Female hormone therapy:

Special Cases

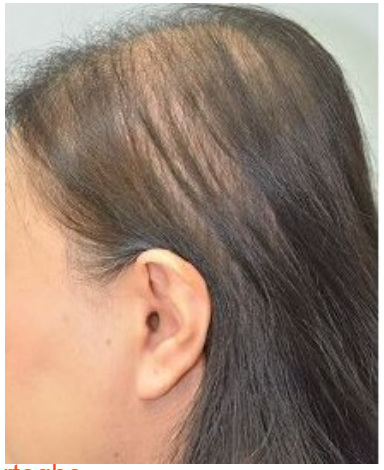
Female pattern hair loss

⇒ Patient needs more estrogen,

⇒ Possibly also topical estrogen cream

Female pattern hair loss in women

Treat the CAUSE(S)



ADD

- Transdermal estradiol: at a medium to high dose (2.25 mg/day) from the 5th to the 25th day of the menstrual cycle
  + Oral progesterone with a low to medium dose from the 18th to the 25th day of the menstrual cycle

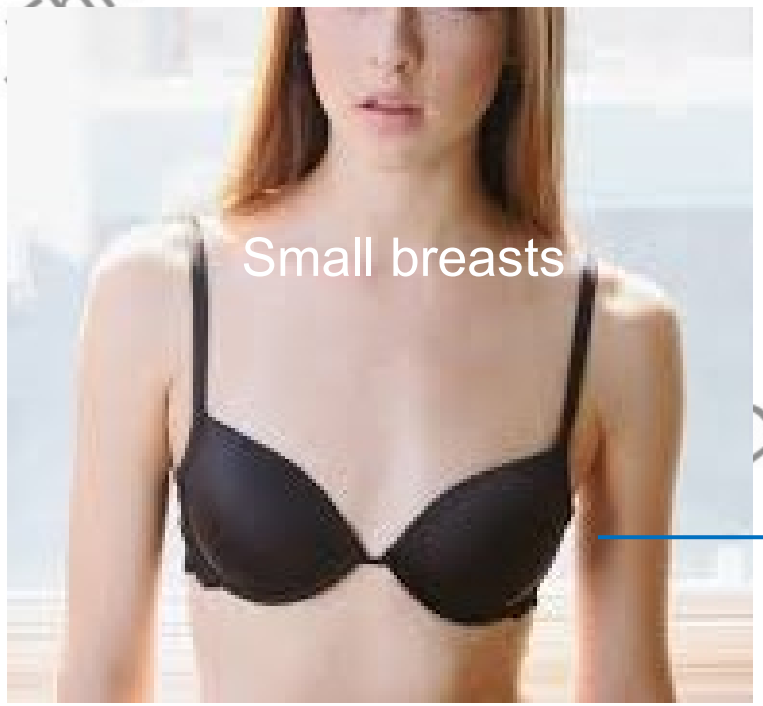
- Thyroid therapy= desiccated thyroid
- Sufficient protein-rich foods: 250 g/day of meat , fish, poultry
- Avoid whole grain bread

- Scalp hair: Topical estrogen & progesterone & melatonin oil 2x/week

Small breasts (micromastia)

In young women => Need to ↑ estrogen dose

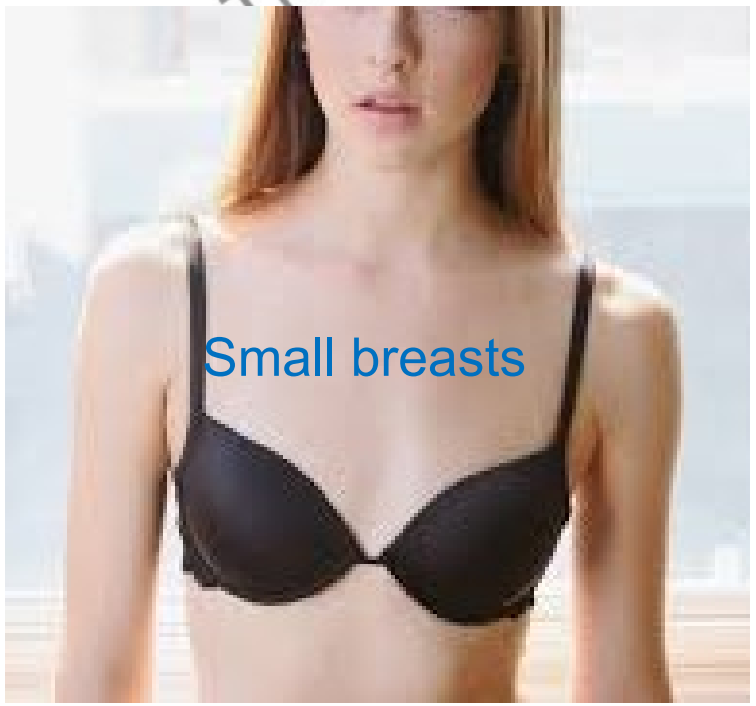
Premenopausal woman, treated with female hormones



↓ Water & ↓ Milk glands
(↓ epithelial cell proliferation)

Insufficient estrogen levels

Small breasts in young women (17-26 years)



ADD transdermal estradiol

at a medium to high dose (2.25 mg/day)

from the 5th to the 25th day of the menstrual cycle

+ Oral progesterone at a low to medium dose

from the 15th to the 25th day of the menstrual cycle

+ High-protein diet

Small breasts (micromastia)

In older women (> 40 years of age)

=> Need to ↑ estrogen, GH, DHEA dose

Small breasts in older postmenopausal women (40-60 years)

Treat the CAUSE

ADD

- Transdermal estradiol: at a medium to high dose (2.25 mg/day) from the 1st to the 25th day of the month
  + Oral progesterone with a low to medium dose from the 1st to the 25th day of the menstrual cycle
- + Growth hormone at a minimum of 0.25-0.35 mg/day
- + DHEA 20-25 mg/day
- + Sufficient protein-rich foods: 250 g/day of meat , fish, poultry

May make BREAST PROTHESIS unnecessary

Postmenopausal woman

→ ↓ Water & ↓ Milk glands
(↓ epithelial cell proliferation)

Insufficient estrogen, GH
progesterone levels

Female subfertility

⇒ Patient needs more estrogen & progesterone

Subfertility in premenopausal women (25-42 years)

Treat the CAUSE(S)

ADD

- Transdermal estradiol: at a medium to high dose (2.25 mg/day) from the 5th to the 25th day of the menstrual cycle
  + Oral progesterone with a low to medium dose from the 18th to the 25th day of the menstrual cycle

Transdermal estradiol => ↑ serum preovulatory estradiol peak

- Thyroid therapy= desiccated thyroid
- Cortisol therapy
  + DHEA 20-25 mg/day
- GH at a minimum of 0.25-0.35 mg/day
- Sufficient protein-rich foods: 250 g/day of meat , fish, poultry
- Avoid whole grain bread

Pregnancy

⇒ Patient needs more progesterone

(& sometimes estrogen)

Pregnancy => Signs of need for more female hormones

Signs of need for more estradiol

Rare

- Fatigue, low mood
- Droopy breasts
- Vaginal bleeding

ADD DAILY 1-2 pumps/d of estradiol

Signs of need for more progesterone

Frequent

- Nervous, irritability,
- Irresistible vomiting

- Painful swollen breasts
- Excessive weight gain & swelling

- Premature uterine contractions

ADD DAILY 100-200 mg/d of progesterone

Rarely up to 1200 mg/d of progesterone
(IM progesterone injections every 2 days)

Topical (cervical) estradiol => no sign. adverse effect (no ↑ uterine contractions) in high-risk pregnancies

40 high-risk obstetric women before induction of labor

Single application of a vaginal (cervical) estradiol valerate gel

No significant effect on uterine contraction

Williams JK, et al. Am J Obstet Gynecol. 1988 Jan;158(1):55-8

Postnatal depression

⇒ Patient needs estradiol (+ progesterone)

Postnatal depressed women => Need for estrogen progesterone

Postnatally depressed woman

⬇⬇ Serum estradiol & progesterone

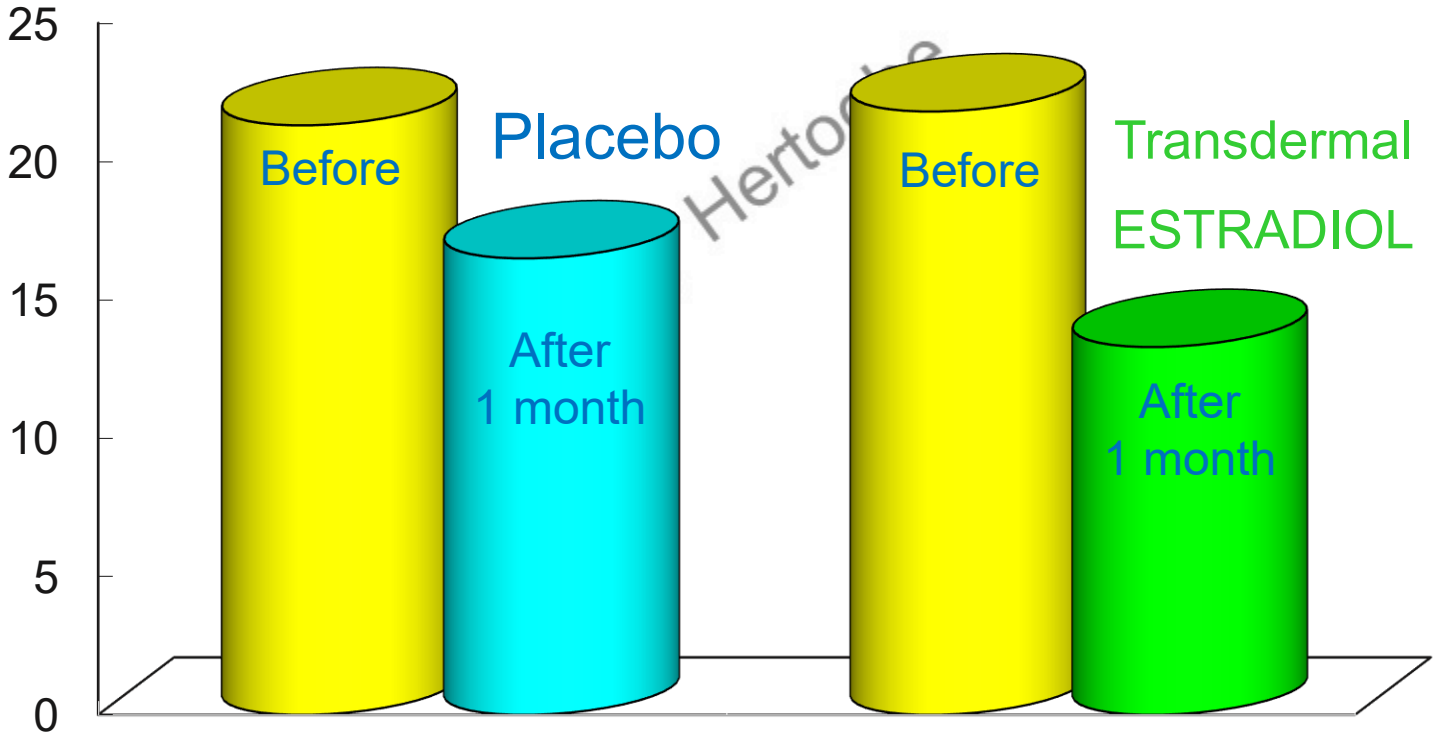
⬇

Fatigue, low mood, etc. similar to postnatal depression

↘

Not compensated by an ⬆ ⬆ Serum oxytocin, if they do not breast-feed!

