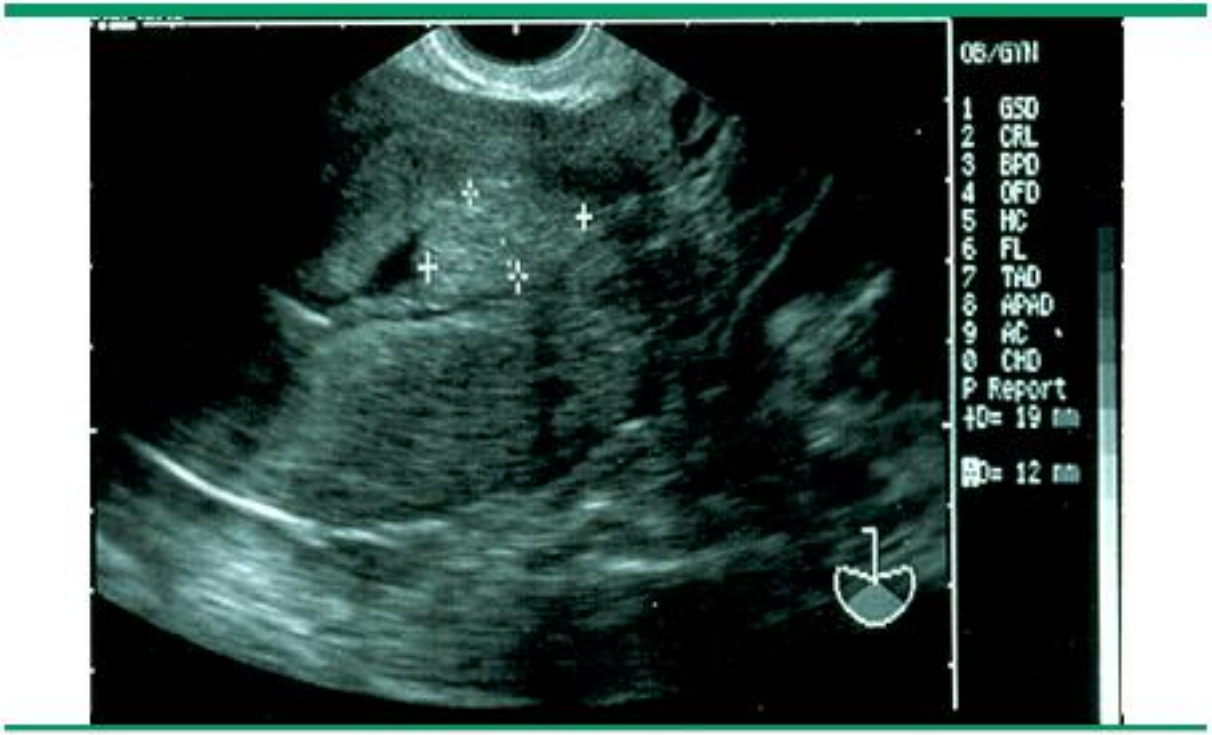
FSH: follicle-stimulating hormone; LH: luteinizing hormone.

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.

How would you treat her ?



Sonohysterogram of an endometrial polyp



An endometrial polyp measuring 1.9 x 1.2 cm is clearly visible. The stalk of the polyp can be seen extending toward the fundus.

Courtesy of Steven Goldstein, MD.

UpToDate®

How would you treat her ?

- Exclude pathology first Polype, myoma,adenomyosis...
  - US & PAP to Exclude endometrial, myometrial cervical pathology)
- Progesteron 14d/ month
- IUD LNG
- OC
- Prog Contraception
- Tranexamic acid (Exacyl)

