TEDAVİDE KULLANILAN HORMONLAR VE KULLANIM PROTOKOLLERİNDEKİ ÖZELLİKLER
(Kullanım yolu, uygulama protokolleri, süre)

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Kasım 2002-Bolu Abant
Türk Menopoz-Osteoporoz Derneği
HRT Konsensus Toplantısı

HRT'nin geldiği nokta 2019 ?

- **Kadınlar**-------bilmiyor, talep etmiyor, KORKUYOR
- **Doktorlar**------bilmiyor, **sorumluluk almak istemiyor**
- **İlaç firmaları**-----yeni ilac piyasaya vermiyorlar, satışlar cok düşük, **ilgilenmiyorlar**
- **Fırsatçılar**----Kanıta dayalı olmayan alternatifler (doğal hormonlar, fitoöstrojenler, vitaminler, bitkiler vs.)

Previously known as ;

Hormone Replacement Therapy (HRT),

Menopause Hormone Therapy (MHT)

ET

EPT

Menopause

- Premature menopause
- Early menopause
- Surgical menopause
- Natural menopause

POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

FDA-APPROVED INDICATIONS

- Vasomotor symptoms (Level I)
- Prevention of bone loss (Level I)
- Premature hypoestrogenism (Level II)
  - Hormone therapy is approved for women with hypogonadism, POI, or premature surgical menopause
- Genitourinary symptoms (Level I)

Indications for HRT

Vasomotor	Hot flushes / perspirations
Psycho-somatic	Sleep disturbances (frequent wake-ups)
	Easy fatigue
	Concentration deficit ("mental fog")
	Mood disturbances
	Lack of interest
	Headache / arthralgia / myalgia
Sexual / urogenital	Vaginal dryness
	Dyspareunia
	Loss of libido
	Recurrent cystitis / vaginitis

MHT Decision

Use

- Mod-severe VMS not relieved by lifestyle changes
- NO contraindications
- Newly menopause

Not Use

- VMS not bothersome
- Symptoms only vaginal- use ET
- Contraindication to E2
- Late menopause

COMMITTEE OPINION

Number 698 • May 2017

Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice in collaboration with committee member Samantha F. Butts, MD, MSCE.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Hormone Therapy in Primary Ovarian Insufficiency

Table 1. Bioequivalent Hormonal Dosages for Hormone Therapy for Primary Ovarian Insufficiency*

	Progestogen	
Estrogen	**Continuous**	**Sequential**
1–2 mg micronized 17β-estradiol (oral)	2.5–5 mg medroxyprogesterone acetate daily (oral)	10 mg medroxyprogesterone acetate daily (oral) for 12 days each month
100 micrograms 17β-estradiol (transdermal) 0.625–1.25 mg conjugated equine estrogen (oral)	100 mg micronized progesterone daily (oral)	200 mg micronized progesterone daily (oral) for 12 days each month

*Select one of the estrogen options to be combined with one of the progestogen options.

Summary table of indication for the prescription of HRT in women with POI 2016

Sequelae of POI	Indication for HRT	Supporting recommendation / conclusion
Vasomotor symptoms	YES	*Hormone replacement therapy is indicated for the treatment of vasomotor symptoms in women with POI.*
Genito-urinary symptoms	YES	*Both systemic & local estrogens are effective in treatment of genito-urinary symptoms.*
Life expectancy	?	*Life expectancy appears to be reduced due to cardiovascular mortality: HRT may be of indirect benefit.*
Bone health	YES	*Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.*
Cardiovascular health	YES	*Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in POI to control future risk of cardiovascular disease; it should be continued at least until* the average age of natural menopause.
Quality of life	?	*Quality of life appears to be reduced: HRT may be of indirect benefit.*
Sexual function	YES	*Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.*
Neurological function	?	*Estrogen replacement to reduce the possible risk of cognitive impairment should be considered in women with POI at least until the average age of natural menopause.*

Who Shouldn't Take Hormone Replacement Therapy?

If you have these conditions, you may want to avoid HRT:

- Blood clots
- Cancer (such as breast, uterine, or endometrial)
- Heart or liver disease
- Heart attack
- Known or suspected pregnancy
- Stroke

Unexplained vaginal bleeding

Androgen

The use of androgen is contraindicated in women with extensive cardiac, hepatic, or renal disease.[48]

Box 2. Conditions that are not contraindications to HRT

- Asthma
- Past history of benign breast disease
- Previous abnormal smears/cervical cancer
- Contact lens wearers
- Depression
- Diabetes
- Controlled blood pressure
- Hyperlipidaemia
- Melanoma
- Multiple sclerosis
- Obesity
- Renal failure
- Sickle cell anaemia
- Smoking
- Thyroid disease

What Are the Side Effects of Hormone Replacement Therapy?

HRT comes with side effects. Call your doctor if you have any of these:

- Bloating
- Breast swelling or tenderness
- Headaches
- Mood changes
- Nausea
- Vaginal bleeding

premenstrual syndrome type of side effects

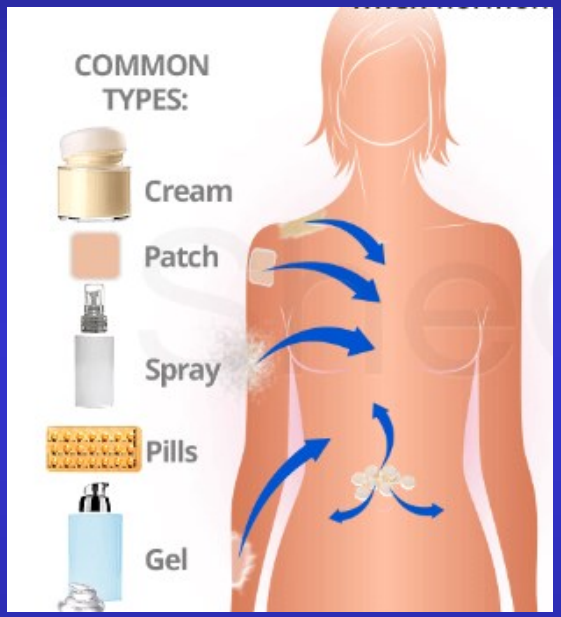
weight gain

heavy or painful withdrawal period

heavy or painful withdrawal period

Östrojen tedavisi-uygulama yolları

- Oral
- Parenteral
  - Transdermal patch
  - Perkutanöz jel
  - Spray
  - Krem
  - S.C İmplant
- Lokal
  - Tablet, krem, halka