Estradiol supplementation => ↓ Severe postnatal depression



61 women with severe postnatal depression

Effect of transdermal estradiol in women with severe postnatal depression (initiated 1 month after delivery)

Gregoire AJ, et al. Lancet. 1996 Apr 6;347(9006):930-3.

Postnatal depression: the association with low E2 levels & improvement with E2 treatment

Estrogen treatment

Sign. ↓ Postnatal depression

1. *Ahokas A, et al. J Clin Psychiatry. 2001 May;62(5):332-6*
2. *Lawrie TA, et al. Cochrane Database Syst Rev. 2000;(2):CD001690*
3. *Gregoire AJ, et al. Lancet. 1996 Apr 6;347(9006):930-3*

Postnatal depression: the association with low E2 levels & improvement with E2 treatment

1. Ahokas A, Kaukoranta J, Wahlbeck K, Aito M. Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. J Clin Psychiatry. 2001 May;62(5):332-6

2. Lawrie TA, Herxheimer A, Dalton K. Oestrogens and progestogens for preventing and treating postnatal depression. Cochrane Database Syst Rev. 2000;(2):CD001690

3. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. Lancet. 1996 Apr 6;347(9006):930-3

Breast-feeding

⇒ Estrogen & progesterone treatments

Breast-feeding women => Need for estrogen progesterone

Breast-feeding women

- ↑↑ Serum prolactin
- ↓↓ Serum estradiol & progesterone

Fatigue, low mood, etc. similar to postnatal depression

But partial compensation by ↑↑ Serum oxytocin

Breastfeeding, postpartum depression => Treatment?

- Breastfeeding
- Postpartum depression

Same treatment as traditional postmenopausal female hormone treatment without menstruation
(but restrict to 1.5 mg/day of estradiol)

START 3 weeks to 1 month after delivery,
not earlier (to allow time for the uterus to shrink back to its normal size)

Postnatally depressed or breast-feeding women

Estradiol will take depression away

Estradiol gel

0.06%)

Progesterone will not inhibit breastfeeding

Progesterone caps

Micronized progesterone

Postnatal E2

1st to 25th day of the month

Or: **1.5 mg E2** (**2 pumps** = 2.5 g)

1st to 25th day of the month

100 mg

Attention for transdermally estrogen-treated young mothers!

The mother should wash her hands & cover her arms or other parts where estradiol has been applied to avoid contaminating the baby!

Transdermal estradiol to breast-feeding women => Safety for the child

Breastfeeding child: no significant adverse effect with transdermal estradiol alone in breastfeeding mother

Transdermal estradiol treatment alone in breastfeeding women-with postpartum depression => No significant effect on serum estradiol and estrone, & infant growth in breast-feeded child

1. Pinheiro E, Bogen DL, Hoxha D, Wisner KL. Transdermal estradiol treatment during breastfeeding: maternal and infant serum concentrations. Arch Womens Ment Health. 2016 Apr;19(2):409-13. (breastfeeding women-with postpartum depression)

Breast feeding => No transfer of transdermal estradiol into breast milk

1. Perheentupa A, Ruokonen A, Tapanainen JS. Transdermal estradiol treatment suppresses serum gonadotropins during lactation without transfer into breast milk. Fertil Steril. 2004 Oct;82(4):903-7. (21 healthy breastfeeding women (aged 20-38 years))

Sensitivity to steroid-negative feedback: the enhancement of the suppression of gonadotropins, inhibin B, and ovarian activity with low-dose transdermal (50 mcg) estradiol patch in premenopausal women during breastfeeding despite no increase of serum estradiol levels

1. Perheentupa A, Critchley HO, Illingworth PJ, McNeilly AS. Enhanced sensitivity to steroid-negative feedback during breast-feeding: low-dose estradiol (transdermal estradiol supplementation) suppresses gonadotropins and ovarian activity assessed by inhibin B. J Clin Endocrinol Metab. 2000 Nov;85(11):4280-6. (19 breast-feeding women using barrier methods of contraception at 6 weeks postpartum)

Women with premature ovarian failure

Iatrogenic premature ovarian failure

OK, indicated, improves

Premature ovarian failure after chemotherapy or total body irradiation

OK, indicated, improves

Cust MP et al, Br Med J, 1989, 299: 1494-97

Women
with medical condition that can aggravate with estrogen therapy

⇒ Edema, endometriosis, fibrocystic breast disease, migraine type headaches

Medical condition that can aggravate with estrogen therapy

- Estrogen => Adapt the dose to the individual needs; rarely a need to stop estrogen therapy
- Progesterone=> Find an adequate balance with progesterone
- Possibly symptomatic medications like potassium (or diuretics) in case of edema

Watts NB, p. 373 in La Ménopause, Dr J. Lorain, Ed. Maloine Paris, 1995

Atherosclerosis

⇒ Patient needs transdermal estradiol & bioidentical progesterone

Estrogen-deficient women with important atherosclerosis

ADVICE:

Low estradiol doses

ADD

- Transdermal estradiol: at a low to medium dose (1.25 -2.25 mg/day) + oral or vaginal progesterone with a low to medium dose

- AVOID non-biodentical estrogens & progestogens

because of

- Inactivity => ↓ estrogen consumption
- Fragile vascular condition

Oral estradiol valerate 1 mg/day
in case of (pre)dementia

Atherosclerosis & blood vessel function: the improvement with oral estradiol alone

Atherosclerosis (carotid artery intima-media thickness (CIMT) and coronary vascular markers (such as HDL ad LDL cholesterol): the better improvement (reduction of intime media thickness) when given in early postmenopausal years with oral estradiol alone for 6-7 years in early and late postmenopausal women

1. Hodis HN, Mack WJ, Shoupe D, Azen SP, Stanczyk FZ, Hwang-Levine J, Budoff MJ, Henderson VW. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause. 2015 Apr;22(4):391-401. (643 healthy postmenopausal women without cardiovascular disease)

Blood vessels: the improvement with oral estradiol alone in coronary atherosclerosis

Forearm blood flow: Attenuation of endothelin-1 induced vasoconstriction obtained after 1 month of oral 17beta estradiol: is not sustained during long-term (3 months) therapy in postmenopausal women with coronary heart disease

1. Jhund PS, Dawson N, Davie AP, Sattar N, Norrie J, O'Kane KP, McMurray JJ. Attenuation of endothelin-1 induced vasoconstriction by 17beta estradiol is not sustained during long-term therapy in postmenopausal women with coronary heart disease. J Am Coll Cardiol. 2001 Apr;37(5):1367-73 (19 postmenopausal women with coronary heart disease)

Peripheral endothelial function (reduced in coronary artery disease): the acute and partial improvement with single dose of (4 mg) of oral estradiol valerate alone in postmenopausal women with coronary artery disease

1. Enderle MD, Sayer R, Balletshofer B, Meisner C, Mück AO, Haasis R, Haering HU, Pfohl M. Acute improvement of peripheral endothelial function in postmenopausal women with coronary artery disease after single oral intake of 17beta-estradiol valerate. Exp Clin Endocrinol Diabetes. 2000;108(5):382-5. (20 postmenopausal women with coronary artery disease (age: 64.9 (7.2) y)

Blood vessels: the improvement with oral estradiol alone, & oral estradiol w/vaginal progesterone in carotid atherosclerosis

Atherosclerosis: the improvement (slower progression of thickening of carotid-artery intima-media thickness) with oral estradiol therapy (with or without vaginal progesterone) for 5 years in recently postmenopausal women (less than 6 years) but no significant effect on coronary atherosclerosis assessed by cardiac computed tomography

1. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M, Dustin L, Kono N, Stanczyk FZ, Selzer RH, Azen SP; ELITE Research Group.. Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. N Engl J Med. 2016 Mar 31;374(13):1221-31. (643 healthy postmenopausal women)

Transdermal estradiol + oral progestogen => ↓ Coagulation

Coagulation/fibrinolysis : the partial improvement of coagulation/fibrinolysis with very low-doses of transdermal estradiol (0.025 mg/day) and norethisterone acetate for 48 weeks (transdermal) (a significant **↓ Factor VII & antithrombin III** at 24 and 48 weeks compared with the placebo group and a ↓ f fibrinogen at 24 weeks, no change in HDL, triglycerides or Lp(a),)

1. Brynhildsen J, Hammar M. Lipids and clotting factors during low dose transdermal estradiol/norethisterone use. Maturitas. 2005 Apr 11;50(4):344-52. (135 healthy women at least 2 years post menopause)

Coagulation, and endothelial markers: the improvement with transdermal estradiol patches combined with oral norethisterone in combination with oral norethisterone for 6 months in postmenopausal women with type 2 diabetes (**↓ Factor VII activity** (↑ factor VII activity has been associated with an ↑ risk of coronary thrombosis), and von Willebrand factor (reduction in von Willebrand factor antigen is consistent with an improvement in endothelial function))

1. Perera M, Sattar N, Petrie JR, Hillier C, Small M, Connell JM, Lowe GD, Lumsden MA. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2001 Mar;86(3):1140-3. (43 women with type 2 diabetes)