Pregnancy risk

- Ages 45 - 49 years, not using contraception= 2 – 3%
- After 50: <1%

- 50-51 : discuss stopping the pill or MHT if necessary

Use of oral contraceptives during the menopausal transition

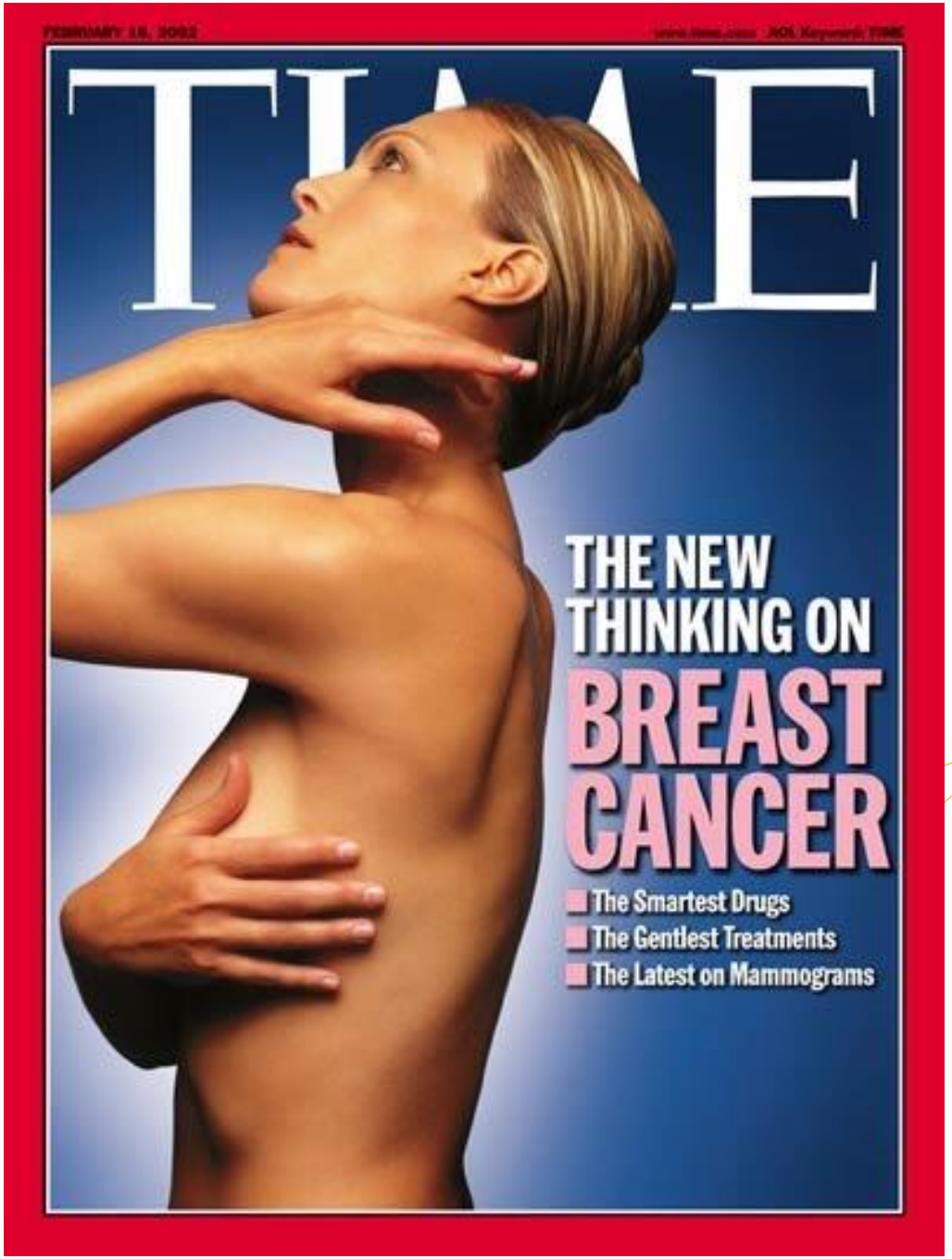
- Low-estrogen oral contraceptive (OC) : relief of menopausal symptoms, need contraception, and control of bleeding.
- OC containing 20 mcg EE / VE2/ Estetrol.
- OCs should be avoided in perimenopausal women with high thrombotic risk (obesity, smoking, hypertension, and migraine headaches.

