Langdurige hormonale substitutie (HST) post-menopausal: bedenkingen.

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Waarom gevraagd als ‘contra’ stem ?

Gecommentarieerd Geneesmiddelen Repertorium (GGR) Hoofdstuk 6.3

- Ter preventie van osteoporose wordt niet aangeraden om postmenopauzale vrouwen langdurig te behandelen met oestrogenen (+/- progestagenen) gezien het risico van trombo-embolie en het (beperkte) risico van borstkanker met oestroprogestagenen en gezien andere behandelingen daarvoor beschikbaar zijn
- Oestroprogestagene associaties:
  De aanbeveling om de behandeling niet langer voort te zetten dan nodig is om de menopauzale klachten te behandelen, blijft voor de meeste vrouwen bestaan.

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- Langetermijntoediening van HST (gedurende 5 à 10 jaar) bij bepaalde risicogroepen voor andere doeleinden, zoals osteoporosepreventie, is van een heel andere orde. Zeker bij dit langetermijngebruik moeten de mogelijke voordelen goed afgewogen worden ten opzichte van de mogelijke risico’s, in samenspraak met de patiënte.

Uitgangspunten 1

Medische ethiek regel 1:
“niet schaden”

Uitgangspunt 2

- We hebben het NIET over vrouwen met zeer vroegtijdige menopauze
- We hebben het NIET over vrouwen die klachten hebben met impact op hun levenskwaliteit
  ➔ die vrouwen moeten een medicamenteus *aanbod* krijgen, waarbij hormonale substitutie (HST) het meest efficient is
  (zie GGR 6.3: “Subjectieve menopauzale klachten: oestrogenen zijn de meest werkzame behandeling.”)

  ➔de vrouw beslist geïnformeerd, de arts stelt regelmatig reëvaluatie voor

  (➔NB klachten 80% >< bij huisarts prevalentie 5% (bij ♀45-65j NHG)

- We hebben het hier WEL over het starten van langdurige (>5j minimaal) HST ter preventie van cardiovasculaire, osteoportische of cognitieve problemen bij (*alle) gezonde perimenopausale vrouwen*

Uitgangspunt 3

- Bij elke (medicamenteuze) behandeling belangrijk het *doel te bewaken*:

➔hier Symptomatisch versus Preventief

- *Symptomatisch* = enkel patiëntenagenda
- *Preventief* “medische agenda” lange termijn belangrijk

- Hier : als (als!) langetermijnbescherming echt nuttig is, dan heeft **elke** perimenopausale vrouw hier recht op en niet enkel wie klachten heeft: er is geen enkel argument dat doet vermoeden dat vrouwen met klachten meer risico hebben op bvb osteoprose of hartproblemen dan vrouwen zonder klachten

In goed gezelschap: wat zeggen richtlijnen vanuit organisaties die niet enkel over menopause gaan?

- NHG
- NICE
- USPSTF

- PRAC

NHG-Standaard “De overgang”

- https://richtlijnen.nhg.org/standaarden/de-overgang laatste aanpassing: juni 2022

Hormoontherapie vanwege vasomotorische klachten

- Evalueer na 3 maanden.
- …Streef naar gebruik < 5 jaar vanwege de geleidelijk oplopende risico’s
- (NB1
- met placebobehandeling: ongeveer 5 opvliegers/nachtelijke zweetaanvallen minder per dag
- met hormoontherapie: ongeveer 8 opvliegers/nachtelijke zweetaanvallen minder per dag)
- NB2 geen ander estrogeen dan estradiol vermeld
- NB3 *NHG* geen melding langetermijnbehandeling, *Farmacotherapeutisch Kompas*: Er is **geen** plaats meer voor oestrogenen bij de preventie van postmenopauzale *osteoporose* vanwege de ernstige langetermijnbijwerkingen zoals een verhoogd risico op het optreden van trombose en mammacarcinoom.

NICE Menopause: diagnosis and management

https://www.nice.org.uk/guidance/ng23 Last updated: 05 December 2019

Long-term benefits and risks of hormone replacement therapy:

Venous thromboembolism

- the risk of venous thromboembolism (VTE) is increased by *oral HRT* compared with baseline population risk
- the risk of VTE associated with HRT is greater for oral than transdermal preparations
- the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk.

