# Hormonska terapija u menopauzi

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# Indikacije

Vazomotorni simptomi-valunzi, znojenja (oko 75% žena) počevši 11 godina pre poslednje menstruacije i 11-12 god posle poslednje menstruacije (Woods and Mitchell, 2005; Politi, 2008; Freeman, 2011)

Loš san, umor, depresivni simptomi (Kravitz and Joffe, 2011); Genazzani, 2021.

30-40% žena navodi da im menopauzalni simptomi smanjuju radnu sposobnost (Griffits, 2016)

# Kardiovaskulani sistem i metabolizam

HT utiče na arterije i vene tako što utiče na koagulaciju, endotelnu funkciju i metabolizam glukoze i lipida (Genazzani, 2021)

WHI studija je prekinuta 2002 g zbog povećanih kardiovaskularnih komplikacija

Pacijenti su praćeni 13 i 18 godina posle prekida studije
Kompleksan odnos izmedju HT i kardiovaskularnih komplikacija

# Starost žena i vreme počinjanja terapije

Žene 50-59 godina su imale manji rizik za kardiovaskulaene komplikacije u odnosu na kontrolnu placebo grupu HR 0,93

60-69 god-HR 0,98

70-79 g HR 1,26.
*CEE/MPA*

Žene koje su  počele HT u roku od 10 godina od poslednje menstruacije (PM) imaju manji rizik od žena koje su počele HT 10 god. posle PM (Rossouw, 2007)

# Vreme počinjanja terapije

Nedostatak estrogena dovodi do promena u endotelu i povićenog rizika za KVB

Raniji početak terapije smanjuje rizik za KVB (Tumikoski, 2014)

ELITE studija < 6 god od PM u odnosu na > 10 g od PM  643 pac.

Grupa <6 god.-smanjeni rizik od ateroskleroze (merena zadebljanje karotidne arterije)

Grupa > 10 g nema razlike u odnosu na kontrolnu grupu (Hodis, 2016).

# Način administracije/tip

Hepaticni faktori koagulacije su značajno manje angažovani pri transdermalnoj i vaginalnoj primeni estrogena
Transdermalni put je više fiziološći jer se oslobadja direktno u krvotok
(Canonico, 2014)

CEE ima veci rizik za VTE od estradiola, preko 80 000 pac/kontrolna grupa preko 300 000 (Vinogradova, 2019)

# Progesteron/gestagen koji se koristi u kombinaciji

WHI studija: samo CEE manji rizik od KVB u odnosu na kombinaciju sa medroksiprogesteron acetatom (MPA) (Rossouw, 2007)

Nomegestrol acetat i promegestone povišeni rizik za VTE (Vinogradova) kao i MPA (Sweetland, 2012)

Progesteron i didrogesteron neutralni ( Vinogradova, 2019)

**Table I** **Therapeutic ranges for estradiol and progesterone hormone therapy in postmenopausal women.**

| Progestogen | Daily dose (mg) | | | |
|---|---|---|---|---|
| | Oral | | Intrauterine/implants | Vaginal |
| | Sequential | Continuous | | |
| Micronized progesterone | 200–300 | 100 | – | 100–200 |
| Dydrogesterone | 10–20 | 2.5–10 | – | – |
| Medroxyprogesterone acetate | 5–10 | 2.5 | – | – |
| Nomegestrol acetate | 5–10 | 2.5 | – | – |
| Norethisterone acetate | 1–2 | 0.5–1.0 | – | – |
| Dienogest | 3–4 | – | – | – |
| Levonorgestrel | – | – | 0.075–0.15 | – |
| Norgestimate | – | – | 0.09 | – |
| Drospirenone | – | 2 | – | – |

(-), not determined.