Case
Perimenopausal woman

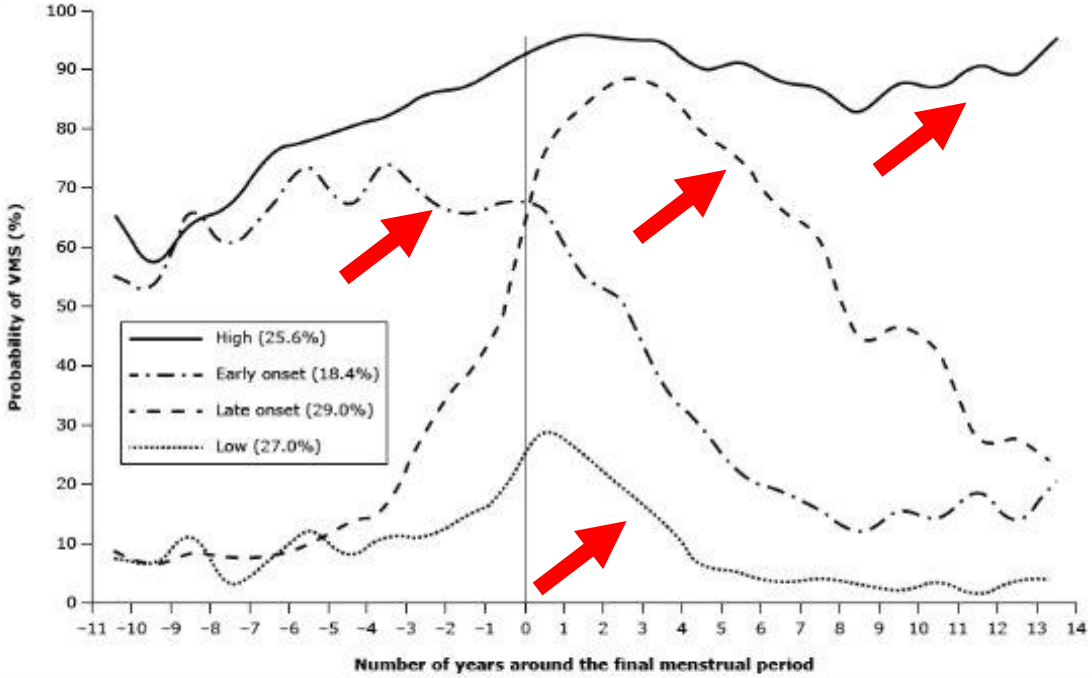
- Mrs C : 50 years
- G3 P2 A1 no particular history
- Symptoms: amenorrhea 6 months, Insomnia, Hot flushes , Arthralgia, Vaginal dryness
- FSH 80 UI/ L , E2 <30 Pg/ml

Women in late menopausal transition or early postmenopause

- Sequential continuous 17-beta E2 (transdermal or oral, + progesterone 200 mg or Didrogesterone 10 mg for 12-14days)
- Moderate symptoms: start with low dose E2
- 80-90% : monthly withdrawal bleeding
- Most women want to switch to continuous combined regimens to avoid bleeding.


FEBRUARY 18, 2002
TIME
THE NEW THINKING ON
BREAST CANCER
The Smartest Drugs
The Gentlest Treatments
The Latest on Mammograms

Trajectories of vasomotor symptoms over the menopause transition

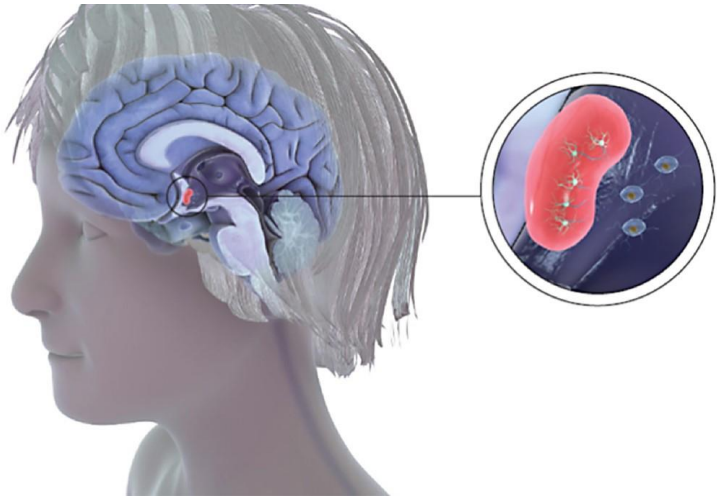


Probability of VMS represents the average observed probability of VMS at each time point within each trajectory subgroup. No factors were included in the model.

VMS: vasomotor symptoms.