Target organs of oestrogen

- Bone
- Urogenital
- Vasomotor
- Heart
- Eyes
- Teeth
- Breast
- Colon

Functions of estrogen

- Regulates body temp
- Improves insulin sensitivity
- Increases basal metabolic rate
- Increases blood flow
- Improves sleep
- Maintains skin collagen
- Decreases risk of cataracts Increases bone density
- Decreases LDL,increases HDL
- Increases mood and energy
- Decreases wrinkles
- Decreases homocysteine
- Increases serotonin formation
- Decreases depression,anxiety,pain sensitivity

Consequences of oestrogen loss

Symptoms (early)	Hot flushes Insomnia Irritability Mood disturbances
Physical changes (intermediate)	Vaginal atrophy Stress (urinary) incontinence Skin atrophy
Diseases (late)	Osteoporosis Cardiovascular disease Dementia of the Alzheimer's type Cancers

Functions of progesterone

Progesterone

- Helps the body use estrogen
- Prevents and treat symptoms of estrogen excess or deficiency (i.e. vasomotor symptoms)
- Natural antidepressant
- Prevents endometrial overgrowth
- Has receptors in almost every cell of the body
- Progesterone is needed not only for its balancing effect on uterine tissue, but also its effect on the breast tissue, heart, brain, bones and its balancing effect on other hormones.

Progesterone vs. Progestins

- Progesterone is the same hormone that is produced and circulates in your body
  - Vital to pregnancy
- Progestins are synthetically produced molecules that produce the same effects on the endometrium as progesterone
  - Do not have the same structure
  - May not function the same as progesterone in other tissues

Progestogens in the Menopause Transition

- Progestogens alone or low-dose oral contraceptives can be offered as alternatives for the relief of menopausal symptoms during the menopausal transition

- E.g.,Oral progesterone 200mg nightly day14-28 of cycle

MHT regimens

- Sequential preparation: progestogen added for 12-14 days each month. Some women will not bleed on sequential preparations and this is not a cause for concern provided that the progestogen is taken correctly.

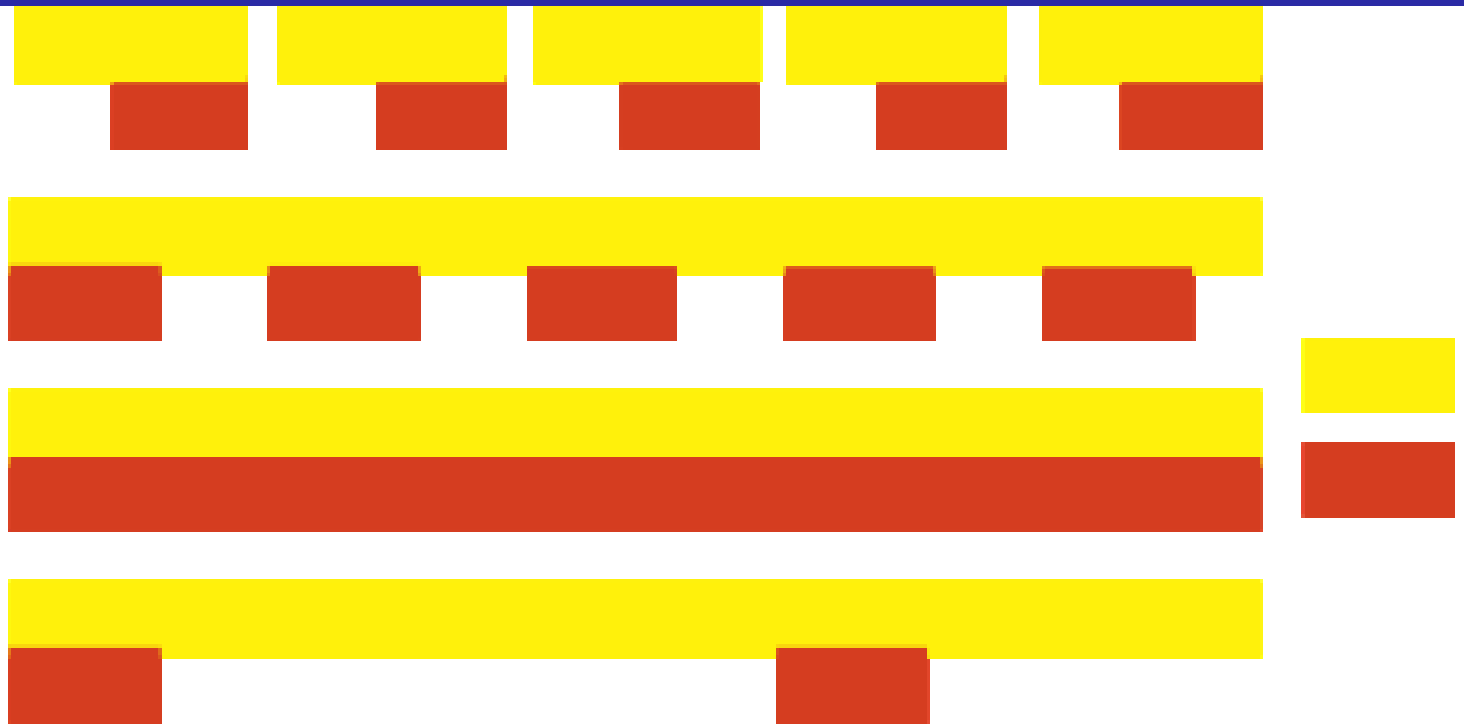
- Continuous combined : give oestrogen and progestogen daily. These preparation induces endometrial atrophy. Intermittent bleeding and spotting are common in the first few month of use. More suitable for women who are at least one year since their last spontaneous period.

Management of irregular bleeding

- Sequential regimen: bleeding should occur at around the time of progestogen withdrawal (on or after day 11). Bleeding occurs at other time or persistent irregular bleeding should be investigated.

- Continuous combined regimen: amenorrhoea should be achieved 4 months after start of treatment. Spotting during the first few months is common. Spotting which occurs after a period of amenorrhoea should be investigated.

Regimens for Hormone Replacement Therapy



Molecules

Estrogens	Progestogens
17-β estradiol	Natural progesterone
Conjugated Equine Estrogens	Dydrogesterone
	Norethisterone
	Drospirenone

Medroxyprogesterone acetate

Levonorgestrel/ norgestrel

Estrogen Therapy

Estrogen Therapy: Doctors generally suggest a low dose of estrogen for women who have had a hysterectomy, the surgery to remove the uterus. Estrogen comes in different forms. The daily pill and patch are the most popular, but the hormone also is available in a vaginal ring, gel, or spray.