Genazzini, 2021

# Doza estrogena

Rizik za ishemične bolesti manji < 1 mg estradiola u odnosu na > 1 mg kod oralne upotrebe

Rizik nije povećan kod transdermalne upotrebe veće doze

15000 pacijenata hospitalozovanih zbog ishemičnih bolesti (Canonico, 2016)

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# Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy

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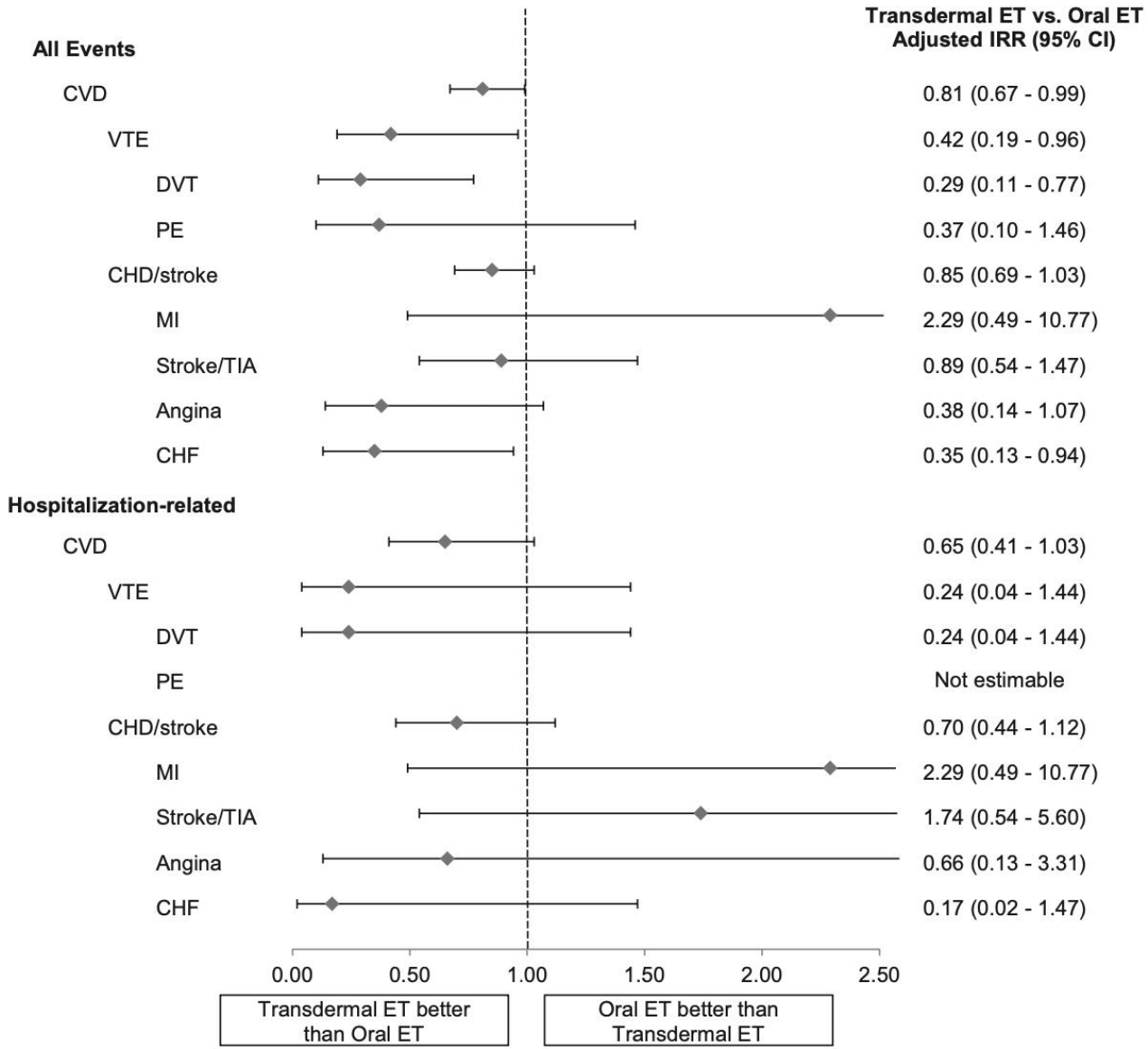
2551 pac. u obe grupe
Period od 10 godina

## *VTE AND CVD IN TRANSDERMAL VERSUS ORAL ET USERS*




Notes:
CVD: cardiovascular disease; ET: estrogen therapy; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CHD: coronary heart disease; MI: myocardial infarction; TIA: transient ischemic attack; CHF: congestive heart failure; IRR: incidence rate ratio.