Cardiovascular disease

- HRT with *oestrogen alone is* associated with no, or reduced, risk of coronary heart disease
- HRT with *oestrogen and progestogen* is associated with little or no increase in the risk of coronary heart disease.
- oral (not transdermal) *oestrogen* is associated with a small increase in the risk of stroke.

NICE

Diabetes

Explain to women that taking *HRT* (either orally or transdermally) is not associated with an increased risk of developing type 2 diabetes

Breast cancer

- HRT with oestrogen alone is associated with little or no change in the risk of breast cancer
- HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer
- any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.

NICE

Osteoporose

- risk of fragility fracture is decreased while taking *HRT* and that this benefit:
- is maintained during treatment but decreases once treatment stops
- may continue for longer in women who take HRT for longer.

Dementie

- the likelihood of *HRT* affecting their risk of dementia is unknown.

Spiersterkte

- HRT may improve muscle mass and strength

((Colonkanker

- Géén gegevens in NICE))

USPSTF (US Prevention Service TaskForce): Hormone Therapy in Postmenopausal Persons: Primary Prevention of Chronic Conditions (nov. 2022)

- https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/menopausal-hormone-therapy-preventive-medication

Postmenopausal persons	The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons.	**D**
Postmenopausal persons who have had a hysterectomy	The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal persons who have had a hysterectomy.	**D**

USPSTF (US Prevention Service TaskForce): Hormone Therapy in Postmenopausal Persons: Primary Prevention of Chronic Conditions (nov. 2022)

Coronary Heart Disease

- Observational evidence has suggested that there might be a protective effect of menopausal hormone therapy on coronary heart disease; however, the WHI and other trials of menopausal hormone therapy have not demonstrated such an effect.
  - A pooled analysis of 3 trials (n = 18,085) showed no significant difference in risk of coronary heart disease events in persons treated with *estrogen plus progestin* compared with placebo (2.8% vs 2.6%; relative risk [RR], 1.12 [95% CI, 0.94-1.33]) during a mean follow-up of 4 years.
  - Similarly, a pooled analysis of 3 trials (n = 11,310) found no significant difference in coronary events between persons taking *estrogen alone* and those taking placebo (RR, 0.95 [95% CI, 0.79-1.14]) during a mean follow-up of 4.1 years.8,9

USPSTF (US Prevention Service TaskForce)

Thromboembolic Events

- Five trials reported on risk of thromboembolism. In the WHI (n = 16,608), persons randomized to *estrogen plus progestin* had an increased risk of venous thrombosis (1.96% vs 0.94%; HR, 2.06 [95% CI, 1.57-2.70]), deep vein thrombosis (1.4% vs 0.8%; HR, 1.87 [95% CI, 1.37-2.54]), and pulmonary embolism (1.0% vs 0.5%; HR, 1.98 [95% CI, 1.36-2.87]) compared with those in the placebo group.[7,26] Other trials either reported few thromboembolic events or were consistent with the WHI findings. In the WHI (n = 10,739), persons randomized to *estrogen alone* had an increased risk of deep vein thrombosis (1.6% vs 1.0%; HR, 1.48 [95% CI, 1.06-2.07]);

Stroke

- The WHI found an increased risk of stroke with both *estrogen plus progestin* and *estrogen-alone* therapy. Stroke risk was significantly higher in persons randomized to estrogen plus progestin compared with those randomized to placebo (1.9% vs 1.3%; HR, 1.37 [95% CI, 1.07-1.76]).[7] Similarly, persons receiving estrogen alone had a statistically significant higher risk of stroke compared with those receiving placebo (3.2% vs 2.4%; HR, 1.35 [95% CI, 1.07-1.70]).[7] A smaller trial reported that stroke risk was similar in estrogen plus progestin and placebo groups, although the confidence interval was quite wide.