- **Estrogen pill** — Pills are the most common treatment for menopausal symptoms. Among the many forms of pills available are conjugated estrogens (Cenestin, Estrace, Estratab, Femtrace, Ogen, and Premarin) or estrogens-bazedoxifene (Duavee). Follow your doctor's instructions for dosing. Most estrogen pills are taken once a day without food. Some have more complicated dosing schedules. As noted above, estradiol is the same estrogen that the ovary makes before menopause. (note there are also combination pills that include both estrogen and progestin)

- **Estrogen patch** — the patch is worn on the skin of your abdomen. Depending on the dose, some patches are replaced every few days, while others can be worn for a week. Examples are Alora, Climara, Estraderm, and Vivelle-Dot. Combination estrogen and progestin patches -- like Climara Pro and Combipatch -- are also available. Menostar has a lower dose of estrogen than other patches, and it's only used for reducing the risk of osteoporosis. It doesn't help with other menopause symptoms.

- **Topical Estrogen –** Creams, gels and sprays offer other ways of getting estrogen into your system. Examples include gels (like Estroge and Divigell), creams (like Estrasorb), and sprays (like Evamist). As with patches, this type of estrogen treatment is absorbed through the skin directly into the bloodstream. The specifics on how to apply these creams vary, although they're usually used once a day. Estrogel is applied on one arm, from the wrist to the shoulder. Estrasorb is applied to the legs. Evamist is applied to the arm.

- **Vaginal estrogen** — Vaginal estrogen comes in a cream, vaginal ring, or vaginal estrogen tablets. In general, these treatments are for women who are troubled specifically by vaginal dryness, itchiness, and burning or pain during intercourse. Examples are vaginal tablets (Vagifem), creams (Estrace or Premarin), and insertable rings (Estring or Femring). Dosing schedules vary, depending on the product. Most vaginal rings need to be replaced every three months. Vaginal tablets are often used daily for a couple of weeks; after that, you only need to use them twice a week. Creams might be used daily, several times a week, or according to a different schedule.

to use them twice a week. Creams might be used daily, several times a week, or according to a different schedule.

Estrogen/Progesterone/Progestin Hormone Therapy

This is often called combination therapy, since it combines doses of estrogen and progestin, the synthetic form of progesterone. It's meant for women who still have their uterus. Taking estrogen with progesterone lowers your risk for cancer of the endometrium, the lining of the uterus.

While generally used as a form of birth control. Progesterone can help treat many menopausal symptoms such as hot flashes

- **Oral progestins** – Taken in pill form, progestin medications include medroxyprogesterone acetate (Provera) and the synthetic progestin pills (norethindrone, norgestrel). Many experts now treat the majority of their menopausal patients with natural progesterone rather than synthetic progestins. Natural progesterone has no negative effect on lipids and is a good choice for women with high cholesterol levels. In addition, natural progesterone might have other advantages when compared with medroxyprogesterone acetate.
- **Intrauterine progestin** – Not approved for this use in the United States, the low-dose intrauterine devices (IUD) levonorgestrel are sold under the brand names: Liletta, Kyleena, Mirena and Skyla). If you had one of these IUDs when you enter perimenopause, your doctor may suggest that you keep it in until after menopause is complete.

2018

TABLE 1. Commonly Prescribed FDA-approved Hormone Therapies for Treatment of Vasomotor Symptoms

Preparation	Dose	Available Doses
Estrogen therapies		
Oral		
Conjugated equine estrogens	0.3 mg/d	0.3, 0.45, 0.625, 0.9, 1.25 mg
Micronized 17-B estradiol	0.5 mg/d	0.5, 1.0, 2.0 mg
Transdermal		
17-B estradiol patch	25 mcg	14, 25, 37.5, 50, 75, 100 mcg
17-B cutaneous gel	0.25-1.25 g	0.25, 0.5, 0.75, 1.0 mg/d
17-B cutaneous spray	1.5 mg/d	1.5, 3.0, 4.5 mg/d
Vaginal ring (systemic)		
Estradiol acetate	0.05 mg/d	0.05, 0.10 mg/d 90 d duration
Progestogen therapies		
Oral		
MPA	2.5 mg/d	2.5, 5.0, 10 mg/d
Norethindrone	0.35 mg/d	0 .35 mg/d
Micronized progesterone	100 mg/d	100, 200 mg/d
Intrauterine progestin		
Levonorgestrel	6 mcg/d	13.5 mg for 3 y
	20 mcg/d	52 mg for 5 yr
Vaginal gel progesterone	4%	4%, 8%; as 45 or 90 mg, app
Combination HT		
Oral		
CEE+MPA	0.3/1.5 mg/d	0.3/1.5; 0.45/1.5; 0.625/2.5; 0.625/5
17B-E2+norethindrone ace	0.5/ 0.1 mg/d	0.5/0.1; 1/0.5 mg/d
17B-E2+drospirenone	0.5/0.25 mg/d	0.5/0.25; 1.0/0.5; 1.0/1.0 mg/d
EE+norethindrone acetate	2.5 mcg/0.5 mg/d	2.5/0.5; 5.0/1.0 mg/d
CEE+BZA	0.45 mg/20 mg/d	1 dose available
Transdermal		
17B-E2+norethindrone ace	50 mcg/0.14 mg	50/0.14; 50/0.25/patch
17-BE2+LNorg	45 mcg/0.015 mg	1 dose available

17-B E2 indicates 17-B estradiol; ace., acetate; BZA, bazedoxifene; CEE, conjugated equine estrogens; EE, ethinyl estradiol; LNorg, levonorgestrel; MPA, medroxyprogesterone acetate.