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# Postmenopausal Hormone Therapy and Risk of Stroke

## Impact of the Route of Estrogen Administration and Type of Progestogen

Marianne Canonico, PhD; Laure Carcaillon, PhD; Geneviève Plu-Bureau, MD, PhD; Emmanuel Oger, MD, PhD; Archana Singh-Manoux, PhD; Pascale Tubert-Bitter, PhD; Alexis Elbaz, MD, PhD; Pierre-Yves Scarabin, MD, MSc

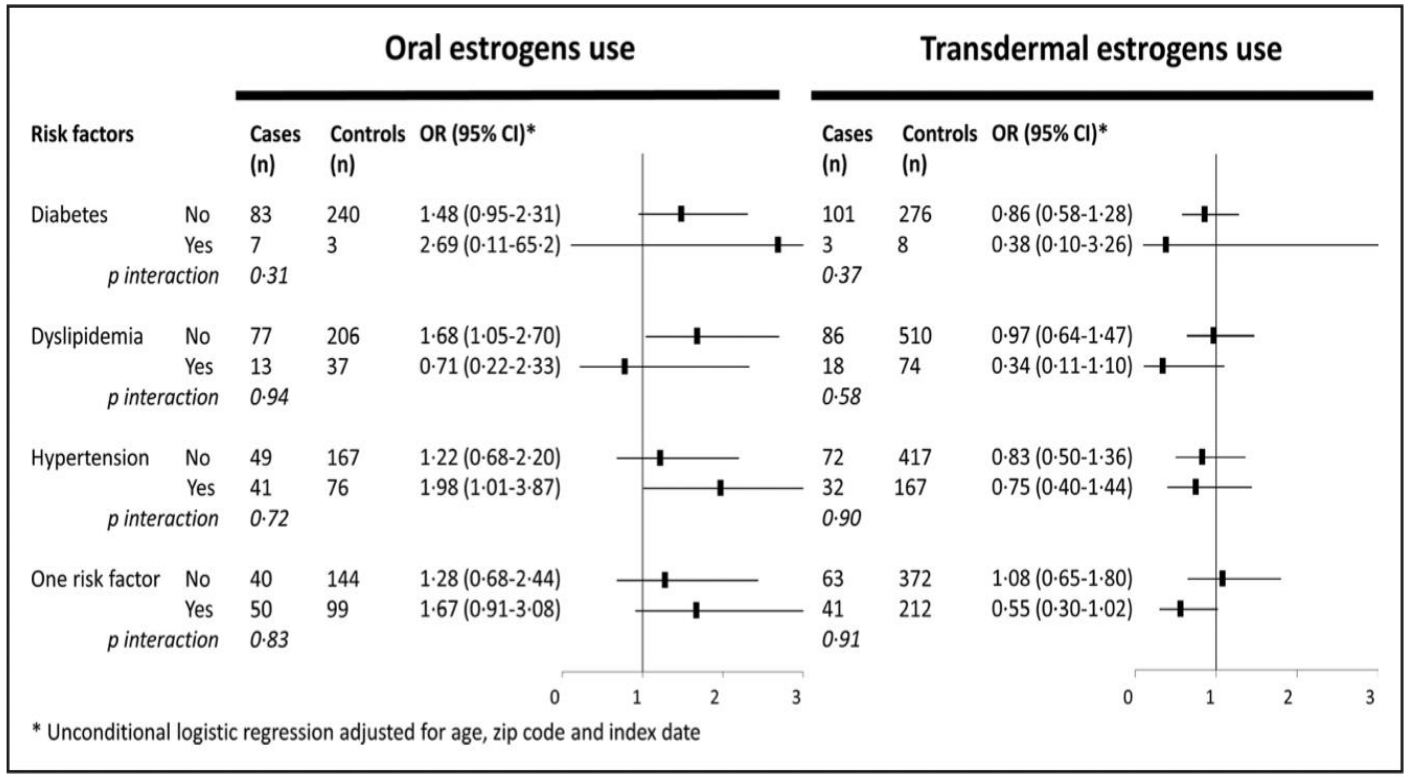


**Figure 3.** Odds ratios of ischemic stroke according to route of estrogen administration by cardiovascular risk factors. *Unconditional logistic regression adjusted for age, zip code, and index date. CI indicates confidence interval; and OR, odds ratio.