Transdermal estradiol alone => ↓ Coagulation

Fibrinogen, plasminogen, and apolipoprotein B: the improvement (**↓ fibrinogen B & ↑ plasminogen**) with oral estradiol alone for 6 monthsin postmenopausal women

1. Conard J, Gompel A, Pelissier C, Mirabel C, Basdevant A. Fibrinogen and plasminogen modifications during oral estradiol replacement therapy. Fertil Steril. 1997 Sep;68(3):449-53. (36 postmenopausal women with natural or surgical menopause)

Coagulation: the improvement with oral estradiol with an oral progestogen

Cardiovascular disease markers (coagulation and fibrinolysis): the improvement (↓ serum factor VII, fibrinogen, antithrombin & plasminogen activator inhibitor-1) with oral low-dose (1 mg) with oral estradiol and norethisterone acetate (NETA for 1 year in postmenopausal

1. Borgfeldt C, Li C, Samsioe G. Low-dose oral combination of 17beta-estradiol and norethisterone acetate in postmenopausal women decreases factor VII, fibrinogen, antithrombin and plasminogen activator inhibitor-1. Climacteric. 2004 Mar;7(1):78-85 (120 healthy postmenopausal women)

Coagulation: the improvement with transdermal estradiol alone but not with transdermal estradiol with an oral progestogen (medroxyprogesterone acetate)

Coagulation (hemostasis): the ↓ fibrinogenfactor VII, antithrombin III, protein S & heparin cofactor II) with continuous transdermal treatment patches alone but not the cyclic version of it) for at least 6 cycles in recent postmenopausal women

1. (No author listed). Effects on haemostasis of hormone replacement therapy with transdermal estradiol and oral sequential medroxyprogesterone acetate: a 1-year, double-blind, placebo-controlled study. The Writing Group for the Estradiol Clotting Factors Study. Thromb Haemost. 1996 Mar;75(3):476-80. (167 women in physiological menopause for 1-5 years)

Coagulation: no significant adverse effect with transdermal estradiol alone

1. Hognert H, Ghanoum B, Gustafsson H, Milsom I, Manhem K. Acute effects of transdermal 17beta-estradiol on hemostatic variables after 24-hour treatment. Clin Appl Thromb Hemost. 2002 Jul;8(3):239-43.. (11 normotensive and 13 hypertensive women, crossover study)

Oral estradiol + progestogen => Detrimental effects on Coagulation

oral estradiol + dydrogesterone for 2 months => ↑ **Thrombin generation & factor VII coagulant activity** in postmenopausal women

1. Rousseau A, Robert A, Gerotziafas G, Torchin D, Zannad F, Lacut K, Libersa C, Dasque E, Démolis JL, Elalamy I, Simon T. Effect of two oral doses of 17beta-estradiol associated with dydrogesterone on thrombin generation in healthy menopausal women: a randomized double-blind placebo-controlled study. Fundam Clin Pharmacol. 2010 Apr;24(2):239-45. (72 healthy postmenopausal women)

Oral estradiol + progestogen (medroxyprogesterone acetate => the detrimental effects on coagulation:

1. Coagulation: the influence (↑ procoagulatory factors, such as fibrinogen, activated FVII (FVIIa) and coagulative **FVII)** & ↑ **fibrinolytic factors such as plasminogen and alpha2-antiplasmin**) with transdermal estradiol and oral medroxyprogesterone acetate for 1 year in postmenopausal women
2. Perrone G, Capri O, Galoppi P, Brunelli R, Bevilacqua E, Ceci F, Ciarla MV, Strom R. Effects of either tibolone or continuous combined transdermal estradiol with medroxyprogesterone acetate on coagulatory factors and lipoprotein(a) in menopause. Gynecol Obstet Invest. 2009;68(1):33-9 (61 postmenopausal women)

Neurodegenerative disease

(Multiple sclerosis,
Parksinson, Alzheimer's,
Lateral amyotrophic sclerosis)

⇒ Patient needs transdermal estradiol
& bioidentical progesterone

Multiple sclerosis, Parksinson, Alzheimer's, amyotrophic lateral sclerosis

Usually insufficient estrogen levels

ADVICE:

Low estradiol doses

because of

- Inactivty (↓ estrogen consumption)
- Fragile vascular condition

Women with Parkinson's , Alzheimer's or ALS

ADD

- Oral estradiol valerate 1 mg/day at a low dose (1.25 mg/day)

  + oral progesterone with a low to medium dose

- AVOID non-biodentical estrogens & progestogens

Estrogen-deficient women with mulitple sclerosis

↓

in case of no cognitive decline
transdermal estradiol low dose 1 g/day
rather than oral

Women with vasculopathy

Stroke patients

Probably OK, except for smokers
=> Use bioidentical hormones with routes of administration

- transdermal estradiol
- + vaginal progesterone

(Avoid oral estrogens & take low estrogen doses & for 6 months (because of inactivity), & then ↑ to average dose, avoid estrogen excess: also take testosterone)

(Paganini-Hill A, Br Med J, 1988: 297:519-522; Henderson BE et al., Arch Intern Med, 1991, 151: 75-78) ↑ risk (esp. with smoking) (Wilson PWF et al, N Engl J Med, 1985; 313: 1038-1043)

Varicose veins

& phlebitis

⇒ Patient needs ↓ dose of transdermal estradiol

\+ more bioidentical progesterone + testosterone

+I

Estrogen excess => Varicose veins

Estrogens, synthetic progestogens, or their associative action

Facilitate varicose vein development in individuals with factors which predispose them to vascular disorders (familial history, prolonged standing, obesity, & sedentary)
=> ↑ varicose veins

Aggravate the superficial venous state in these patients
=> ↑ spider veins

Vin F, et al. J Dermatol Surg Oncol. 1992 Oct;18(10):888-92

Varicose veins: hormone causes

Estradiol excess → Veins => Vasodilatation

Oral estrogens → => ↑ SHBG & ↓ testosterone production => Testosterone deficit => Weak venous muscular walls

Progesterone deficiency → Estrogen excess => ↑ Vasodilatation

Testosterone deficiency → Veins => Weak muscular walls

Varicose veins

Use bioidentical hormones with the best routes of administration

- Transdermal estradiol +
- Vaginal progesterone

- Avoid oral estrogens
- Avoid estrogen excess => Take low estrogen doses (because of possible vasodilation & stasis with estrogens)
- Take testosterone

Phlebitis = Hormone causes

Estradiol excess → Veins => blood stagnation

Oral estrogens → Testosterone deficit => ↑ coagulation => ↑ phlebitis

Progesterone deficiency → Estrogen excess => ↑ blood stagnation

Testosterone deficiency → Veins => ↓ coagulation => ↑ phlebitis

Deep vein thrombosis => Caution

Probably a momentary contra-indication, although no sufficient solid material to confirm

⇒ STOP oral estrogens, synthetic progestogens & oral contraceptives

⇒ as they can ↑ risk of trombo-embolic accidents

Young RL et al, Maturitas, 1991; 13: 189-192; Devor et al, Am J Med, 1992; 92: 283-85

Arterial hypertension

⇒ Patient needs transdermal estradiol & bioidentical progesterone

Arterial hypertension in estrogen-deficient women

ADD

- Transdermal estradiol: at a low to medium dose (2.25 mg/day) + vaginal progesterone with a low to medium dose

- AVOID non-biodentical estrogens & progestogens

- Drink water
- Magnesium (200-600 mg/day elemental Mg)

Arterial hypertension: the reduction with estrogen treatment

1. Paoletti AM, Cagnacci A, Di Carlo C, Orrù MM, Neri M, D'Alterio MN, Melis GB. Clinical effect of hormonal replacement therapy with estradiol associated with noretisterone or drospirenone. A prospective randomized placebo-controlled study. Gynecol Endocrinol. 2015 May;31(5):384-7.
2. Harrison-Bernard LM, Schulman IH, Raij L. Postovariectomy hypertension is linked to increased renal AT1 receptor and salt sensitivity. Hypertension. 2003 Dec;42(6):1157-63
3. Clark JT, Chakraborty-Chatterjee M, Hamblin M, Wyss JM, Fentie IH. Estrogen depletion differentially affects blood pressure depending on age in Long-Evans rats. Endocrine. 2004 Nov;25(2):173-86
4. Peng N, Clark JT, Wei CC, Wyss JM. Estrogen depletion increases blood pressure and hypothalamic norepinephrine in middle-aged spontaneously hypertensive rats. Hypertension. 2003 May;41(5):1164-7
5. Cagnacci A, Tarquini R, Perfetto F, Arangino S, Zanni AL, Cagnacci P, Facchinetti F, Volpe A. Endothelin-1 and nitric oxide levels are related to cardiovascular risk factors but are not modified by estradiol replacement in healthy postmenopausal women. A cross-sectional and a randomized cross-over study. Maturitas. 2003 Feb 25;44(2):117-24.
6. Angerer P, Stork S, von Schacky C. Influence of 17beta-oestradiol on blood pressure of postmenopausal women at highvascular risk. J Hypertens. 2001 Dec;19(12):2135-42
7. Manhem K, Ahlm H, Dellborg M, Milsom I. Acute effects of transdermal estrogen in postmenopausal women with coronary artery disease. Using a clinically relevant estrogen dose and concurrent antianginal therapy. Cardiology. 2000;94(2):86-90 *("resting diastolic blood pressure was significantly decreased due to estrogen")*
8. Fisman EZ, Tenenbaum A, Shapira I, Motro M, Pines A. Lack of effects of transdermal estradiol on diastolic function: a randomized placebo-controlled double-blind short-term trial. Climacteric. 1999 Sep;2(3):174-80.
9. Cagnacci A, Rovati L, Zanni A, Malmusi S, Facchinetti F, Volpe A. Physiological doses of estradiol decrease nocturnal blood pressure in normotensive postmenopausal women. Am J Physiol. 1999 Apr;276(4 Pt 2):H1355-60.
10. Seely EW, Walsh BW, Gerhard MD, Williams GH. Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women. Hypertension. 1999 May;33(5):1190-4.
11. Mercuro G, Zoncu S, Piano D, Pilia I, Lao A, Melis GB, Cherchi A. Estradiol-17beta reduces blood pressure and restores the normal amplitude of the circadian blood pressure rhythm in postmenopausal hypertension. Am J Hypertens. 1998 Aug;11(8 Pt 1):909-13Del Rio G, Velardo A, Zizzo G, Avogaro A, Cipolli C, Della Casa L, Marrama P, MacDonald IA. Effect of estradiol on the sympathoadrenal response to mental stress in normal men. J Clin Endocrinol Metab. 1994 Sep;79(3):836-40Pang SC, Greendale GA, Cedars MI, Gambone JC, Lozano K, Eggena P, Judd HL. Long-term effects of transdermal estradiol with and without medroxyprogesterone acetate. Fertil Steril. 1993 Jan;59(1):76-82
12. Hassager C, Riis BJ, Strøm V, Guyene TT, Christiansen C. The long-term effect of oral and percutaneous estradiol on plasma renin substrate and