Adapted from Stuenkel et al,[1] and The North American Menopause Society.[2]

Table X. Estrogen therapy products approved for postmenopausal use in the United States

Oral products		
Composition	**Product name(s)**	**Range of available dose strengths**
Conjugated estrogens	Premarin	0.3-1.25 mg
Synthetic conjugated estrogens, A*	Cenestin	0.3-1.25 mg
Synthetic conjugated estrogens, B**	Enjuvia	0.3-1.25 mg
Esterified estrogens	Menest	0.3-1.25 mg
17β-estradiol	Estrace, various generics	0.5-2.0 mg
Estradiol acetate	Femtrace	0.45-1.8 mg
Estropipate	Ortho-Est	0.625 mg (0.75 mg estropipate, calculated as sodium estrone sulfate 0.625 mg) to 5.0 mg (6.0 mg)
Transdermal products		
Composition	**Product name(s)**	**Dose details**
17β-estradiol matrix patch	Alora, Climara, Esclim, Fempatch, Menostar, Vivelle, Vivelle-Dot, various generics	0.014-0.1 mg delivered daily; applied once or twice weekly
17β-estradiol reservoir patch	Estraderm	0.05-0.1 mg delivered daily; applied twice weekly
17β-estradiol transdermal gel	EstroGel, Elestrin, Divigel	Applied daily via metered pump or packet delivering 0.52-0.75 mg of 17β-estradiol in gel
17β-estradiol topical emulsion	Estrasorb	2 packets applied daily
17β-estradiol transdermal spray	Evamist	1 spray/d, up to 2-3/d if needed

* 9 estrogens

Table X. Estrogen therapy products approved for postmenopausal use in US (cont'd)

Vaginal products

Composition	Product name(s)	Dose details
17β-estradiol vaginal cream*	Estrace Vaginal Cream	Initially 2-4 g/d for 1-2 wk, followed by maintenance dose of 1 g/d (0.1 mg active ingredient/g)
Conjugated estrogens cream*	Premarin Vaginal Cream	For vaginal atrophy: 0.5-2 g/d for 21 d then off 7 d For dyspareunia: 0.5 g/d for 21 d then off 7 d , or twice weekly (0.625 mg active ingredient/g)
17β-estradiol vaginal ring	Estring	Device containing 2 mg releases 7.5 µg/d for 90 days (for vulvovaginal atrophy)
Estradiol acetate vaginal ring	Femring	Device containing 12.4 mg or 24. 8 mg estradiol acetate releases 0.05 mg/d or 0.10 mg/d estradiol for 90 days (both doses release systemic levels for treatment of vulvovaginal atrophy and vasomotor symptoms)
Estradiol hemihydrate vaginal tablet	Vagifem	Initially 1 tablet/d for 2 wk, followed by 1 tablet twice weekly (tablet 10 µg of estradiol hemihydrates, equivalent to 10 µg of estradiol; for vulvovaginal atrophy)

*N.B. Higher doses of vaginal estrogen are systemic, meant to relieve hot flashes as well as vaginal atrophy; the lower doses are

Table XX. Combination EPT products comparing estrogen and progestogen doses

Product name(s)	Standard/low dose	Estrogen	Progestogen
Prempro	Standard	0.625 mg conjugated estrogens	2.5 or 5 mg medroxyprogesterone acetate
	Low	0.3 or 0.45 conjugated estrogens	1.5 mg medroxyprogesterone acetate
Femhrt	Standard	5 µg ethinyl estradiol	1 mg norethindrone acetate
	Low	2.5 µg ethinyl estradiol	0.5 mg norethindrone acetate
Activella	Standard	1 mg 17β-estradiol	0.5 mg norethindrone acetate
	Low	0.5 mg 17β-estradiol	0.1 mg norethindrone acetate
Angeliq	Low	0.5 mg 17β-estradiol	1 mg drospirenone
	Lower	0.25 mg 17β-estradiol	0.5 mg drospirenone

Türkiyede Menopoz Tedavisi Endikasyonlu İlaclar

GYNOFLOR	IBRAHIM	ESTRADIOL + LACTOBACILLUS ACIDOPHILUS
ESTROFEM	NOVO NORDISK	ESTRADIOL
CYCLO PROGINOVA	BAYER	ESTRADIOL + NORGESTREL
ESTRIOL	ASSOS ILAC	ESTRIOL
TRISEQUENS	NOVO NORDISK	ESTRADIOL + NORETHISTERONE
CLIMARA	BAYER	ESTRADIOL
VAGIFEM	NOVO NORDISK	ESTRADIOL
CLIMEN	BAYER	CYPROTERONE + ESTRADIOL
ANGELIQ	BAYER	DROSPIRENONE + ESTRADIOL
DIVINA	IBRAHIM	ESTRADIOL + MEDROXYPROGESTERONE
ACTIVELLE	NOVO NORDISK	ESTRADIOL + NORETHISTERONE
KLIOGEST	NOVO NORDISK	ESTRADIOL + NORETHISTERONE
COLPOTROPHINE	MERCK SERONO	PROMESTRIENE
ESTRADERM TTS	NOVARTIS	ESTRADIOL
ESTREVA	MERCK SERONO	ESTRADIOL
LIVIAL	M.S.D.	TIBOLONE

Table 1. Treatment Options for Menopausal Vasomotor Symptoms

Treatment	Dosage/Regimen	Evidence of Benefit*	FDA Approved
	Hormonal		
Estrogen-alone or combined with progestin			
• Standard Dose	Conjugated estrogen 0.625 mg/d	Yes	Yes
	Micronized estradiol-17β 1 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.0375–0.05 mg/d	Yes	Yes
• Low Dose	Conjugated estrogen 0.3–0.45 mg/d	Yes	Yes
	Micronized estradiol-17β 0.5 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.025 mg/d	Yes	Yes
• Ultra-Low Dose	Micronized estradiol-17β 0.25 mg/d	Mixed	No
	Transdermal estradiol-17β 0.014 mg/d	Mixed	No

Dose of progestogen

Dose	Progesterone	Dydrogesterone	Norethisterone	Drospirenone
Standard	200 mg	10 - 20 mg	1 - 5 mg (per os) 250 µg (transdermal)	-
Low	100 mg	5 - 10 mg	0.5 mg (per os) 125 µg (transdermal)	2 mg
Ultra-low	50 mg	2.5 - 5 mg	0.25 mg (per os) 63 µg (transdermal)	1 mg