# Telesna masa, distribucija masnog tkiva

Menopauza povećava visceralne masti (Genazzani, 2006)

HT smanjuje visceralne masti (Jensen, 2013)

Smanjenje telesne mase i obima stomaka (Margolis, 2004; Kanaya, 2004)

Smanjuje rizik za diabetes tipa 2, ali smanjenje rizika nestaje posle prestanka HT (Manson, 2013)

# Centralni nervni sistem

HT efikasna u tretmanu vazomotornih simptoma , kombinacija estrogen-progesteron efikasnija u nekima studijama (Maclennan, 2004)

HT poboljšava kognitivnu funkciju, naročito kod hiruški izazvane menopauze (Vergese, 2000)

Žene koje su uzimale HT do 5 godina imaju 30 % manji rizik za Alzheimerovu bolest (Shao, 2012)

HT poboljsava san i kvalitet sna (Hays, 2003), prirodni progesteron ima bolji efekat na san od MPA-manja studija (Gambacciani, 2005)

# Koža

## Does hormone therapy improve age-related skin changes in postmenopausal women?

### A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women

Tania J. Phillips, MD, FRCPC,[a,c] James Symons, PhD,[b] Sandeep Menon, MPH,[a] and the HT Study Group*
*Boston and Chestnut Hill, Massachusetts; and Ann Arbor, Michigan*

Bolji rezultati ako se počne u perimenopauzi

7

## Skin connective tissue and ageing

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Estrogen povećava kolagen, debjlinu i elastičnost kože, smanjuje suvoću kože

# Mišićno-koštani sistem

HT smanjuje rizik za prelom kuka 34%, i 24 % za sve prelome (WHI, 2002)

Povećava gustinu kostiju i smanjuje osteoporozu (Manson, 2013)

Manje bolova u zglobovima (WHI, 2002)

# Urogenitalni sistem

Vaginalni estrogen smanjuje vaginalnu suvoću, povećava elastičnost vagine, smanjuje rizik za urinarne infekcije, smanjuje dispareuniju i pozitivno utiče na seksualnost ( Genazzini, 2021)

Estradiol ili estriol, manje potentan

# HT i karcinom

Karcinom dojke (najčešći razlog što se ne počinje ili prestaje HT)

WHI studija pokazala poviđen rizik kod CEE i MPA, bez povićenog rizika samo sa CEE
Nije bio povišeni rizik za žene koje nisu koristile HT pre ulaska u studiju (WHI, 2002)

Samo estrogen kod histerektomiziranih žena ne povećava rizik za karcinom dojke posle 15 g HT (Chen, 2006)

Povišen rizik posle 5-10 godina (Anderson, 2006)

Povišena smrtnost posle 15 god HT (Holm, 2019)

Smrtnost je smanjena hod žena koje koriste HT ( Mikkola, 2016)

Nema razlike izmedju oralne i dermalne primene (Farell, 2016)

Tip gestagena: MPA daje povišeni rizik (WHI, 2002), didrogesteron smanjuje rizik (Chen, 2006)

# HT i karcinom

BRCA 1 i 2

HT posle odstranjivanja jajnika?

Observacione studije nisu pokazale povišen rizik, narocito kod žena koje nisu imale karcinom dojke (Rebeck, 2005)

Samo estrogen se preporučuje kod BRCA (Gordhandas, 2019), hormonska spirala ili gestageni 3-4 x godišnje (Kotsopulos, 2018)

# Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies

*Collaborative Group on Epidemiological Studies of Ovarian Cancer**

## Summary

**Background** Half the epidemiological studies with information about menopausal hormone therapy and ovarian cancer risk remain unpublished, and some retrospective studies could have been biased by selective participation or recall. We aimed to assess with minimal bias the effects of hormone therapy on ovarian cancer risk.

*Lancet* 2015; 385: 1835–42

Published Online
February 13, 2015

**Interpretation** The increased risk may well be largely or wholly causal; if it is, women who use hormone therapy for 5 years from around age 50 years have about one extra ovarian cancer per 1000 users and, if its prognosis is typical, about one extra ovarian cancer death per 1700 users.