Blood pressure & arterial hypertension

Blood pressure: the improvement with transdermal estradiol

Systolic and diastolic blood pressure: the improvement (reduction) of unopposed transdermal estradiol patches for 2 months in postmenopausal women, but no significant effect on serum endothelin (vasoconstrictor) or nitric oxide levels (endothelial substances)

1. Cagnacci A, Tarquini R, Perfetto F, Arangino S, Zanni AL, Cagnacci P, Facchinetti F, Volpe A. Endothelin-1 and nitric oxide levels are related to cardiovascular risk factors but are not modified by estradiol replacement in healthy postmenopausal women. A cross-sectional and a randomized cross-over study. Maturitas. 2003 Feb 25;44(2):117-24. (20 healthy postmenopausal women, cross-over study)

Systolic blood pressure: the improvement (reduction) with transdermal estradiol alone for 8 weeks in postmenopausal women but no significant effect on diastolic blood pressure and left ventricular diastolic function

1. Fisman EZ, Tenenbaum A, Shapira I, Motro M, Pines A. Lack of effects of transdermal estradiol on diastolic function: a randomized placebo-controlled double-blind short-term trial. Climacteric. 1999 Sep;2(3):174-80. (45 postmenopausal women aged 50.8 +/- 3.6 years)

Nocturnal blood pressure: the improvement (magnification of the natural nocturnal reduction in blood pressure back to premenopausal levels) with transdermal estradiol patches alone for 2 months in normotensive healthy postmenopausal women but no effect on daytime blood pressure, restoring the absent 24-rhythm of mean blood pressure in 50% of the women in whom it was absent and amplifying in the remaining 50% of the subjects

1. Cagnacci A, Rovati L, Zanni A, Malmusi S, Facchinetti F, Volpe A. Physiological doses of estradiol decrease nocturnal blood pressure in normotensive postmenopausal women. Am J Physiol. 1999 Apr;276(4 Pt 2):H1355-60. (218 normotensive healthy postmenopausal women)

Blood pressure: the improvement with transdermal estradiol alone, and with transdermal estrafiol and vaginal progesterone

Blood pressure (BP): the improvement (reduction all nocturnal systolic, diastolic, and mean BP with 4-5 mm of, and of daytime mean BP) with 10 weeks of transdermal high-dosed (0.2 mg/day) estradiol with or without progesterone in postmenopausal women

1. Seely EW, Walsh BW, Gerhard MD, Williams GH. Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women. Hypertension. 1999 May;33(5):1190-4. (15 healthy postmenopausal women)

Blood pressure: the improvement with transdermal estradiol alone, transdermal estrafiol combined to oral progesterone (which does not change the beneficial effects of estradiol), and oral estradiol combined to a progestogen

Systolic and diastolic blood pressure: the improvement (no age-related increase) with oral estradiol and cyproterone aceta or transdermal estradiol aloje for 1 year and then with oral progesterone during 1year in postmenopaual women; transdermal estradiol is better because it does not increase serum renin levels in contrast with oral estradiol; bioidentical progesterone has no influence on these parameters

1. Hassager C, Riis BJ, Strøm V, Guyene TT, Christiansen C. The long-term effect of oral and percutaneous estradiol on plasma renin substrate and blood pressure. Circulation. 1987 Oct;76(4):753-8. (110 early postmenopausal women)

Women with cardiopathy

Women with cardiopathy (e.g. myocardial infarction, valvular surgery, etc.)

= Indication for HRT

But use bioidentical hormones
with best routes of administration

- transdermal estradiol
- + vaginal progesterone

- Avoid oral estrogens
- Avoid estrogen excess => outside of emergency => Start at low estrogen doses & gradually ↑ to average dose
- First day of myocardial infarct => Higher E + P doses

Watts NB, p. 373 in La Ménopause, Dr J. Lorain, Ed. Malvine Paris, 1995

Coronary heart disease

⇒ Patient needs transdermal estradiol & bioidentical progesterone

Coronary heart disease in estrogen-deficient women

Treat the CAUSE(S)

ADD

- Transdermal estradiol: at a medium to high dose (2.25 mg/day)+ Oral progesterone with a low to medium dose

- AVOID non-biodentical estrogens & progestogens

- Drink water
- Magnesium (200-600 mg/day elemental Mg)
- Coq10 (100-200 mg/day)

Coronary arteries

Coronary arteries

Coronary constriction by vasoconstrictor: the improvement (reduction) with intracoronary estradiol alone

Coronary artery constriction by high doses of vasoconstrictor methylergometrine: the improvement (attenuation) with acute intracoronary estradiol in postmenopausal women

1. Rosano GM, Collins P, Gerbara O, Sheiban I, Silvestri A, Wajngarten M, Ramires JA, Fini M, Mercuro G. Effect of estradiol 17beta upon coronary artery vasoconstrictor response to methylergometrine maleate in female menopausal patients. Int J Cardiol. 2006 Feb 15;107(2):254-9. (16 postmenopausal women)

Coronary heart disease the improvement with intracoronary estradiol (DBPC trials)

Coronary heart disease: the improvement with intracoronary estradiol

1. Collins P, Rosano GM, Sarrel PM, Ulrich L, Adamopoulos S, Beale CM, McNeill JG, Poole-Wilson PA. 17 beta-Estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. Circulation. 1995 Jul 1;92(1):24-30. (9 postmenopausal women 59, and 7 men 52 years old with proven coronary artery disease)

Coronary heart disease: the improvement with sublingual estradiol alone (delay in exercise-induced ischemia)

1. Rosano GM, Caixeta AM, Chierchia S, Arie S, Lopez-Hidalgo M, Pereira WI, Leonardo F, Webb CM, Pileggi F, Collins P. Short-term anti-ischemic effect of 17beta-estradiol in postmenopausal women with coronary artery disease. Circulation. 1997 Nov 4;96(9):2837-41 (16 postmenopausal women with coronary artery disease)

Coronary heart disease: the improvement with transdermal estradiol alone (-50% ↓ angina crisis's)

1. Rosano GM, Peters NS, Lefroy D, Lindsay DC, Sarrel PM, Collins P, Poole-Wilson PA. 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. J Am Coll Cardiol. 1996 Nov 15;28(6):1500-5. (25 postmenopausal patients with syndrome X)
2. Albertsson PA, Emanuelsson H, Milsom I. Beneficial effect of treatment with transdermal estradiol-17-beta on exercise-induced angina and ST segment depression in syndrome X. Int J Cardiol. 1996 Apr 19;54(1):13-20. (15 postmenopausal women (mean age 58 years) with syndrome X+ 8 healthy women (mean age 58), crossover trial)

Coronary heart disease: no beneficial or adverse effects with transdermal estradiol alone

1. Schuchert A, Liebau M, Behrens G, Mueck AO, Meinertz T. Are the acute effects of transdermal estradiol in postmenopausal women with coronary disease related to changes of the autonomic tone? Z Kardiol. 2002 Feb;91(2):156-60. (15 postmenopausal women with symptomatic coronary heart disease, cross-over study)

Agina pectoris crisis

⇒ Patient needs ↑ transdermal estradiol

& ↑ bioidentical progesterone

Angina pectoris in estrogen-progesterone deficient women

Treat the CAUSE(S)

Increase the (estrogen &) progesterone doses

- + 1.5 -2 mg Transdermal estradiol: (medium dose)
- + 200 mg oral progesterone (high dose)

- Drink water
- Magnesium (600 mg/day elemental Mg)
- Coq10 (800 mg/day)

Myocardial infarction

⇒ Patient needs transdermal estradiol & bioidentical progesterone

Myocardial infarction in estrogen-progesterone treated women

CONTINUE

- Transdermal estradiol: at a medium to transiently high dose (1.5-2.25 mg/day) + Oral progesterone with medium dose (100-200 mg/day)

- Drink water
- Magnesium (400-800 mg/day elemental Mg)
- Coq10 (800 mg/day)

Transdermal estradiol alone => Safe for the blood vessels of women (↓ viscosity)

Forearm vascular resistance and blood viscosity; the improvement (lower forearm vascular resistance and blood viscosity, increase in red blood cell velocity) with transdermal estradiol (without progesterone) for 3 months in overweight/obese (nondiabetic)recently postmenopausal women

1. Panazzolo DG, da Silva LH, Maranhão PA, Souza MG, Nogueira Neto JF, Leão LM, Bouskela E, Kraemer-Aguiar LG. Short-term effects of low-dose estradiol on endothelial function and blood viscosity in nondiabetic postmenopausal overweight women: a double-blind, placebo-controlled study. Menopause. 2016 Oct;23(10):1114-21. (44 nondiabetic overweight/obese women wit h a history of recent menopause)

Vascular: the improvement (increased markers of vascular repair and improved microvascular reactivity without changing the inflammatory biomarkers) with transdermal estradiol without progesterone for 3 months in recently postmenopausal women

1. da Silva LH, Panazzolo DG, Marques MF, Souza MG, Paredes BD, Nogueira Neto JF, Leão LM, Morandi V, Bouskela E, Kraemer-Aguiar LG. Low-dose estradiol andendothelial and inflammatory biomarkers in menopausal overweight/obese women. Climacteric. 2016 Aug;19(4):337-43 (44 menopausal women (47-55 years; body mass index 27.5-34.9 kg/m²

Plasma levels of nitric oxide: the improvement (65 to 82% increases) with short-term (1 week) transdermal estradiol alone in postmenopausal women