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Androgen therapy in women

Key points

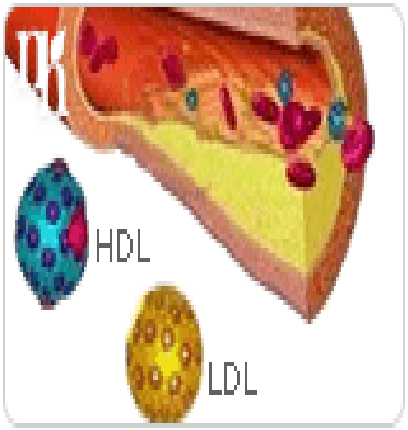
- Androgen levels decline with age in women with no significant change associated with the natural menopause [A]
- There is strong evidence that androgens influence female sexual function and that testosterone therapy may be useful for women with arousal or desire disorders [A]
- Women should be fully assessed for other treatable causes of sexual dysfunction before testosterone therapy can be considered
- Testosterone therapy should be considered as a clinical trial which should not be continued if a woman has not experienced benefit by 6 months [A]

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

Testosterone replacement therapy side effects

As with estrogen and progesterone replacement therapy, women undergoing synthetic testosterone are prone to side effects. The following have all been linked to testosterone replacement therapy in women, particularly in postmenopause:

- Increase in "bad" cholesterol (LDL)
- Decrease in "good" cholesterol (HDL)
- Unexplained fatigue
- Mood changes
- Fluid Retention



Natural Hormone Replacement Therapy

- The medical community's growing interest in finding a more “natural” approach to hormone therapy has focused attention on natural hormones. Natural hormones, also known as **bioidentical hormones**, are used to **treat menopause symptoms** and other manifestations of hormonal imbalance.
- Natural hormones are **plant-derived hormones** that are custom-mixed in order to be chemically identical to **estradiol**, **estrone**, **estriol**, progesterone, and testosterone, the endogenous hormones made by the body.

Bio-identical Estrogens

Estrone (E1):

- Second strongest estrogen
- Converted from estradiol & released from adrenal glands
- Main estrogen in menopause-converted from androstenedione in adipose tissue,liver and skin

Estradiol (E2):

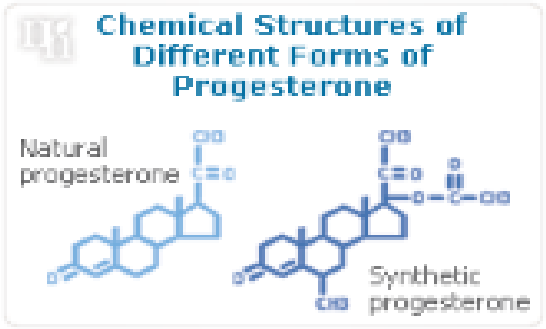
- Strongest estrogen
- Mainly made from the ovary
- Formed by testosterone aromatization
- Primary estrogen in menstrual cycle

Estriol (E3):

- Weakest estrogen, end metabolite of estrogen pathway
- Dominant in pregnancy
- Considered possibly protective from more potent proliferative effects of E1 and E2

Understanding Natural Hormone Replacement Therapy

The most important difference between natural hormones and traditional hormone replacement therapy (HRT) is that natural hormones are derived from plants as opposed to synthetic chemicals.



Synthetic HRT functions similarly to the body's natural hormones; unlike natural hormones, however, synthetic hormones do not have chemically-identical structures. Additionally, dosages for HRT and other synthetic formulations are usually standardized, whereas natural hormone treatments are "personalized".

The "natural" part of natural hormones generally means **fewer side effects**. The medical community has become increasingly interested in alternative medicine in the face of evidence that suggests a strong link between HRT and serious conditions like breast and ovarian cancer, heart disease, blood clots, and stroke.

Although natural hormones are generally considered safer than synthetic versions, the scientific community has only recently begun to study accompanying their risks and side effects. Since October 2010, the FDA's stance on natural hormones has been that further testing and research is needed. For more information on natural solutions for menopause symptoms and hormonal imbalance, go to alternatives to hormone replacement therapy.

Transdermal v oral route

No First-pass Effect

Less of an effect on:

- Clotting factors
- Triglycerides
- C-reactive protein
- Sex hormone-binding globulin

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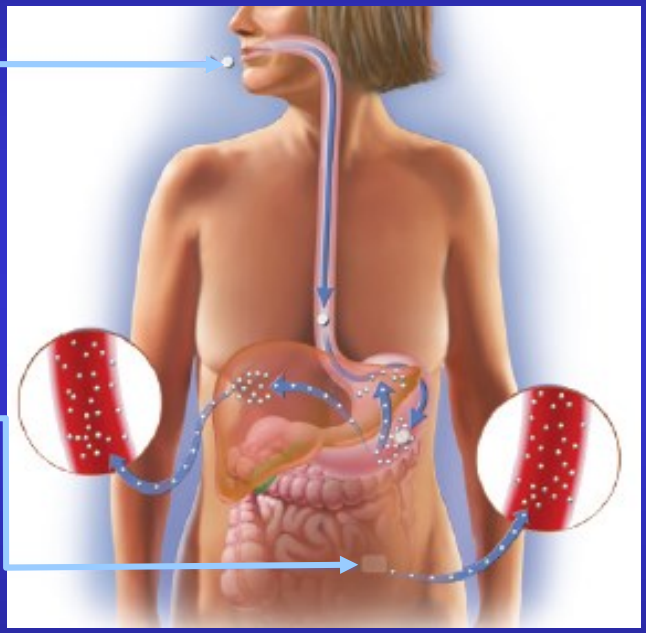
ET Drug Delivery

- Oral delivery
  - Requires larger total doses than patch ET*
  - Undergoes first-pass hepatic metabolism and is rapidly metabolized by the liver[1]
  - Taken once daily
- Transdermal patch delivery
  - Requires smaller total doses than oral ET*
  - Absorbed through the skin directly into the bloodstream, avoiding first-pass hepatic metabolism[1]
  - Applied once or twice weekly



***Therapeutic levels are achieved with smaller transdermal doses compared to oral therapy. This does not imply differences in safety or efficacy.**

Favoring Transdermal Estrogen

- Women's preference
- NIDDM
- History of DVT
- Hypertension
- Hypertriglyceridemia
- Cholelithiasis
- Liver disease
- Obesity
- Smoking
- Migraine
- İnability yo use oral tablets

- Patches (oestrogen only or combined preparation) or oestrogen gels
- Skin irritation may be a problem but new matrix patches and the gels are usually well tolerated

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IMS governing principles on MHT

- Menopausal hormone therapy (MHT) remains the most effective therapy for vasomotor symptoms and urogenital atrophy
- Other menopause-related complaints such as mood swings, joint and muscle pains and sleep disturbance may improve with MHT
- The administration of individualized MHT (including androgenic preparations, when appropriate) may improve both sexuality and quality of life
- Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women
- MHT must be individualized and tailored according to symptoms, the need for prevention, personal and family history, results of investigations and each woman's preferences and expectations
- The risks and benefits of MHT differ with age and years since the last menstrual period