USPSTF (US Prevention Service TaskForce)

Breast Cancer

- In the WHI (n = 16,608), persons randomized to *estrogen plus progestin* had a significantly increased risk of invasive breast cancer compared with those taking placebo (2.4% vs 1.9%; hazard ratio [HR], 1.24 [95% CI, 1.01-1.53]),[7] which persisted during postintervention follow-up.[20] Other trials either reported few cases of breast cancer or were generally consistent with the WHI findings in direction of effect. In the WHI, during 20.3 years of follow-up, the point estimate of the risk of breast cancer mortality was higher for persons in the estrogen plus progestin group than those in the placebo group, although the difference did not reach statistical significance (HR, 1.35 [95% CI, 0.94-1.95]).[19]
  Four trials reported on the effects of *estrogen alone* on breast cancer; however, only the WHI followed participants for more than 3 years. At 20.7 years of follow-up, the WHI reported a lower risk of invasive breast cancer among persons assigned to estrogen alone compared with those assigned to placebo (HR, 0.78 [95% CI, 0.65-0.93]),[20] although the risk of breast cancer was not significantly lower during the study's 7.2-year intervention phase.[7,21] The other trials reported very few cases of breast cancer.[8,9] The WHI also reported on breast cancer mortality. At 20.7 years of follow-up, persons who received estrogen alone during the intervention phase had a lower risk of breast cancer mortality than those in the placebo group (HR, 0.60 [95% CI, 0.37-0.97]).

USPSTF (US Prevention Service TaskForce)

Diabetes

- Two trials reported on the effects of menopausal hormone therapy on incident diabetes. In the WHI (n = 15,874), fewer persons randomized to *estrogen plus progestin* reported a new diagnosis of diabetes compared with those taking placebo (HR, 0.81 [95% CI, 0.70-0.94]).[7,24] In the WHI (n = 9917), fewer persons taking *estrogen alone* reported a new diagnosis of diabetes compared with those taking placebo (1.34% annualized vs 1.55% annualized; HR, 0.86 [95% CI, 0.76-0.98]).[7]

Colorectal Cancer

- Four trials reported on the incidence of colorectal cancer in persons randomized to *estrogen plus progestin* therapy. In the WHI estrogen plus progestin trial (n = 16,608), persons randomized to estrogen plus progestin had a lower risk of colorectal cancer than those in the placebo group (0.59% vs 0.93%; HR, 0.62 [95% CI, 0.43-0.89]) over a median follow-up of 5.6 years.[7] The other trials either reported few cases of colorectal cancer or were generally consistent with the WHI findings in direction of effect. The WHI *estrogen-alone* trial (n = 10,739) reported no significant difference in the risk of colorectal cancer between persons randomized to estrogen alone and those taking placebo (1.2% vs 1.1%; HR, 1.15 [95% CI, 0.81-1.64]) during 7.2 years.

USPSTF (US Prevention Service TaskForce)

Fractures

- Five trials reported on fracture risk in persons randomized to *estrogen plus progestin* compared with placebo. A pooled analysis of these trials (n = 20,499) found a statistically significant reduction of fractures in persons taking estrogen plus progestin (8.7% vs 10.9%; RR, 0.79 [95% CI, 0.66-0.94]).[8,9]
- The WHI (n = 10,739) also found a lower risk of total fractures in persons taking *estrogen alone* compared with placebo during the intervention phase (1.53% annualized vs 2.14% annualized; HR, 0.72 [95% CI, 0.64-0.80]),[7] which persisted during 4.3 years of postintervention follow-up.[22]

Dementia

- The Women's Health Initiative Memory Study was a substudy of the WHI, evaluating the risk of dementia in persons randomized to estrogen plus progestin or estrogen alone compared with placebo. That study found that persons randomized to *estrogen plus progestin* (n = 4523) had a higher risk of probable dementia than those taking placebo (1.8% vs 0.9%; HR, 2.05 [95% CI, 1.21-3.48]).[28]
  No significant increase in risk of probable dementia was found in persons taking *estrogen alone* (n = 2947).

