

First-line Hormone Therapy Options: Transdermal Estrogen and Micronized Progesterone

“Growing body of evidence that each type of estrogen and progestogen, route of administration and timing of therapy has distinct beneficial and adverse effects.”

The North American Menopause Society. *Menopause*, 2010;17(2):242-55.

Overall Benefits of Hormone Therapy (HT)

- ↓ Vasomotor symptoms
- ↓ Urogenital atrophy
- ↓ Risk of colorectal cancer
- ↓ Risk of osteoporotic fractures
- ↓ Somatic pain, arthralgia
- Mood stabilization

SOGC MENOPAUSE AND OSTEOPOROSIS UPDATE 2009: Recommendations for Hormone Therapy

J Obstet Gynaecology Can, 2009; Jan;31(1)(Suppl 1).

- HT should be prescribed at the appropriate dose, route and duration according to symptoms and to achieve treatment goals
- Primary indication for HT: Management of moderate to severe menopausal symptoms (Grade A)
- Vaginal therapy for vaginal symptoms only
- Prolonged therapy may be offered with appropriate assessment and counselling
- HT should **not** be prescribed for primary or secondary prevention of cardiovascular disease or primary prevention of dementia (Grade A)

Micronized Progesterone

- Metabolized primarily by the liver
- Metabolites act at non-sex-steroid receptor sites
- Beneficial effects of metabolites:
 - Sedation with higher doses of oral progesterone (**utilized therapeutically for sleep**)
 - 11-deoxycorticosterone has aldosterone properties (may reduce fluid retention)
- Adverse effects of metabolites:
 - May cause nausea and dizziness
 - Contraindicated in patients with peanut allergy

Progestogen Indications

(NAMS. *Menopause*, 2010.)

- Primary menopause-related indication is endometrial protection from unopposed ET
- Not necessary with standard doses of vaginal ET (including vaginal ring)
- Adequate progestogen (as CC-EPT or CS-EPT) recommended with intact uterus
- Progestogen not generally indicated with ET post-hysterectomy

	Micronized Progesterone	Medroxyprogesterone Acetate
CHD The Writing Group for the PEPI Trial. <i>JAMA</i> , 1995; 273:202.	CEE with cyclic MP has the most favourable effect on HDL-C and no excess risk of endometrial hyperplasia In a woman with a uterus, CEE with cyclic MP has the most favourable effect on HDL-C and no excess risk of endometrial hyperplasia	
Breast Cancer French E3n Cohort Study, Fournier, Br Ca Res. Treat, 2008;107:103-111.	Estrogen in combination with micronized progesterone is not associated with an increased risk of breast cancer Estrogen/Progesterone RR 1.00 (0.83-1.22) Estrogen/dydrogesterone RR 1.16 (0.94-1.43)	Estrogen therapy used with progestin has been associated with an increased risk of breast cancer within three to five years of starting therapy: Estrogen/progestin RR 1.69 (1.50-1.9)
VTE Rosano GM, et al. <i>J AM Coll Cardiol</i> , 2000;36:2154-2159.	Micronized progesterone does not counteract estrogen-mediated effects on blood vessels	Medroxyprogesterone Acetate may negate the beneficial effects of estrogen on the blood vessels
Bleeding Patterns Lorrain J, et al. <i>Int J Gynecol Obstet</i> , 1991;13:297-311. Marengo M, et al. <i>Proceedings of the 4th International Symposium in Osteoporosis</i> , 1993:331-333.	Micronized progesterone is associated with a lower incidence of bleeding overall	

Transdermal Estrogen

The key differences between oral and transdermal therapy is in their metabolism:

- Orally-administered HT must go through **first-pass metabolism** in the liver and digestive tract before entering the circulation.
- Transdermal preparations do not go through this route, entering directly into the circulation.

Prescribe as a first-line therapy to relieve menopausal symptoms for any woman, in addition to patients with underlying medical conditions which may make transdermal HT the preferred route of administration:

- Higher risk of DVT or PTE
- Gall bladder disease
- High triglyceride levels
- Hypertension

Clinical Pearls

- Total surface area gel spread determines level of circulating estrogen, i.e., ↑ surface area ↑ level
- Surface area of patch determines rate of absorption and circulating levels of estrogen

To maintain stable levels:

- The gel must be applied to same surface area with regular frequency as prescribed
- The patch can be applied to any area with regular frequency as prescribed

Tapering down transdermal estrogen:

- Surface area of the same dose of gel can be decreased, or decrease the number of pumps
- All matrix patches can be cut down as necessary to decrease surface area for absorption
- Results in decreasing levels of circulating estrogen
- Reservoir patches cannot be cut (i.e., Estraderm)

	Transdermal estrogen	Oral estrogen
<p>Risk of stroke</p> <p>Scarabin P-Y et al. <i>Lancet</i>, 2003; 362 :428-432. Santen RJ et al., Postmenopausal hormone therapy: an Endocrine Society Scientific Statement. <i>J Clin Endocrinol Metab</i>, 2010; 95 Suppl 1:S7-S66. Canonico M, et al. <i>Circulation</i>, 2007; 115:840.</p>	<p>Transdermal estrogen does not increase venothrombotic episode risk</p>	<p>Increased risk of stroke with oral HT, including low-dose estrogen, estrogen alone or combined estrogen plus progestin oral</p> <p>These types of hormone therapy may increase stroke risk—this translates into an absolute excess risk of about 4.5 additional cases per 1000 women per 5 years of use</p>
<p>Cardiovascular risk</p> <p>Sanada N, et al. <i>Menopause</i>, 2004;11:331. Walsh BW, et al. <i>N Engl J Med</i>, 1991;325:1196. Modena MG. et al. <i>Am J Med</i>, 2002; 113:331-4. Lewandowski KC. <i>J Clin Endo</i>, 2006; 91: 3123-30. Che MC. <i>Am J Ob Gyn</i>, 2008; 199: 526.e1-526.e7. The Writing Group for the PEPI trial. <i>JAMA</i>, 1995; 273:199-208.</p>	<p>Decreased CV risk in patients with metabolic syndrome</p> <p>Tryglicerides decreased</p> <p>Less favourable for HDL and LDL changes</p>	<p>Oral estrogen can further elevate trygliceride levels</p>
<p>Metabolism</p>	<p>Transdermal preparations bypass liver, entering directly into the circulation</p>	<p>HT must go through first-pass metabolism in the liver and digestive tract before entering the circulation</p>
<p>Steady State</p>	<p>Daily mood swings</p> <p>Migraine headaches</p> <p>Patients who do shift work</p>	
<p>Compliance</p>	<p>Stomach upset due to oral estrogen intake</p> <p>Problems with using a daily pill</p>	

Contraindications to HT	Non-contraindications to HT
<ul style="list-style-type: none"> • Unexplained/undiagnosed vaginal bleeding prior to investigation • Known or suspected breast carcinoma • Acute liver disease • Active thromboembolic disease (estrogen only) • Pregnancy 	<ul style="list-style-type: none"> • Smoking • Diabetes • Hypertension • Migraine