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

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IMS governing principles on MHT

- Women experiencing a spontaneous or iatrogenic menopause before age 45 and particularly before age 40 are at higher risk of cardiovascular disease and osteoporosis. In these women, in the absence of contraindications, MHT is advised at least until the average age of menopause
- Counseling on MHT should convey risks and benefits in clear and comprehensible terms, ideally expressed as absolute risk in real numbers
- MHT should not be recommended without a clear indication for its use
- Women taking MHT should have at least an annual medical consultation
- There are no reasons to place a mandatory limit on the duration of MHT
- Dose and duration of MHT should be consistent with treatment goals
- Whether or not to continue should be decided at the discretion of the well-informed woman and her health professional

2016 IMS Recommendations. *Climacteric* 2016;19:109–50

British Menopause Society

Home | Find a Specialist

Summary consensus statement

Hormone replacement therapy

Summary points

1 All women should have access to advice so that they can make informed decisions about diet and lifestyle and treatment options to optimise their menopause transition and postmenopausal health.

2 HRT dosage, regimen and duration should be individualised, with annual evaluation of advantages and disadvantages.

3 Transdermal estradiol is unlikely to increase the risk of venous thrombosis or stroke above that of non-users and is associated with lower risk compared with oral estradiol.

4 Limited evidence suggests that micronised progesterone and dydrogesterone may be associated with lower risk of breast cancer and venous thrombosis compared to other progestogens.

5 Arbitrary limits should not be placed on the duration of use of HRT; if symptoms persist, the benefits usually outweigh the risks.

6 HRT prescribed before the age of 60 or within 10 years of the menopause has a favourable benefit /risk profile and is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality.

7 If HRT is used in women over 60 years of age, low doses should be started, preferably with a transdermal estradiol preparation.

8 Women with POI should be encouraged to use hormonal therapy at least until the average age of the menopause. HRT or the combined contraceptive pill would be suitable. However, HRT may confer a more favourable improvement in bone density and cardiovascular markers compared with the combined contraceptive pill.

Duration of systemic HRT treatment

- Depends on the endpoints of treatment.
- For women with a premature/ early menopause it is recommended that treatment is continued until the average age of the natural menopause (ie early 50s) and then reassessed.
- Vasomotor symptoms are the commonest indication for MHT and treatment should be continued for up to 5 years and then stopped to see if they are still present.
- There are no arbitrary limits regarding the duration of use of MHT - it can be used for as long as the woman feels the benefits outweigh the risks for her and decisions must be made on an individual basis. Routine discontinuation after 5 years or at age of 65 is not recommended.

The North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65

- Moderate to severe vasomotor symptoms have been documented in 42% of women aged 60 to 65 years. Thus, many women will continue to have vasomotor symptoms after age 65, and these symptoms can disrupt sleep and adversely affect health and quality of life.Provided that

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Provided that the woman has been advised of the increase in risks associated with continuing HT beyond age 60 and has clinical supervision, extending HT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks. Use of HT should be individualized and not discontinued solely based on a woman's age.[5] The decision to continue or discontinue HT should be made jointly by the woman and her healthcare provider.

Estrogen based therapies: stopping systemic treatment

- The main issue is that it is impossible to predict whether individual women will still be symptomatic or not when they stop systemic HT.
- The limited evidence available shows no advantage of tapering down or stopping abruptly. Anecdotally, older women need less estrogen to control their symptoms and thus a lower dose can be tried before stopping.
- A Finnish cohort study found that discontinuation of systemic HT is associated with an increased risk of cardiovascular deaths especially within the first year and in those aged under 60 years.

Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O. Increased Cardiovascular Mortality Risk in Women Discontinuing Postmenopausal Hormone Therapy. J Clin Endocrinol Metab. 2015;100:4588-94.

- gradually reducing HRT may limit recurrence of symptoms in the short term
- gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term.

Table 3

Presenting symptoms of genitourinary symptoms of menopause

Vulvo-Vaginal Symptoms	Sexual Symptoms	Urinary Symptoms
Vaginal dryness	Dyspareunia	Dysuria
Burning	Bleeding with intercourse	Urinary frequency
Vulvar irritation	Decreased lubrication with arousal	Recurrent urinary tract infections
Vaginal discharge		
Introital retraction		
Decreased vaginal elasticity		

Vaginal Estrogens

Low-dose, local, prescription vaginal ET products FDA-approved for vaginal atrophy

- 17β Estradiol Vaginal cream (Estrace)
- Conjugated EE vaginal cream (Premarin)
- Estradiol vaginal ring (Estring)
- Estradiol hemihydrate vaginal tablet 10 mcg (Vagifem)

- No need to add a progestogen as for systemic HRT, if the recommended low dose regimes are used
- VVA/ GSM is a chronic condition and symptoms will return when treatment is stopped

Intrarosa (Prasterone)

Vaginal DHEA for moderate to severe dyspareunia

- Once-daily vaginal insert
- Two 12-week trials showed reduction in the severity of pain during sexual intercourse compared to placebo
- Most common adverse reactions were vaginal discharge and abnormal Pap tests
- The product was not studied in women with breast cancer
- Converted into estrogen and androgen locally
- Contraindicated:
  - Undiagnosed vaginal bleeding
  - History of breast cancer

Treatment for Dyspareunia

Oral ospemifene (Osphena) 60mg

- FDA approved for the treatment of dyspareunia associated with vulvovaginal atrophy
- Estrogen agonist/antagonist (SERM)
- NAMS
  - The estrogen agonist/antagonist ospemifene is an oral agent for the treatment of moderate to severe dyspareunia due to GSM/VVA. (Level I)

(Level I based on good and consistent scientific evidence)

