Leading Article

Menopausal Hormone Therapy with Oestrogen and Progestogen

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Preamble

Since the introduction of oestrogen therapy / oestrogen and progestogen therapy (ET/EPT), there has been a general consensus that vasomotor symptoms are relieved by ET/EPT. Following WHI and Million Women studies, which indicated significant adverse effects of ET/EPT including (Deep Vein Thrombosis) DVT, Stroke, (Ischemic Heart Disease) IHD and breast carcinoma, there was an overall decline in hormone therapy use.

However, the review of the WHI results indicated systemic progesterone therapy was associated with breast cancer and that estrogens were beneficial. National and international menopause organisations advocated that reports of harm attributed to ET/EPT were exaggerated. Secondly an overall net benefit of ET/EPT, particularly on the vascular health, was seen in women who initiated treatment during the menopause transition or early postmenopause rather than late postmenopause. This approach was often referred to as the "timing hypothesis" (i.e. a critical window for favourable outcomes of hormone therapy treatment). In addition to these, oestrogen only preparations were thought to be 'breast protective' and transdermal preparations were thought to have less systemic side effects. Notwithstanding this, a recent Lancet article showed an elevated breast cancer risk following ET/EPT. This called for a review of the generalisability of the above-mentioned consensus on ET/EPT by the international and national organisations. Therefore, Menopause Society of Sri Lanka thought it is prudent to revise its position statement on oestrogen and progestogen ET/EPT.

Introduction

Menopause is defined as the final menstrual period (North American Menopause Society, 2017). The average age at menopause is approxi mately 51 years, with a normal range of 45–55 years. Women who had their final period between the ages of 40 and 45 years are regarded as having early menopause and those less than 40 years as premature menopause, or premature ovarian insufficiency. Prior to the final period, women have a phase of fluctuating ovarian function and hormone levels known as peri - menopause, which typically lasts several years.

Menopause results in a number of physiological changes affecting the cardiovas cular, musculoskeletal, urogenital and central nervous systems. There is an increase in incidence of cardiovascular disease and osteoporosis after menopause.

Menopausal hormone therapy (ET/EPT)

ET/EPT 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 post menopausal women.

ET/EPT is replacement of estrogen when ovarian endocrine function fails, either at the time of natural menopause or due to premature menopause due to a variety of causes.

Estrogen supplementation has to be coupled with either oral progestogen or levonorgestrel intra uterine system for endometrial protection for women who have not had a hysterectomy.

Previous evidence base for ET/EPT

Benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause. There are no arbitrary limits regarding the duration of use. In the absence of contraindications it can be used for as long as benefits out weight he risks on an individual basis (Neves-e-castro et al., 2015). Duration of treatment with ET/EPT should be determined on an individual basis with no mandatory limit in the absence of obvious contraindications (Baber et al., 2016).

The 2016 Revised Global Consensus Statement on Menopausal Hormone Therapy endorsed by several international bodies, states that in women under 60-years or who are within 10-years of menopause with no contraindications, the risk-benefit ratio is most favourable for treatment of bothersome vasomotor symptoms and for those at elevated risk for osteoporosis or fracture (*Villiers et al., 2016*).

The 2017 hormone therapy position statement of The North American Menopause Society reiterated that, for women who start ET/EPT after 10-years from menopause or are aged 60 years or more, the risk-benefit ratio appeared less favourable because of higher risks of coronary heart disease, stroke, venous thromboem bolism, and dementia. It added further that longer durations of therapy should be for documented indications such as persistent vasomotor symptoms or osteoporosis. For bothersome vulvovaginal symptoms that are not relieved with over-the counter therapies and without indications for use of systemic ET/EPT, low-dose vaginal estrogen therapy or other therapies were recommended (*North American Menopause Society, 2017*).
Until now evidence on breast cancer risk and menopausal hormone therapy (ET/EPT) were inconsistent, with little evidence on long-term effects (*Panay et al., 2013; Neves-e-castro et al., 2015; National Institute for Health and Care Excellence, 2018; Green J, Reeves G, Floud S, 2019*).

NICE stated that ET/EPT with oestrogen and progestogen can be associated with an increased risk of breast cancer, which is "related to treatment duration and reduces after stopping." It did not provide any advice on how long ET/EPT should be used (National Institute for Health and Care Excellence, 2018). The risk of breast cancer is primarily associated with combined oestrogen/ progestogen therapy and related to the duration of use. The risk of breast cancer attributable to combined ET/EPT is small and decreases after treatment is stopped. Oestrogen alone has not been shown to increase breast cancer risk in high quality randomized controlled trials (Panay et al., 2013).