USPSTF (US Prevention Service TaskForce)

Gallbladder Disease

- Two trials reported on the risk of gallbladder disease in persons taking menopausal hormone therapy. The WHI (n = 14,203) reported a significantly higher risk of gallbladder disease in persons randomized to estrogen plus progestin treatment compared with those randomized to placebo (1.31% annualized vs 0.84% annualized; HR, 1.57 [95% CI, 1.36-1.80]) and in persons randomized to *estrogen alone* (n = 8376; 1.64% annualized vs 1.06% annualized; HR, 1.55 [95% CI, 1.34-1.79]).[7]

Urinary Incontinence

- Two trials reported on incident urinary incontinence (self-reported) in persons taking *estrogen plus progestin*; both found increased risk. In the WHI (n = 10,073), 16.6% (annualized) of persons taking estrogen plus progestin reported incident incontinence after 1 year of treatment, compared with 11.1% (annualized) of those taking placebo (HR, 1.49 [95% CI, 1.36-1.63]).[7] A smaller trial also reported increased risk.[31] Similarly, in persons randomized to *estrogen alone*, the WHI found a higher risk of urinary incontinence at 1 year (22.6% annualized vs 14.0% annualized; HR, 1.61 [95% CI, 1.46-1.79]) and 6.6 years after stopping treatment (28.6% vs 23.1%; HR, 1.24 [95% CI, 1.13-1.35]).[7]

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All-Cause Mortality

- A pooled analysis of 3 trials (n = 19,580) showed no significant difference in all-cause mortality between persons taking *estrogen and progestin* therapy and those taking placebo (RR, 1.01 [95% CI, 0.88-1.16]) during 3.2 to 5.6 years of follow-up.
- Similarly, a pooled analysis of 3 trials (n = 11,587) showed no significant difference in all-cause mortality between persons receiving *estrogen alone* and those receiving placebo (RR, 1.04 [95% CI, 0.89-1.21]) during a mean follow-up of 7.1 years.[8,9]

Europese Geneesmiddelenbewakingscomité (PRAC) van het Europees Geneesmiddelenbureau (EMA) (Folia aug 2020)

- Mei 2020 update van de Samenvatting van de Kenmerken van het Product (SKP) en de bijsluiter van alle geneesmiddelen die als HST gebruikt worden.
- Voor **HST op basis van oestrogeen + progestageen:**
  - *verscherping van de waarschuwingen over het verhoogde risico van borstkanker*;
  - toelichting over de toename van het risico met de duur van de behandeling (het risico treedt op na ongeveer 3 jaar behandeling) en over het aanhouden van het risico na stopzetting van de HST (risico dat 10 jaar of langer kan aanhouden voor een behandeling van meer dan 5 jaar).
- Voor **HST op basis van oestrogeen alleen:**
  - *verscherping van de waarschuwingen over het verhoogde risico van borstkanker; de toename is geringer dan met HST op basis van oestrogeen + progestageen*;
  - toelichting over de toename van het risico met de duur van de behandeling (het risico treedt op na ongeveer 3 jaar behandeling) en over het aanhouden van het risico na stopzetting van de HST (risico dat 10 jaar of langer kan aanhouden voor een behandeling van meer dan 5 jaar).

Balans

Per 1000 vrouwen die oestrogenen + progesteron nemen gedurende 5-6 jaar (vergeleken met 1000 vrouwen die placebo nemen):

MINDER	MEER
Botbreuken: **23**	Incontinentie: **56**
Diabetes: **9**	Galblaasproblemen: **26**
Darmkanker: **3** (niet voor OE alleen)	Bloedklonters: **12** (niet voor pleisters)
	Dementie: **8**
	Borstkanker: **5** (niet voor OE alleen)
	Beroerte: **5**
	Sterfte door longkanker: **4** (niet voor OE alleen)

Bron: USPSTF , voor longkankersterfte: cochrane

Conclusie

- Een vrouw met beperkte of afwezige perimenopausale klachten is een gezond individu.

- Geneesmiddelen toedienen (gedurende jaren) bij gezonde individuen is ethisch maar aanvaardbaar als heel duidelijk bewezen is dat de baten opwegen tegen de risico's, de kosten en het medicaliseren van een fysiologische toestand
- We hebben nauwelijks argumenten om HST te ontzeggen aan wie klachten heeft, ook langdurig
- Wij hebben onvoldoende argumenten om HST langdurig toe te dienen aan vrouwen die geen klachten hebben