1. Cicinelli E, Ignarro LJ, Schönauer LM, Matteo MG, Galantino P, Balzano G. Effects of short-term transdermal estradiol administration on plasma levels of nitric oxide in postmenopausal women. Fertil Steril. 1998 Jan;69(1):58-61. (28 healthy postmenopausal women)

Plasma levels of nitric oxide; the improvement (+77% increase in nitric oxide metabolite levels with acute (effects within 24h) (100 µg/day of) transdermal estradiol patches in postmenopausal women

1. Cicinelli E, Ignarro LJ, Lograno M, Matteo G, Falco N, Schonauer LM. Acute effects of transdermal estradiol administration on plasma levels of nitric oxide in postmenopausal women. Fertil Steril. 1997 Jan;67(1):63-6. (20 healthy postmenopausal women)

Estradiol treatment => ↑ Cardiac performance (output, DBPC trials)

Cardiac performance: the improvement with intranasal estradiol

1. Kaya D, Cevrioglu S, Onrat E, Fenkci IV, Yilmazer M. Single dose nasal 17beta-estradiol administration reduces sympathovagal balance to the heart in postmenopausal women. J Obstet Gynaecol Res. 2003 Dec;29(6):406-11. (19 postmenopausal women)

Cardiac performance: the improvement with oral estradiol alone in hypertension

1. Aldrighi JM, Alecrin IN, Caldas MA, Gebara OC, Ramires JA, Rosano GM. Effects of estradiol on myocardial global performance index in hypertensive postmenopausal women. Gynecol Endocrinol. 2004 Nov;19(5):282-92. (34 hypertensive postmenopausal women)
2. Luotola H. Blood pressure and hemodynamics in postmenopausal women during estradiol-17 beta substitution. Ann Clin Res. 1983;15 Suppl 38:1-121 (20 normotensive and 20 hypertensive postmenopausal women)

Cardiac performance and blood pressure: the improvement with transdermal estradiol alone, & transdermal estradiol with an oral progestogen

1. Alfie J, Lugones L, Belardo A, Tutzer M, Galarza CR, Waisman GD, Cámera MI. Hemodynamic effects of transdermal estradiol alone and combined with norethisterone acetate. Maturitas. 1997 Jun;27(2):163-9. (29 postmenopausal women (47-62 years))

Women with gallbladder problems

Women with gallbladder problems

No major contra-indication

But prefer the use of

- transdermal estradiol
- + vaginal progesterone

(avoid oral &
avoid estrogen excess)

Watts NB, p. 373 in La Ménopause, Dr J. Lorain, Ed. Malvine Paris, 1995

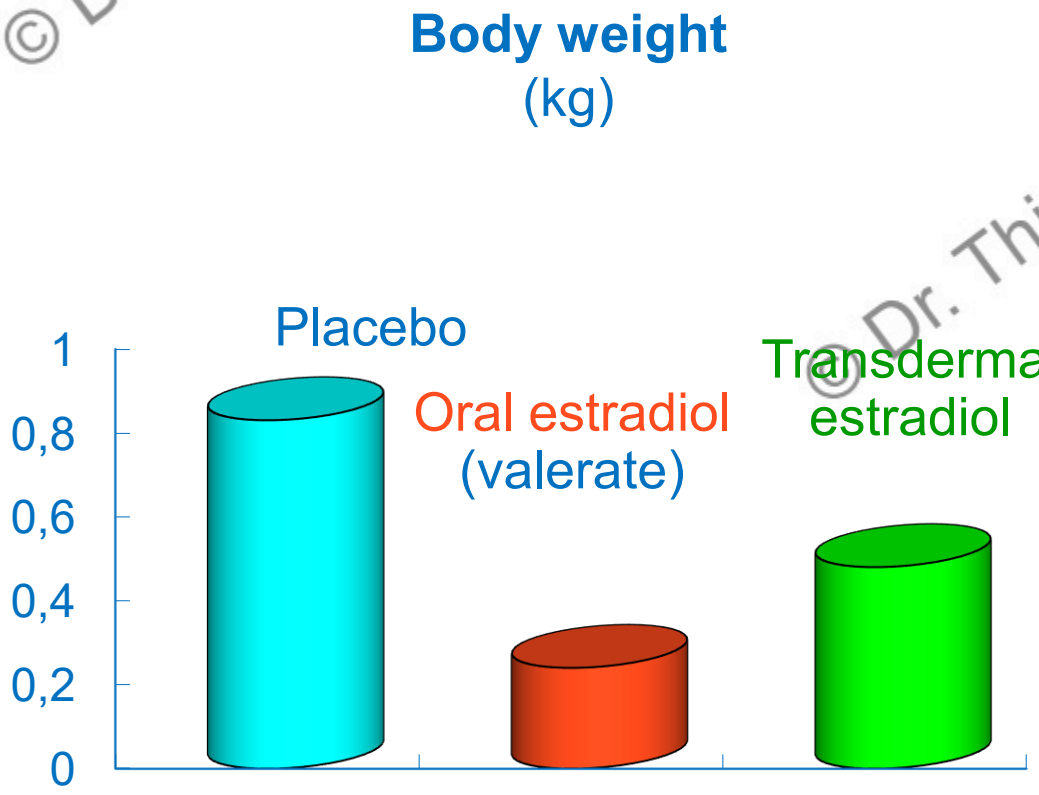
Obese women

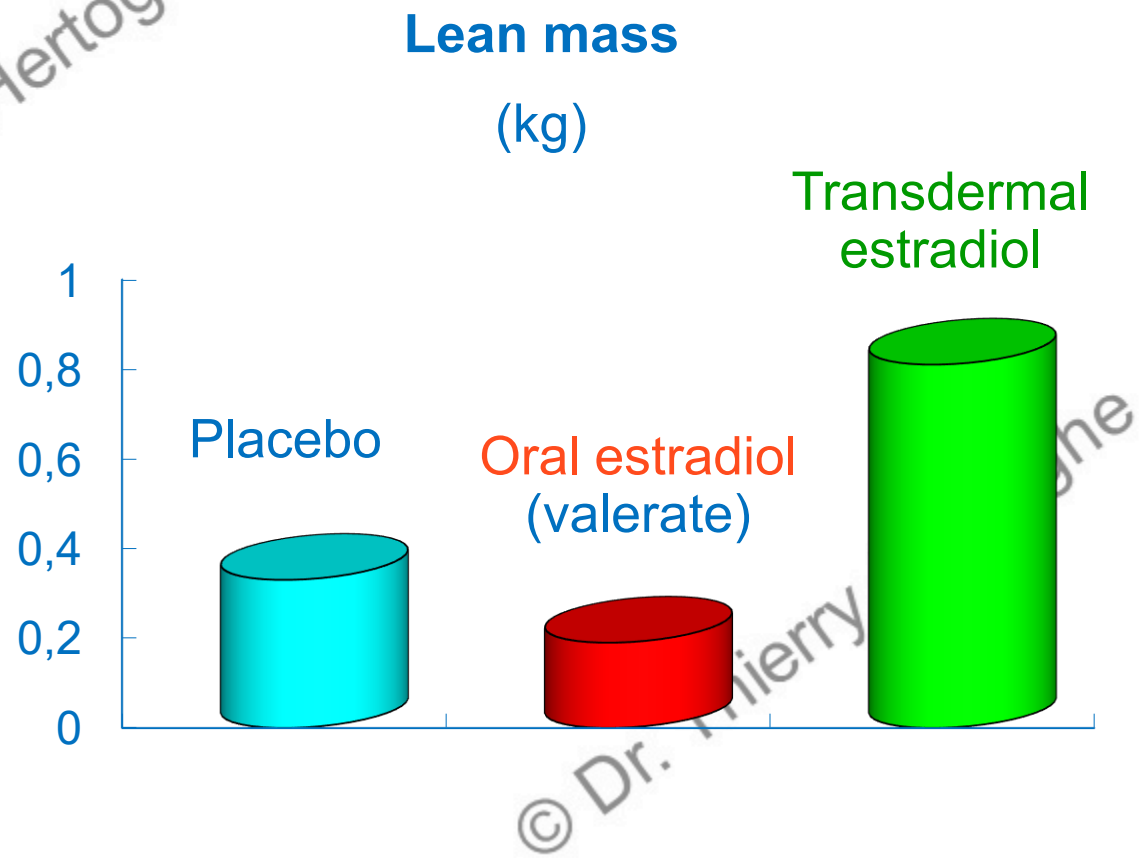
⇒ Patient needs (much?) less transdermal estradiol (& possibly more bioidentical progesterone)

Obese women

Estrogen therapy =>↓ Body weight & subcutaneous fat

110 postmenopausal women during 2 years of
oral versus transdermal estrogen treatment