IMS Key Treatment Recommendations

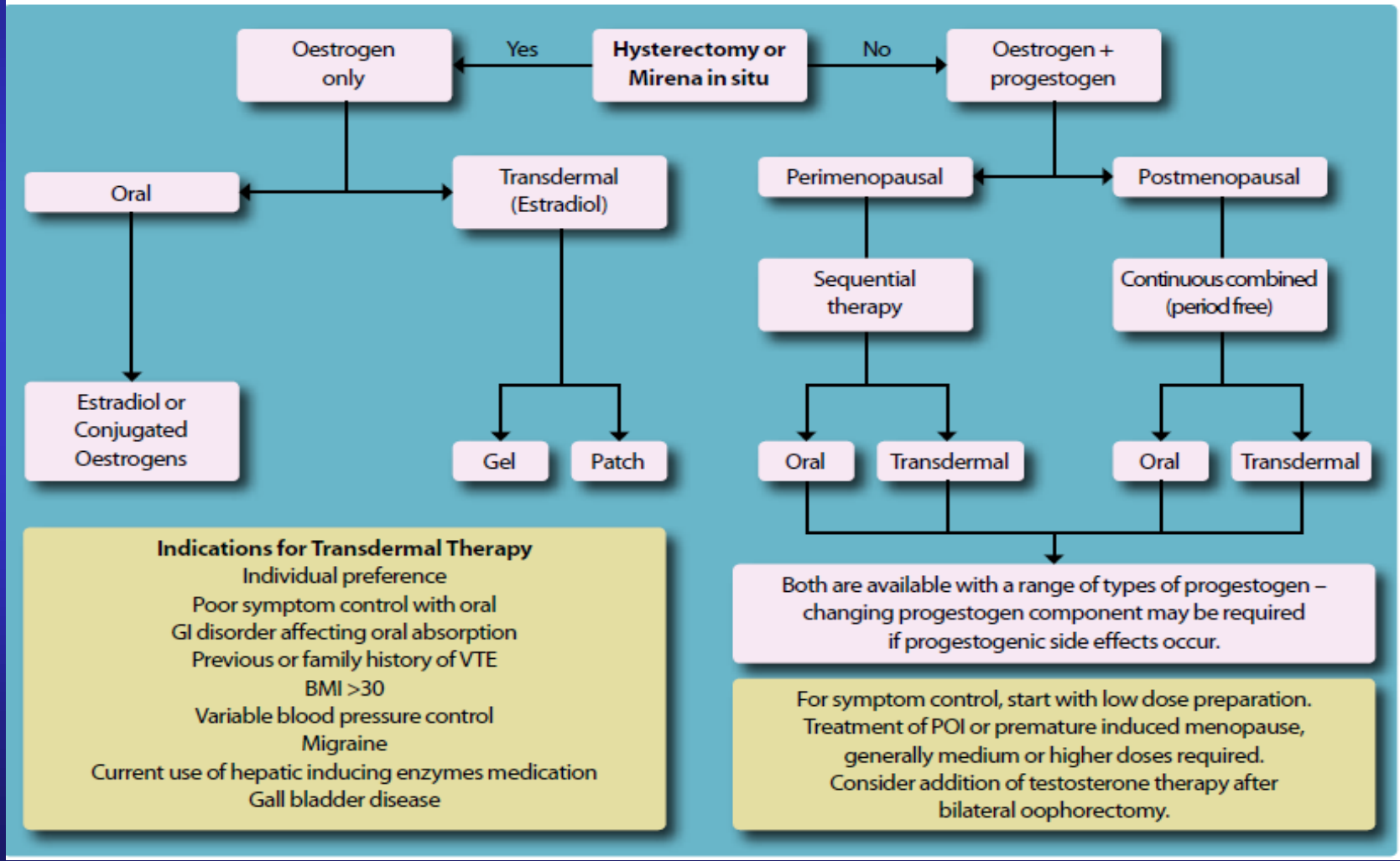
1. Start treatment early,before atrophic changes have occurred.
2. Continued treatment is needed to maintain the benefits.
3. All local estrogen preparations are effective.
4. Patient preference will usually determine the treatment that is used.
5. Additional progestin is not indicated when appropriate low- dose, local estrogen is used. If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness.

