Hormone Replacement Therapy: Recent Recommendations

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BENEFICIAL EFFECTS OF HORMONE REPLACEMENT THERAPY

A Cochrane systematic review summarized the results of 24 placebo-controlled randomized trials; this showed a clear beneficial effect with estrogen replacement compared with placebo.

The short-term use of hormone replacement therapy (HRT) may improve mood and depressive symptoms during the menopausal transition and in early menopause. Women with severe depression and those who do not respond to HRT will require psychiatric assessment.

Sexual Function

Estrogen, systemic or topical, may improve sexual function in women. It is particularly helpful in women with dyspareunia secondary to vaginal atrophy, through its proliferative effect on the vulval and vaginal epithelium and by improving vaginal lubrication.

Urogenital Symptoms

Estrogen treatment has been shown to be effective in treating symptoms related to vaginal atrophy, such as vaginal dryness and superficial dyspareunia.

Low-dose vaginal estrogen preparations can be used long term in symptomatic women as required, and all topic estrogen preparations have been shown to be effective in this context.

Nonhormonal preparations and lubricants can be used as an alternative, but these are not as effective as estrogen therapy.

Estrogen therapy has a protective effect against connective tissue loss and may possibly reverse this process in menopausal women receiving HRT.

Progestogens/Side Effects

After a minimum of 1 year of HRT, or 1 year after the last menstrual period (2 years in premature ovarian insufficiency), women who wish to avoid a monthly withdrawal bleed may attempt a switch to a continuous combined regimen which aims to give bleed-free HRT; this will also minimize the risk of endometrial hyperplasia.

Women can be switched to the tissue-selective agent tibolone. If bleeding is heavy or erratic on a sequential regimen, the dose of progestogen can be doubled or duration increased to 21 days. Persistent bleeding problems beyond 6 months warrant investigation with ultrasound scan and/or endometrial biopsy.

Progestogens have a Variety of Effects

Symptoms of fluid retention are produced by the sodium-retaining effect of the renin–aldosterone system, triggered by stimulation of the aldosterone receptors.

Androgenic side effects, such as acne and hirsutism are a problem of the testosterone-derived progestogens due to stimulation of the androgen receptors. Mood swings and premenstrual syndrome-like side effects. The dose can be halved and duration of progestogen can be reduced to 7 to 10 days to minimize progestogenic side effects. This may result in bleeding problems and hyperplasia.

Progesterone and dydrogesterone generally have less side effects due to progestosterone receptor specificity; progestogen is available in oral micronized form, vaginal pessaries, and gel.

Long-term Effects of HRT

Initiating HRT after the age of 60 years for the sole purpose of the prevention of osteoporotic fractures is not recommended.
The bone-protective effect of estrogen is dose related. The use of HRT for a few years around menopause may provide a long-term protective effect many years after stopping HRT. Bisphosphonates and other pharmacological agents can be used as an alternative to HRT to preserve bone density, but there can be side effects. Long-term therapy with alendronate can predispose to femoral shaft fragility fractures.

Cardiovascular

Data from the Danish osteoporosis trial have shown that hormone therapy reduces the incidence of coronary heart disease by around 50% if commenced within 10 years of menopause; this is referred to as the “window of opportunity” for primary prevention.

The “Kronos Early Estrogen Prevention Study” randomized controlled trial using lower doses of estradiol and progesterone in women less than 3 years from their last menstrual period reported neutral impact on cardiovascular risk markers, such as coronary calcium scores and intima media thickness.

Cognition

Hormone replacement therapy should not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women.

Recent critique of the Women’s Health Initiative (WHI) and Million Women Study has clearly illustrated a number of key flaws that limit the ability of the trials to establish a causal association between HRT and cancer.

Ovarian Cancer

A recent report from the Danish National Cancer Registry revealed a small but significant increase in the incidence of ovarian cancer following 8 years use of unopposed estrogen and estrogen/progesteron therapy.