Karcinom jajnika: 1 više na 8300 žena sa HT (Morch, 2009)

# HT i karcinom

Smanjeni rizik za karcinom endometriuma sa kombinovanom terapijom (Chlebowski, 2015)

Kod gojaznih žena je smanjen rizik ako se kontinuirano kosriste gestageni (Beral, 2005)

HT smanjuje rizik za kolorektalni karcinom (WHI 2002; Morois, 2012)

# Procena rizika

Absolutne kontraindikacije:

Estrogen zavisni tumori
Aktivna bolest jetre
Kardiovaskularne bolesti
VTE, nasledne i stečene trombifilije
Ekstremna gojaznost
Ishemične bolesti
Porfiria
Hipertrigliceridemija

Migrena, eventualno pogorsanje (kontinuirani progesteron)
Endometrioza
Psihijatrijske bolest

# Trajanje HT

Početi do 10 godina od poslednje menstruacije, sto ranije manji rizik za kardiovaskularne bolesti

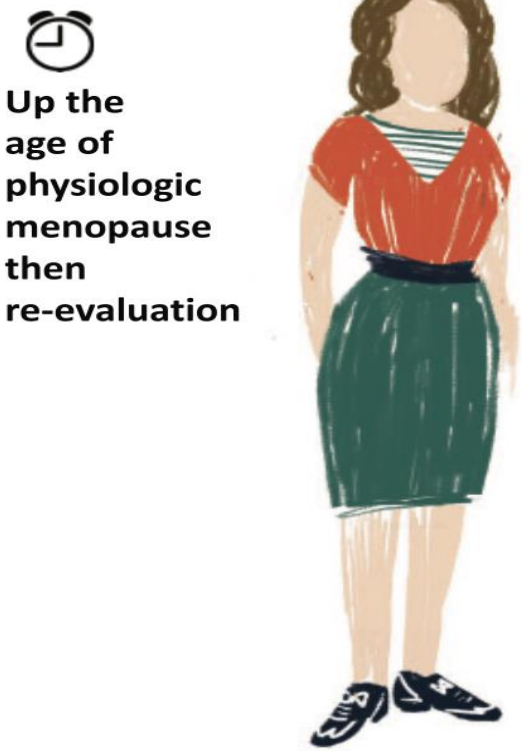
Nema konsenzusa kada prestati, procena koristi i rizika
(npr VMS prestaju 7,4 god od poslednje menstruacije)

Godisnja kontrola

Prestati postepeno, rizik od pogoršanja depresije, ishemičnih bolesti, KVB
(Genazzini, 2021)

Informisati pacijenta o svim eventalnim rizicima, gestagen/progesteron

**Premature menopause**



**Up the age of physiologic menopause then re-evaluation**

***ESTROPROGESTINS:***

**ORAL**

***Contraception need***

- 17βE2+ NOMAC
- E2V+Dienogest

***Non contraception need***

***Sequential***

- E2 2 mg+ Dydrogesterone 10 mg
- CEE 0.625 + Progesterone 100-200 mg

**TRANSCUTANEOUS (Gel or Spray)**

***Continuous***

- 17 βE2 1,5-2 mg

**plus continuous or cyclical**

Micronized Progesterone oral or vaginal 100- 200 mg
or Dydrogesterone 10 mg oral

**TRANSDERMAL**

- 17βE2 50 µg +LNG 150 µg
- 17βE2 50 µg + NETA 250 µg

- 17βE2 50-100 µg

**plus continuous or cyclical**

Micronized Progesterone oral or vaginal 100 or 200 mg
or Dydrogesterone 10 mg oral
or 20 µg LNG-IUD

***TOPICAL THERAPIES:***

- Estradiol cps vg 10 µg
- Estradiol 7,5 µg/24 h, vaginal ring
- Estriol cream 500 µg/day
- Estriol gel 50 µg/day
- Promestriene cps 10 mg
- DHEA cps 6.5 mg
- Testosterone 1% cream (0.1 ml)

***ANDROGENS:***

- DHEA 10-25 mg oral*

*in case Female Sexual Dysfunction and low DHEA-S

**Figure 6 Recommended hormone therapy regimens for women who experience primary ovarian insufficiency.** Patients who experience premature menopause can take several commercially available hormone therapy (HT) up to the age of physiologic menopause and then they should be re-evaluated clinically. Oral contraception or sequential estroprogestins compounds, transcutaneous or transdermal continuous estrogens plus continuous or cyclical progestogens compounds or levonorgestrel (LNG)-IUD, topical therapies and different doses of oral DHEA should be recommended for these women. DHEA, dehydroepiandrosterone.