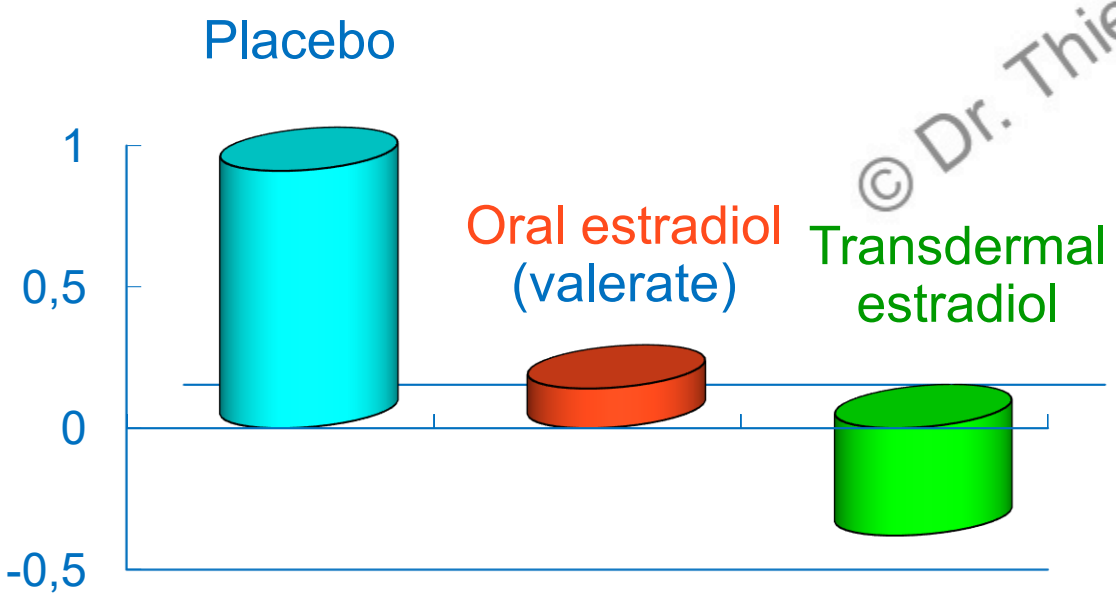


Hassager C et al, metabolism, 1989, 38: 662-5

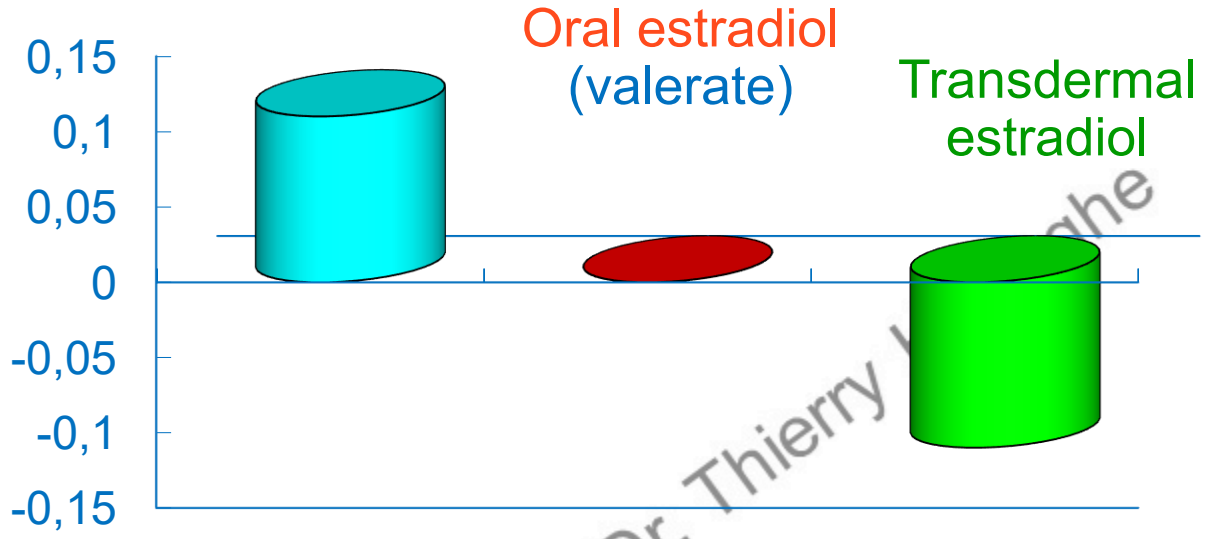
Estrogen therapy =>↓ Body weight & subcutaneous fat

110 postmenopausal women during 2 years of
oral versus transdermal estrogen treatment

Fat mass
(kg)



Arm skinfold
(mm)



Hassager C et al, metabolism, 1989, 38: 662-5

Obese estrogen-deficient women with important fat mass

ADVICE: Low estradiol doses

because of

- ↑ production of estrogen by fat tissue (from testosterone)
- ↑ estrogen receptors

ADD

- Transdermal estradiol: at a low to medium-low dose (1.25 -2 mg/day) + oral or vaginal progesterone with a low to medium dose

- AVOID non-biodentical estrogens & progestogens
- Avoid oral estrogens (swellling +++)

Insulin sensitivity: the improvement with transdermal alone (DBPC trials)

Insulin sensitivity: the improvement (increased glucose disposal rate) with transdermal estradiol alone for 1 week in recently early postmenopausal women, whereas it was reduced (harmful) when estradiol treatment was given in 10 or more years after the start of the postmenopause

1. 255. Pereira RI, Casey BA, Swibas TA, Erickson CB, Wolfe P, Van Pelt RE. Timing of estradiol treatment after menopause may determine benefit or harm to insulin action. J Clin Endocrinol Metab. 2015 Dec;100(12):4456-62. (22 early postmenopausal (≤ 6 yrs of final menses) & 24 late postmenopausal (≥ 10 yrs since last menses) women naive to HT)

Postprandial triglycerides and insulin: the improvement (reduction) with transdermal estradiol for 2 weeks in postmenopausal women with no effect on oxidation or storage of dietary fatty acids. Estradiol increased the proportion of small adipocytes in femoral (but not abdominal) subcutaneous adipose tissue

1. 256. Bessesen DH, Cox-York KA, Hernandez TL, Erickson CB, Wang H, Jackman MR, Van Pelt RE. Postprandial triglycerides and adipose tissue storage of dietary fatty acids: impact of menopause and estradiol. Obesity (Silver Spring). 2015 Jan;23(1):145-53. (12 postmenopausal women)

Glucose rates of appearance and disposal and adrenaline (epinenehrine) during exercise: the improvement (reduction) with transdermal estradiol for 6 days in amenorrheic premenopausal women

1. 257. Ruby BC, Robergs RA, Waters DL, Burge M, Mermier C, Stolarczyk L. Effects of estradiol on substrate turnover during exercise in amenorrheic females. Med Sci Sports Exerc. 1997 Sep;29(9):1160-9. (6 amenorrheic females)

Insulin sensitivity: no significant beneficial effects of unopposed transdermal estradiol patches for 6 weeks in women with surgically induced menopause

1. Duncan AC, Lyall H, Roberts RN, Petrie JR, Perera MJ, Monaghan S, Hart DM, Connell JM, Lumsden MA. The effect of estradiol and a combined estradiol/progestagen preparation on insulin sensitivity in healthy postmenopausal women. J Clin Endocrinol Metab. 1999 Jul;84(7):2402-7. (22 healthy women after a surgically induced menopause)

Transdermal (not oral) estradiol => ↑ Energy expenditure & fat breakdown

Calorie consumption: the improvement with transdermal estradiol alone

Energy expenditure: the improvement (preventing the reduction in energy expenditure caused by gonadotropin releasing hormone agonist) with transdermal estradiol alone for 1 week in premenopausal women treated with a gonadotropin releasing hormone agonist

1. Melanson EL, Gavin KM, Shea KL, Wolfe P, Wierman ME, Schwartz RS, Kohrt WM. Regulation of energy expenditure by estradiol in premenopausal women. J Appl Physiol (1985). 2015 Nov 1;119(9):975-81 (69 premenopausal women + leuprolide acetate (gonadotropin releasing hormone agonist) therapy)

Lipolysis in femoral subcutaneous and abdominal overall adipose tissue, basal lipid oxidation: the ↓ (and, thus, fat mass loss) with a single dose (4 mg/day) of oral estradiol in postmenopausal women

1. 262. Gormsen LC, Høst C, Hjerrild BE, Pedersen SB, Nielsen S, Christiansen JS, Gravholt CH. Estradiol acutely inhibits whole body lipid oxidation and attenuates lipolysis in subcutaneous adipose tissue: a randomized, placebo-controlled study in postmenopausal women. Eur J Endocrinol. 2012 Oct;167(4):543-51. (16 postmenopausal women (age, 59.5 years; BMI, 24.82.9), crossover study)

Body mass index: the ↑ (at higher serum total and free estradiol: levels) with oral estradiol alone for 2 years in postmenopausal women

1. Karim R, Mack WJ, Hodis HN, Roy S, Stanczyk FZ. Influence of age and obesity n serum estradiol, estrone, and sex hormone binding globulin concentrations following oral estrogen administration in postmenopausal women. J Clin Endocrinol Metab. 2009 Nov;94(11):4136-43. (180 postmenopausal women)

Oral estradiol + oral progestogen => NO or ↓ insulin sensitivity

Insulin sensitivity: no effectswith oral estradiol with an oral progestogen or sllght adverse effects at higher dose

Insulin sensitivity (index): no change with a continuous combined low-dose (1/0.5 mg/day) oral estradiol-norethisterone acetate treatments for 3 months in nondiabetic postmenopausal women, but small ↓ insulin sensitivity possible with high-dose (2/1 mg) oral estradiol-norethisterone acetate

1. Kimmerle R, Heinemann L, Heise T, Bender R, Weyer C, Hirschberger S, Berger M. Influence of continuous combined estradiol-norethisterone acetate preparations on insulin sensitivity in postmenopausal nondiabetic women. Menopause. 1999 Spring;6(1):36-42. (54 postmenopausal nondiabetic women (FSH > 40 mIU/mL, mean aged 56 years)

Insulin sensitivity: the adverse effects (reduction) with oral estradiol and an oral progestogen

Insulin sensitivity: ↓ insulin sensitivity with sequential combined oral estradiol & norethisterone acetate for 6 months in early postmenopausal women (single blind study)

1. Walker RJ, Lewis-Barned NJ, Sutherland WH, Goulding A, Edwards EA, de Jong SA, Gold E, Walker HL. The effects of sequential combined oral 17beta-estradiol norethisterone acetate on insulin sensitivity and body composition in healthy postmenopausal women: a randomized single blind placebo-controlled study. Menopause. 2001 Jan-Feb;8(1):27-32. (30 fit healthy postmenopausal women)

Type 2 Diabetes

=> Same adjustments as for obese patients

Estrogens => Diabetes

Oral estrogens

- ↑ Insulin resistance
- ↑ Glycemia

Kalkhoff RK et al, Ann Rev Med, 1972, 23: 429-38

Transdermal estradiol

- ↓ diabetes type I (↑ secretion + hypertrophy of ilets of Langherhans)
- ↓ diabetes type II (progesterone less efficient than E2)