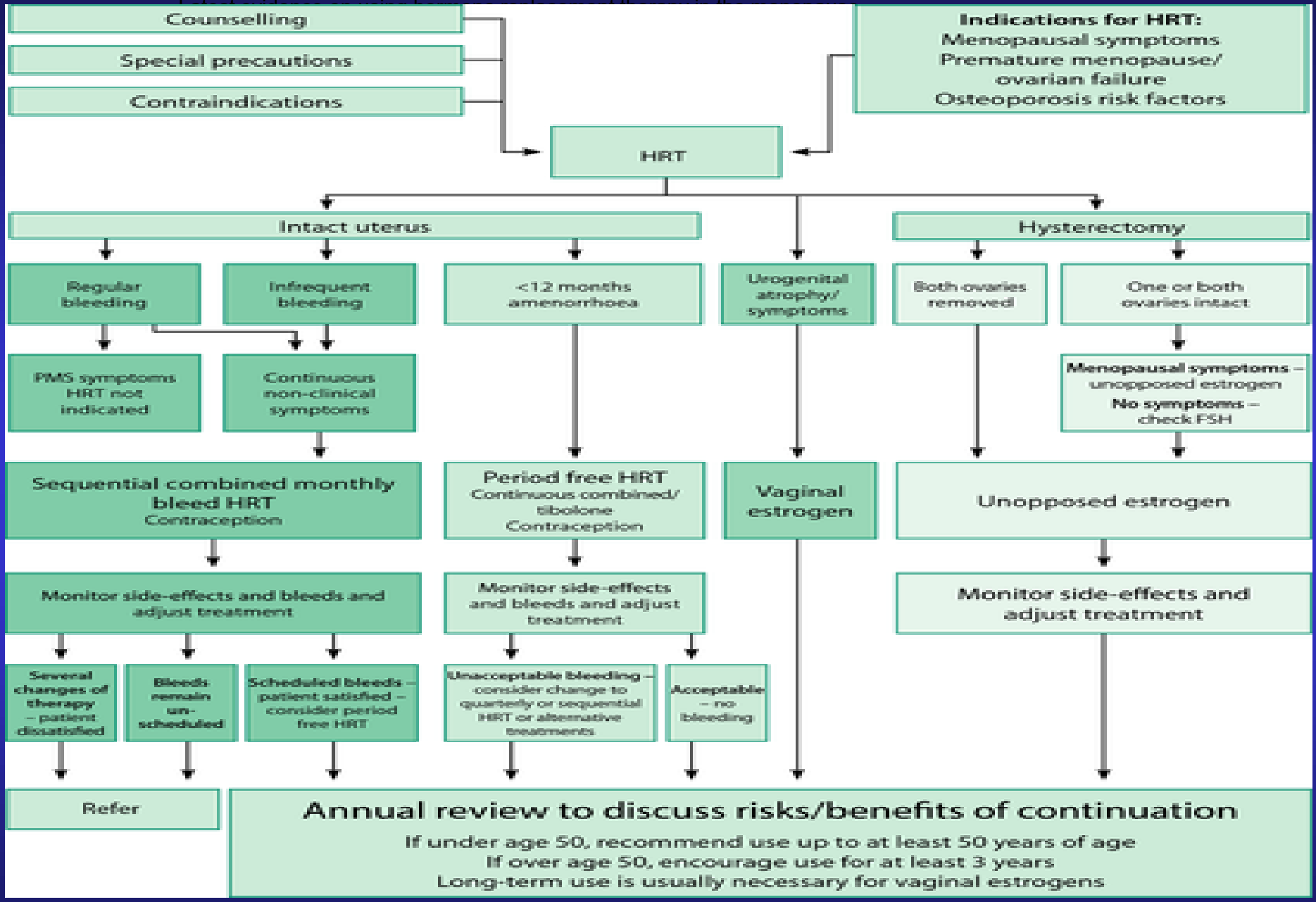
MHT-6 RULES

- IS SHE AT THE WINDOW OF OPPORTUNITY?
- RULE OUT CONTRAINDICATIONS FOR MHT
- EVALUATE CARDIOVASCULAR RISK
- EVALUATE BREAST CANCER RISK
- UTERUS PRESENT ?
- IS THE PATIENT ON ADEQUATE DOSES OF PROGESTERONE ?

British Menopause Society

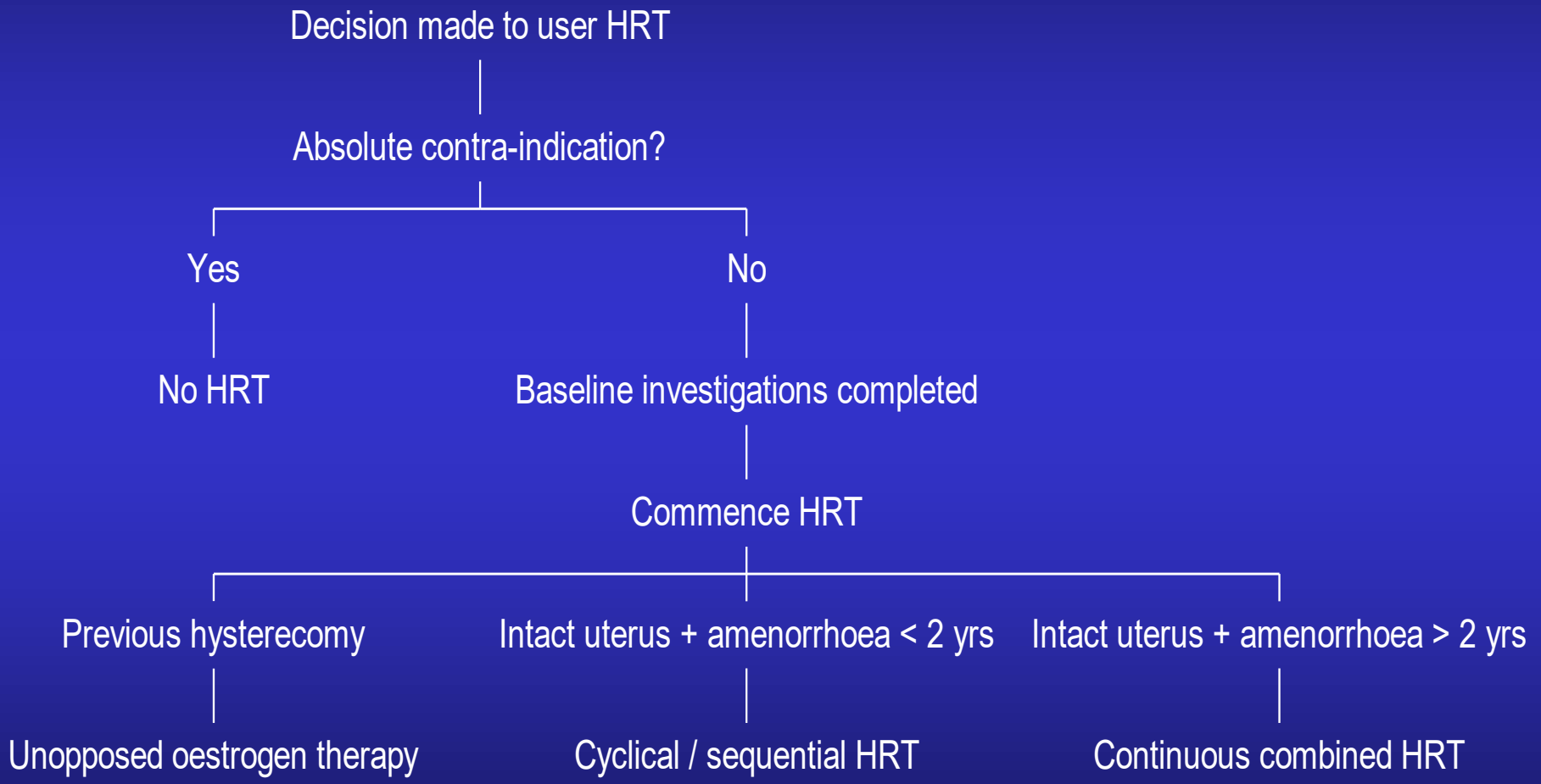
Systemic HRT Treatment





The Obstetrician & Gynaecologist, Volume: 17, Issue: 1, Pages: 20-28, First published: 19 December 2014, DOI: (10.1111/tog.12155)

An algorithm for the administration of HRT



Summary

- HRT is a safe option for healthy, symptomatic women, who are within 10 years of menopause or < 60 years and do not have contra-indications to HRT
- Combined (estrogen – progestogen) therapy should be used for women with intact uterus; unopposed estrogen should be used for women who have undergone hysterectomy.
- Transdermal 17-beta estradiol is suggested as first-line estrogen. The transdermal route is particularly suggested in women with hypertriglyceridemia or risk factors for thromboembolism.
- Micronized progesterone/dydrogesterone is suggested as first-line progestogen, as it is effective for endometrial hyperplasia, metabolically neutral and does not increase the risk of breast cancer or CHD.
- For women who experience recurrent symptoms after HRT discontinuation, HRT at the lowest dose or non-hormonal options are suggested.