Endometrial Cancer

Unopposed estrogen therapy increases the incidence of endometrial cancer by the use of combined sequential estrogen and progesterone therapy. Long-term use of combined HRT for more than 5 years is associated with a small increase in risk of endometrial cancer.

Colorectal Cancer

The WHI trial showed that colorectal cancer risk was reduced in women taking combined conjugated equine estrogen (CEE) and medroxyprogesterone acetate, but there was no effect of CEE only therapy.

Ospemifene

Ospemifene is nonhormonal and may be particularly suited to women in whom estrogen is contraindicated. It would also be of advantage to women with vulval and vaginal atrophy symptoms who do not wish to administer vaginal products of systemic estrogen.

Venous Thromboembolism (VTE) and HRT

Oral HRT increases the risk of VTE two- to fourfold, with the highest risk in the first year of use. Venous thromboembolism risk is further increased in those with a personal or family history of VTE, advanced age, obesity, and other risk factors, such as surgery or hospitalization.

Stroke

The WHI studies revealed an overall increased incidence of stroke in women using estrogen and progesterone therapy or estrogen alone. Reanalysis of the combined data from the estrogen and progesterone study and that of the estrogen-alone study revealed a smaller increase in incidence of stroke in women who commenced HRT between the ages of 50 and 59. The heart and estrogen progesterone replacement study found no increased incidence of stroke with HRT.

Premature Ovarian Insufficiency

Hormonal replacement therapy in premature ovarian insufficiency simply replaces ovarian hormones that should normally be produced. Hormone therapy should generally continue at least until the estimated age of natural menopause (on average 51 years). Hormonal replacement therapy is also important to preserve uterine function in women planning ovm donation.

The contraceptive pill can be used as an alternative to control symptoms, but there are few data on long-term benefit for protection against osteoporosis and cardiovascular disease.

Routes and Regimens

The vaginal route of progestogen and progesterone administration, for example, levonorgestrel system and progesterone gel and pessaries, provides adequate endometrial protection with reduced systemic side effects.

A total of 12 to 14 days of progestogen should be given for women with intact uterus to avoid endometrial hyperplasia and minimize the risk of endometrial cancer with unopposed estrogen.

Progestogen side effects may be reduced by using natural progesterone in the form of oral capsules, transvaginal pessaries, or gels. The levonorgestrel-releasing intrauterine system provides adequate endometrial protection in
women receiving estrogen therapy. Systemic side effects were reduced though not completely eliminated.

Continuous combined regimens avoid the need for regular withdrawal bleeds, but may be associated with continuous low-grade progestogen side effects. Ultra-low-dose estradiol/progestogen continuous combined regimens appear to maintain the benefits of higher dose regimens while allowing minimal use of progestogen to reduce side effects.

**Sexual Function/Androgens**

Tibolone has a weak androgenic effect that can have a beneficial effect on mood and libido.

Testosterone gels licensed for male use are available in 50 mg, 5 mL sachets or tubed. Unlicensed prescription by specialists is an option for female androgen replacement, at a reduced dosage of 0.5 to 1.0 mL/day or one-fourth sachet/tube on alternate days.

Androgenic side effects and risks are minimal and reversible if testosterone levels are maintained within the female physiological range. Some studies have shown skeletal, cognitive, well-being, and vaginal benefits; these data require confirmation.

Dehydroepiandrosterone use requires further research.

**Pharmacological Alternatives**

Evidence exists for the efficacy of selective serotonin reuptake inhibitors, such as fluoxetine and paroxetine in treating vasomotor symptoms; the most convincing data for the serotonin–norepinephrine reuptake inhibitor (venlafaxine) at a dose limits the usefulness of this agent. Gabapentin has shown efficacy for hot flush reduction compared with placebo.

**Newer Therapies**

Conjugated estrogen/bazedoxifene maintains the benefits of traditional HRT while avoiding the need for progestogen. Protection of the endometrium is achieved through bazedoxifene, a selective estrogen receptor modulator. This product is particularly beneficial in women with progestogen intolerance.

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