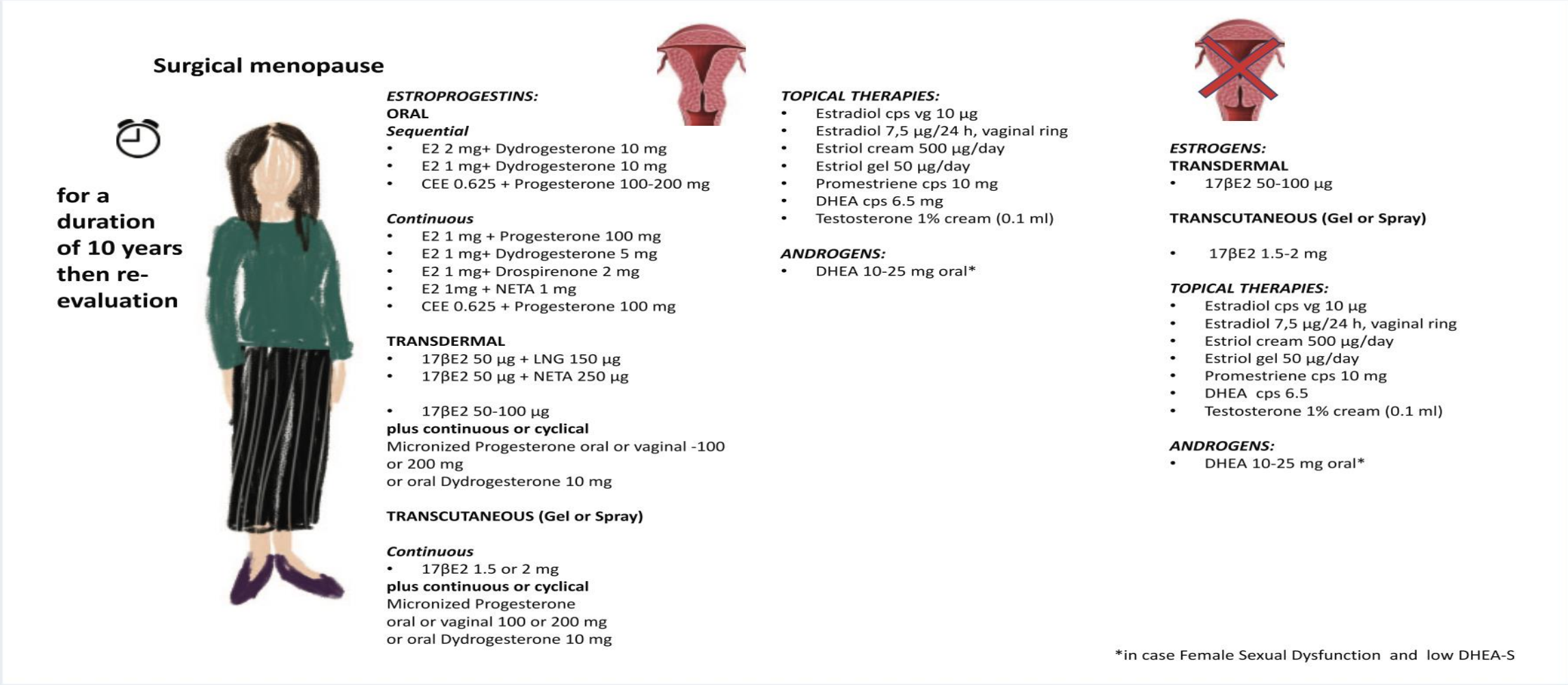
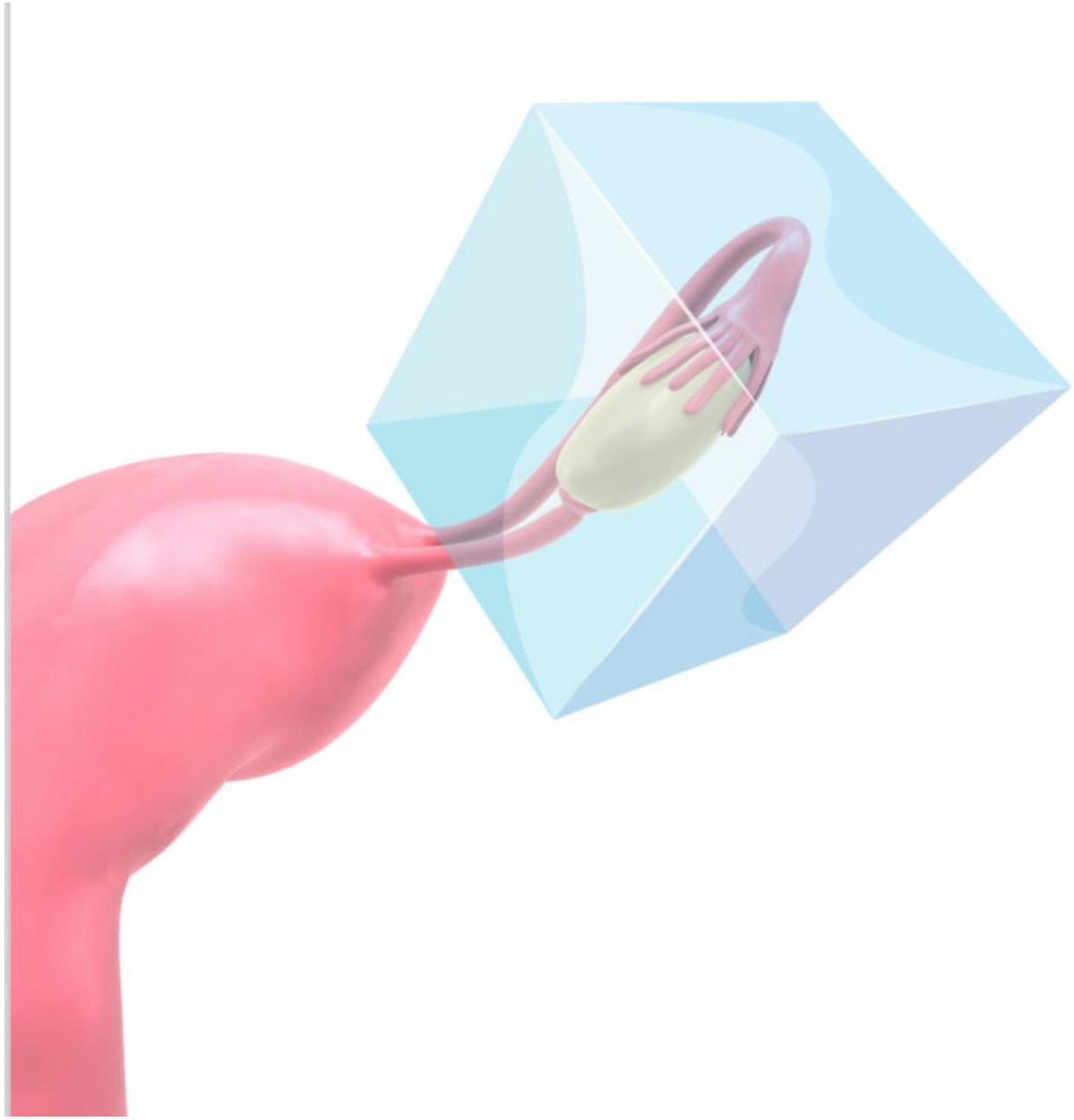



**Figure 5 Recommended hormone therapy regimens for women who undergo surgical menopause.** Nonhysterectomized patients can take several commercially available hormone therapy (HT). Sequential or continuous oral, transderamal and transcutaneous estroprogestins compounds, topical therapies and different doses of oral DHEA should be recommended for climacteric symptoms of these women. For hysterectomized women, continuous transderamal and transcutaneous estrogens, topical therapies and different doses of oral DHEA should be recommended. Both hysterectomized and nonhysterectomized patients can take the aforementioned therapies according to their preferences and needs for 10 years and then they should be re-evaluated clinically. DHEA, dehydroepiandrosterone.



Hvala na pažnji