Garris DR, Proc Soc Exp Biol Med, 1990, 193: 39-45

Cyclical migraine

⇒ Patient more OR less transdermal estradiol

OR more bioidentical progesterone

+I

Migaine in the follicular phase due to estradiol deficiency

Estradiol deficiency

Poor brain blood flow => brain nerve ischemia

Especially in the follicular phase

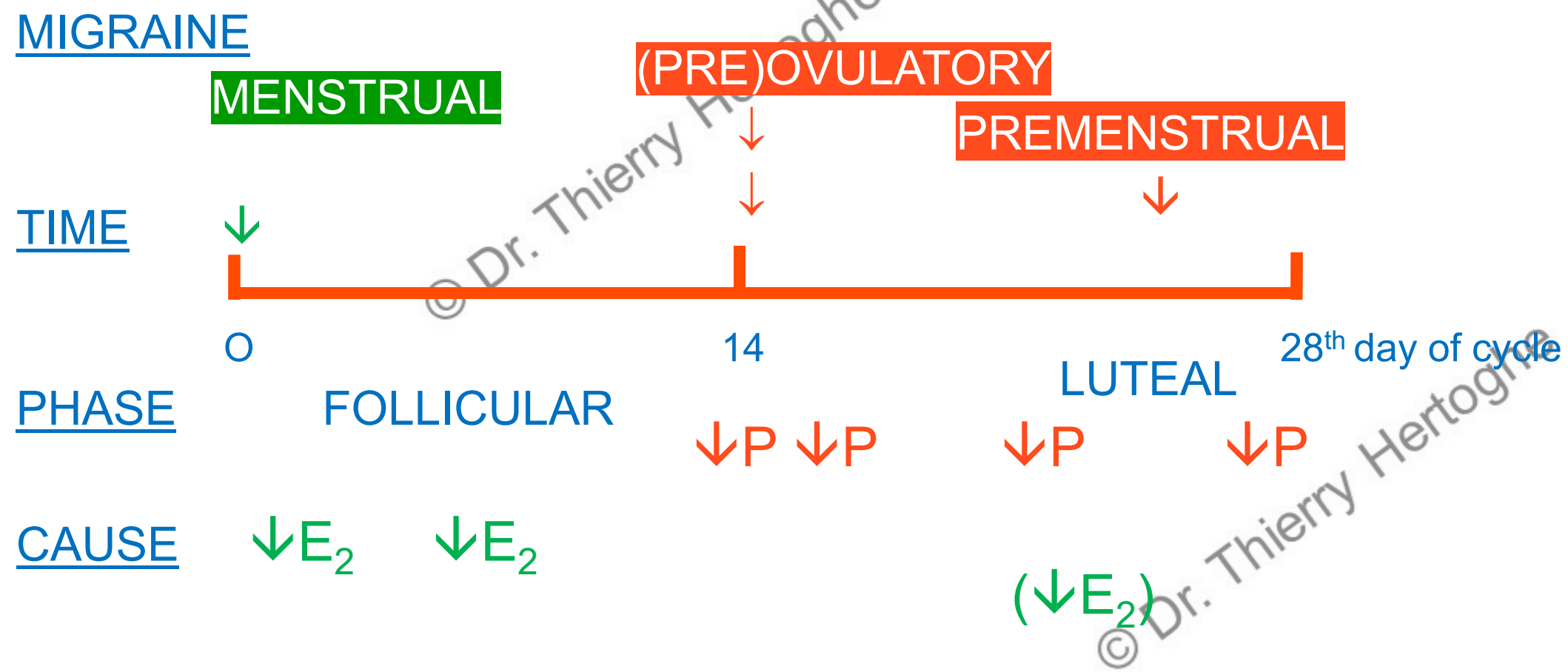
Migaine in the premenstrual period due to progesterone deficiency

Progesterone deficiency

- Brain edema

Especially in the premenstrual phase

Women with cyclical migraine



Difficult-to-treat PMS

⇒ Patient needs more bioidentical **progesterone**

⇒ OR more transdermal estradiol or thyroid or cortisol or …

PMS with anxiety-nervousness due to progesterone deficiency

Progesterone deficiency

Most frequent!

- Water retention => Brain edema
- Catecholestrogen accumulation => Estrogen excess

Especially in the premenstrual phase

PMS with depression due to estradiol deficiency

Estradiol deficiency

- Poor brain blood flow
- Catecholestrogen deficiency

in follicular & premenstrual phases

Premenstrual syndrome due to estrogen- & progesterone deficiencies

Treat the CAUSE(S)

ADD

- Transdermal estradiol: at a low to medium to dose (0.75-1.5 5 mg/day)
- + Oral progesterone with a medium to high dose (150-200 mg/day)

- Magnesium (2x 200-300 mg/day elemental Mg)
- Vitamin B6 (2x 100 mg/day)

PMS with muscle weakness due to testosterone deficiency

Testosterone deficiency

- Overexcited brain due to catecholamin excess => adrenaline outbursts => dramatizing
- Testosterone deficency (testo =precursor to E2) => estradiol deficiency => (dramatic) depression

in follicular & premenstrual phases

PMS with muscle weakness due to testosterone deficiency

Treat the CAUSE(S)

ADD

- Transdermal estradiol:
- Oral progesterone

- Transdermal estosterone: 0.5% gel or cream: 5 mg/day
- Or possibly: testosterone enanthate IM injections 50-100 mg/month
  + finasteride 2.5-7.5 mg/day

PMS with puffy face & weight gain due to hypothyroidism

Thyroid deficiency

- Brain edema (myxedema)
- Poor ovulation => progesterone deficiency => estrogen excess

in follicular phase with aggravation in premenstrual phase

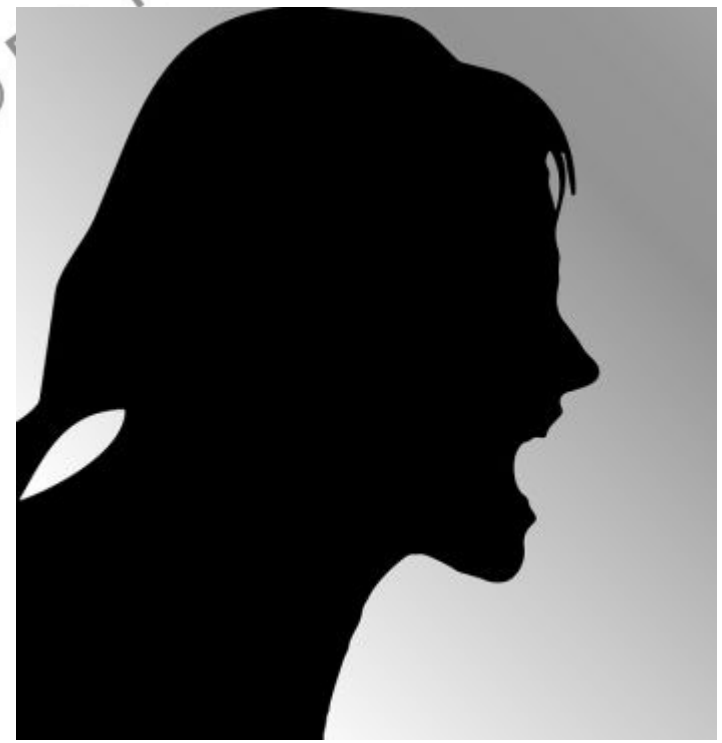
PMS with puffy face & weight gain due to hypothyroidism

Treat the CAUSE(S)

ADD

- Desiccated thyroid 30-150 mg/day upon awakening & at lunch
- Or T3-T4 combinations 10-50 µg to 40-200 µg/day

PMS with adrenaline outbursts due to cortisol deficiency



Cortisol deficiency

- Brain inflammation
- Catecholamin excess => adrenaline outbursts
- Poor ovulation=> progesterone deficit => estrogen excess

in follicular phase with aggravation in premenstrual phase

PMS with adrenaline outbursts due to cortisol deficiency

Treat the CAUSE(S)

ADD

- Hydrocortisone 2x 10 mg/day upon awakening & at lunch
- DHEA 20 mg/day
- (+ Fludrocortisone 0.1 mg/day in case of fainting, drowsiness ++)

PMS with mood & energy swings due to yeast infection

Yeast overgrowth

- Brain intoxication by mycotoxins
- Binding & inactivation of progesterone & cortisol by a steroid binding globulin in yeast => progesterone & cortisol deficiencies
- Poor ovulation=> estrogen, but more progesterone & deficits

in follicular phase with aggravation in premenstrual phase

PMS with mood & energy swings due to yeast infection

Treat the CAUSE(S)

ADD

- Antifungal medication
- STOP eating cereals (grains), dairy (milk) products, sweets, preserved foods

PMS with spasmophilia due to magnesium & calcium deficiencies

Magnesium & calcium deficiencies

- Overstimulation of brain & nerves => muscle spasms & carmps
- Poor ovulation => progesterone deficitency

in follicular phase with aggravation in premenstrual phase

PMS with spasmophilia due to magnesium & calcium deficiencies

Treat the CAUSE(S)

ADD

- Magnesium citrate (exciting), glycerophosphate (calming): 200-600 mg elemental magnesium)
- Calcium citrate 500-1500 mg/day
- AVOID ACID DRINKS (cola, coffee, Red bull, tea) , soft drinks => cause ↑ urinary magnesium & calcium excretion

PMS with muscle tenseness due to vitamin B6 deficiency

Pyridoxine deficiency

- Overtenseness of brain & nerves => tensed muscles
- Poor ovulation => progesterone deficiency

in follicular phase with aggravation in premenstrual phase

PMS with muscle tenseness due to vitamin B6 deficiency

Treat the CAUSE(S)

ADD

- Pyridoxin: 2x 100 mg/day
- Or Pyidoxal-5-phosphate 1-2x 50 mg/day

PMS with exhaustion & collapse due to endocrine disruptors

Dioxins, pesticides with estrogenic structures

- Breakdown of brain & nerves => exhaustion
- Overstimulation of estrogen receptors
- Poor ovulation => progesterone deficiency

in follicular phase with aggravation in premenstrual phase

PMS with exhaustion & collapse due to endocrine disruptors

Treat the CAUSE(S)

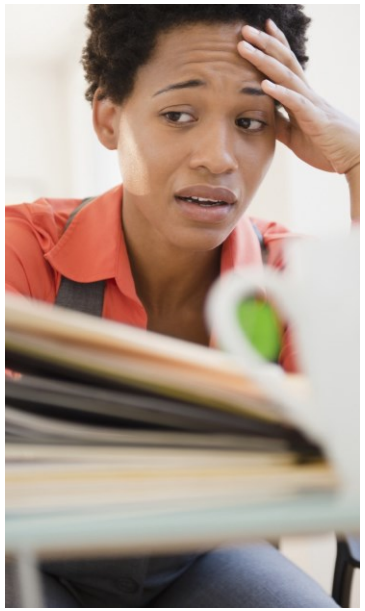
- Breath fresh & clean, unpolluted outdoor air
- Eat organic foods
- Avoid plastic food packaging
- Avoid indoor pollutants: carpets, wood preservatives, formaldehyde, etc.
- Wear natural clothes (cotton), no synthetic