KNDy neurons and thermoregulation

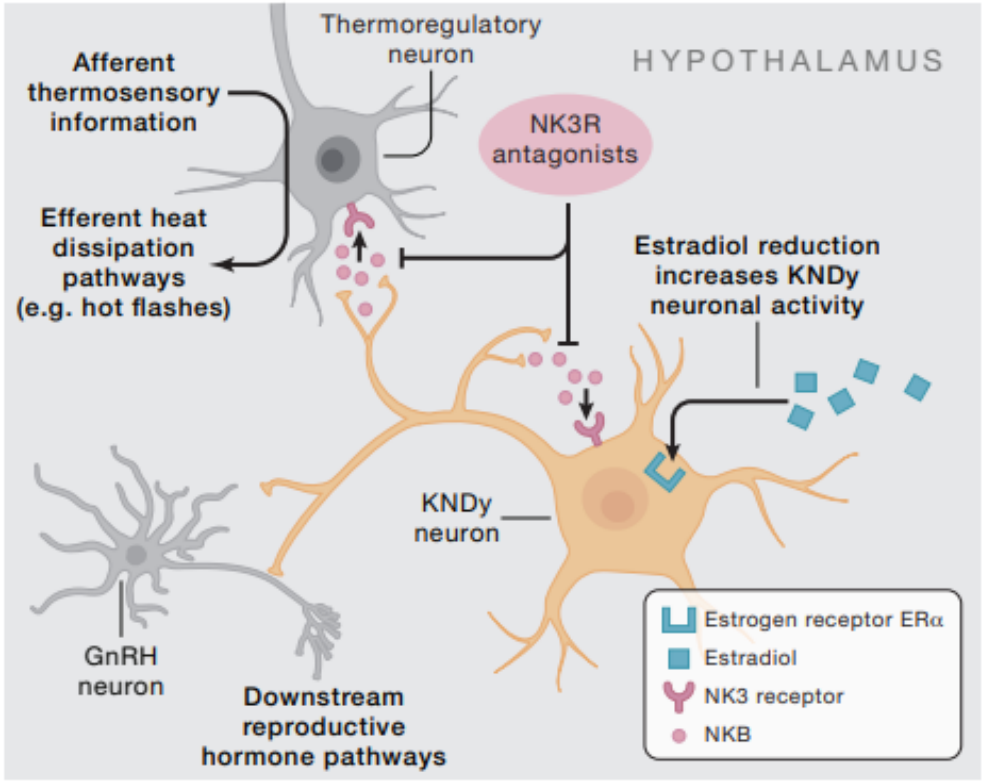
The thermoregulatory center is innervated by KNDy neurons that coordinate various functions, including thermoregulation[1,2]



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.

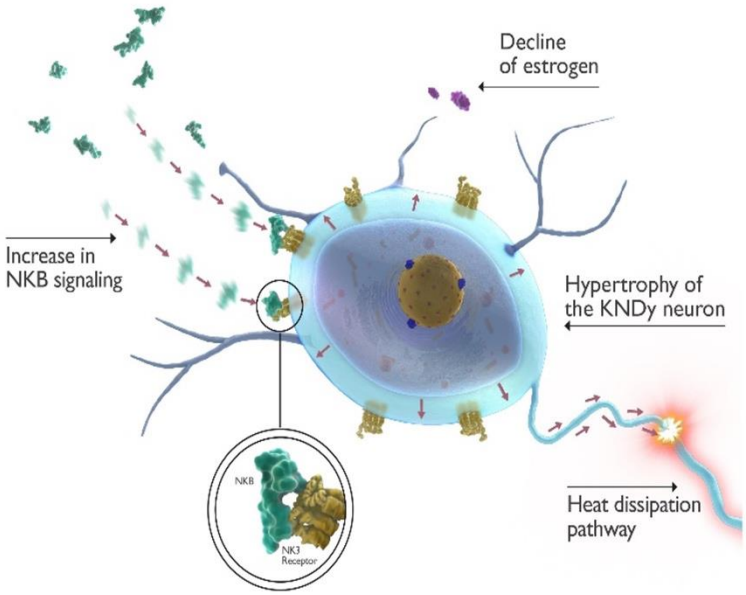
Neurokinin 3 receptor antagonism for menopausal hot flashes



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.

Comninos AN, Dhillo WS. Cell. 2023 Aug 3;186(16):3332-3332.e1. doi: 10.1016/j.cell.2023.07.011. PMID: 37541194.

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.

OPEN

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 (≈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–

JAMA Internal Medicine | Original Investigation | WOMEN'S HEALTH

Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause

A Phase 3 Randomized Clinical Trial

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Claudio N. Soares, MD, PhD, MBA; Rebecca C. Thurston, PhD; Maja Francuski, MD; Cecilia Caetano, MD; Kelly Genga, MD, PhD; Claudi
Nazanin Haseli Mashhadi, MSc; Kaisa Laapas, MSc; Susanne Parke, MD; Christian Seitz, MD, PhD, MSc; Judith Schwarz, PhD; Lineke Zu

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 resulting 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 symptomatology