Premenstrual syndrome => Causes

MOST 2 FREQUENT	Main feature	Info
Progesterone deficiency	Anxious PMS, weight gain	
Estradiol deficiency	Depressive PMS	
10 LESS FREQUENT		
Thyroid deficiency	Slow reactive, weight gain	
	or type A (excessively active) PMS	
Cortisol deficiency :	Stressed PMS	sugar cravings
Androgen deficiency	PMS w/ low physically endurance	
Magnesium & calcium deficiency	**Spasmophilic PMS**	
Vitamin B_6 (pyridoxine) deficiency	Muscle tensed PMS	
Yeast infection		**Irregularly nactivates cortisol & progesterone more than P_4 and E_2**
Estrogenic disruptors	Exhaustied, toxic PMS	Dioxines, estrogenic pesticides (PCP, …)
Alcohol		↗ testo → E_2

Severe premenstrual syndrome due to multiple deficiencies

Treat the CAUSE(S)



- Oral progesterone
- Transdermal estradiol
- Transd.testosterone 5 mg/day (or IM 50-100 mg/mo +finasteride)

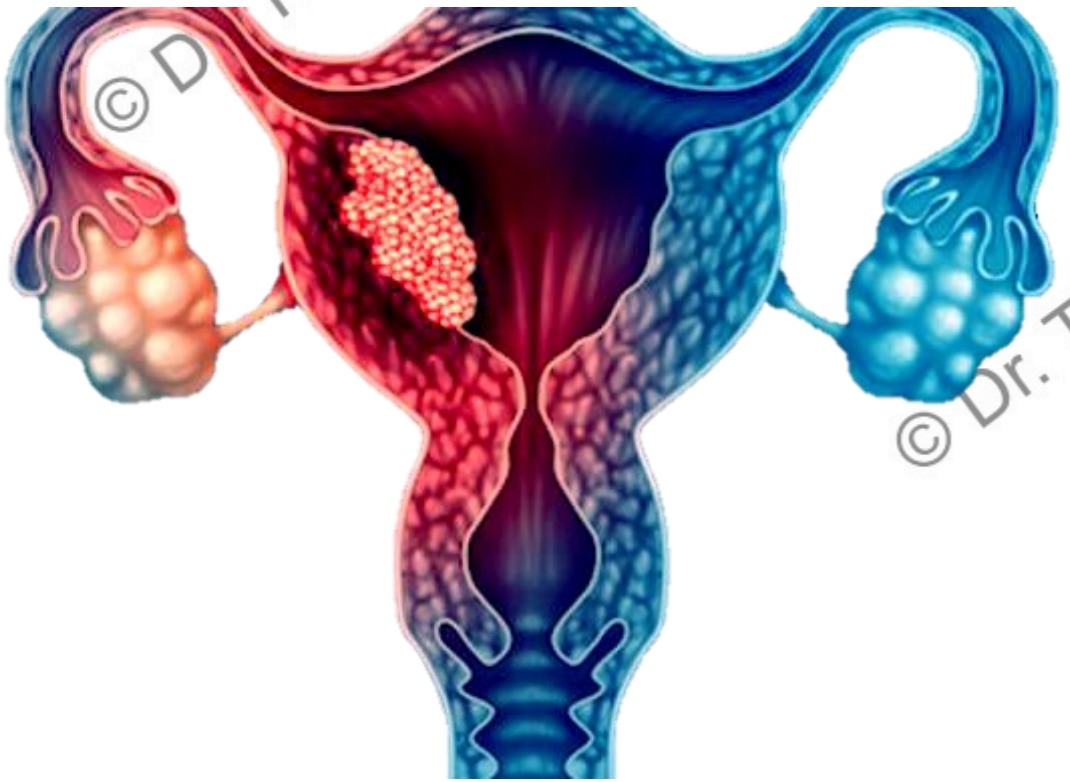
- Oral thyroid treatment: 30-150 mg desiccated thyroid
- Oral hydrocortisone 2x 10 mg + DHEA 20 mg/day

- Magnesium (2x 200-300 mg/day elemental Mg)
- Calcium (500-1500 mg/day)
- Vitamin B6 (2x 100 mg/day)

- Stop acid drinks, stop caffeine
- Antifungal diflucan 50 mg/day (4-6 wks), stop dairy, sweets, grains

Endometrial cancer

Estrogen excess => Endometrial cancer



1. Aleem FA, Moukhtar MA, Hung HC, Romney SL. Plasma estrogen in patients with endometrial hyperplasia and carcinoma. Cancer. 1976 Nov;38(5):2101-4 *(" … total plasma estrogen levels in the endometrial hyperplasia and endometrial carcinoma groups were significantly higher than those measured in the control group.")*

2. Lindahl B, Willén R. Endometrial hyperplasia following estrogen treatment without the addition of gestagen. A follow-up study after withdrawal of estrogens. Anticancer Res. 1991 Nov-Dec;11(6):2071-3 *("The frequency of carcinomatous development was much higher for exogen estrogen induced hyperplasias compared to earlier findings for endogenously estrogen-induced endometrial hyperplasias. It is recommended that non-opposed estrogen treatment should be used in rare circumstance")*

↓ Progesterone levels => ↑ Endometrial cancer

1. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev. 2013 Feb;34(1):130-62. (Insufficient progesterone action strikingly increases the risk of endometrial cancer.)

Progesterone treatment => ↓ Endometrial cancer

1. Ørbo A, Rise CE, Mutter GL. Regression of latent endometrial precancers by progestin infiltrated intrauterine device. Cancer Res. 2006 Jun 1;66(11):5613-7 ("87 patients .. Biopsies .. scored as containing a latent endometrial precancer. All groups had a similar proportion of latent precancers at intake but differed after therapy. …The IUD group had the highest rate of regression, with a 62% pretherapy and 5% post-therapy rate of latent precancers. This contrasted to nonsignificant changes for the oral progestin and untreated control groups.")
2. Lin MC, Burkholder KA, Viswanathan AN, Neuberg D, Mutter GL. Involution of latent endometrial precancers by hormonal and nonhormonal mechanisms. Cancer. 2009 May 15;115(10):2111-8 ("The frequency of latent precancers was found to be significantly reduced in oral contraceptive-exposed (13%; odds ratio [OR], 0.19 [P < .001]) and intrauterine device-exposed (18%; OR, 0.42 [P = .015]) women compared with respective matched controls (43% and 34%).")
3. Yang S, Thiel KW, De Geest K, Leslie KK. Endometrial cancer: reviving progesterone therapy in the molecular age. Discov Med. 2011 Sep;12(64):205-12. (While still in the preclinical stage, we believe this strategy to re-establish PR expression will result in resensitization of endometrial tumors to progestin therapy.)

Substance abuse

⇒ Patient needs more progesterone

Progesterone treatment => ↓ Tobacco & cocaine abuse

Progesterone treatment

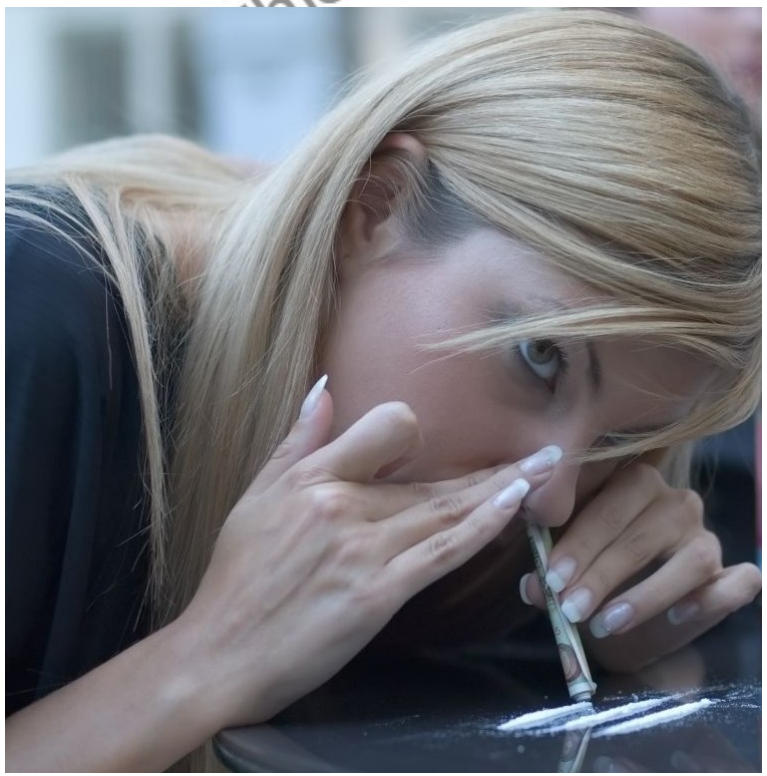
↓ Smoking abuse during pregnancy & postpartum

1. Forray A, Gilstad-Hayden K, Suppies C, Bogen D, Sofuoglu M, Yonkers KA. Progesterone for smoking relapse prevention following delivery: A pilot, randomized, double-blind study. Psychoneuroendocrinology. 2017 Dec;86:96-103.
2. Allen SS, Allen AM, Lunos S, Tosun N. Progesterone and postpartum smoking relapse: A pilot double-blind placebo-controlled randomized trial. Nicotine Tob Res. 2016 Nov;18(11):2145-2153

↓ Cocaine craving & use

1. Milivojevic V, Fox HC, Sofuoglu M, Covault J, Sinha R. Effects of progesterone stimulated allopregnanolone on craving and stress response in cocaine dependent men and women. Psychoneuroendocrinology. 2016 Mar;65:44-53. (Individuals in the high versus the low progesterone group showed … reduced cocaine craving)
2. Sofuoglu M, Poling J, Gonzalez G, Gonsai K, Oliveto A, Kosten TR. Progesterone effects on cocaine use in male cocaine users maintained on methadone: a randomized, double-blind, pilot study. Exp Clin Psychopharmacol. 2007 Oct;15(5):453-60.

↑ Serum progesterone => ↑ Serum cortisol response to stress in cocaine-dep. men & women



Men & women with ↑ serum progesterone

vs subjects with ↓ serum progesterone

↑ Serum cortisol response to stress

Milivojevic V, et al. Psychoneuroendocrinology. 2016 Mar;65:44-53

Thank you for your attention!