More recently, KEEPS study also supported the value and safety of the use of ET/EPT in recently menopaused women. Researchers concluded that estrogen/progesterone treatment started soon after menopause appeared to be safe; relieved many of the symptoms of menopause; and improved mood, bone density, and several markers of cardiovascular risk. They concluded that these findings provide an outlook for future research to optimize ET/EPT and improve the health of postmenopausal women (Miller et al., 2019).

New evidence on breast cancer in ET/EPT users

A recent meta-analysis in Lancet on the "Type and timing of menopausal hormone therapy and breast cancer risk" has serious implications for the use of ET/EPT (Collaborative Group on

Hormonal Factors in Breast Cancer, 2019). The relevance of the main findings in this study lies in the implication for the absolute risks during and after ET/EPT use for women who start it between 40–59 years.

For a given preparation, the relative risks during years 5–14 of current use were much greater for oestrogen-receptor-positive tumours than for oestrogen-receptor-negative tumours, and were similar for women starting ET/EPT at ages 40–44, 45–49, 50–54, and 55–59 years, irrespective of age category. What was interesting was that the excess risk persisted for more than 10 years even after stopping with its magnitude depending on the duration of use. However, there was only little excess when used for less than 1 year.

The excess risk was more for current users, but some risk persisted for more than a decade after stopping ET/EPT. About half the excess would be during the first 5 years of use, and the rest would be during the next 15 years of past use. Risks also did not differ substantially between the main oestrogenic constituents, or by route whether oral or transdermal. There appeared to be little risk from topical vaginal oestrogen preparations.

The absolute risk was one in every 50 users for oestrogen-plus-daily-progestogen ET/EPT, one in 70 users for oestrogen plus - intermittent - pro gestagen ET/EPT, one in 200 users for oestrogen- only ET/EPT. The risks were not related to the progestagenic constituents and were lower for dydrogesterone.

Initial evaluation prior to ET/EPT and follow-up

Before consideration of any therapeutic regimen, including oestrogen therapy / oestrogen progestogen therapy (ET/EPT), all women should have a complete health evaluation, including a comprehensive history and physical examination. Mammography should be performed according to national guidelines and age, but preferably within the previous 12 months before initiation of therapy. Other specific examinations, such as bone densitometry, should be considered on a case - by-case basis.

New recommendation

In addition to the above, screening for BRCA gene mutation would be of benefit for pre-treatment risk stratification in all users in spite of a negative hereditary breast and ovarian cancer syndrome. If the duration of treatment of oestrogen exceeds 1-year, it has to be under specific individualized indications with intense follow-up and monitoring.

Contraindications to oral ET/EPT & relative contraindications to transdermal ET/EPT

- Established cardiovascular disease
- Venous thromboembolic disease
- Active liver disease
- Migraine with aura
- Well controlled hypertension is not a contraindication.

Progestogen component of ET/EPT

The primary menopause-related indication for progestogen use is endometrial protection from unopposed ET which significantly increases the risk of endometrial cancer. Progestogen is generally not indicated when low-dose estrogen is administered vaginally for Genito-Urinary Syndrome (GSM). Recent evidence shows that users of LNG-IUS had a strongly reduced risk of ovarian and endometrial cancer with no increased risk of breast cancer (Jareid et al., 2018).

Routes of ET/EPT therapy

The transdermal (gels or patches) and the subcutaneous (implants) routes of estrogen administration avoid the first pass metabolism through the liver and are not associated with an increased risk of venous thrombosis (Panay et al., 2013).

New evidence

There has been no new evidence against this recommendation. In addition, contrary to the existing belief, breast cancer risk with transdermal route is comparable to oral ET/EPT (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). Recent evidence shows that there is no excess risk of breast cancer with vaginal oestrogens.

(Collaborative Group on Hormonal Factors in Breast Cancer, 2019).

ET/EPT in the management of menopause related issues

Vasomotor symptoms (VMS)

Treatment of moderate to severe vasomotor symptoms (i.e., hot flashes and night sweats) remains the primary indication for systemic ET and EPT (ACOG, 2014; Neves-e-castro et al., 2015; NAMS, 2017; RANZCOG, 2017).

2019 new recommendation

There has been no new evidence against this recommendation. Whilst ET/EPT, both systemic and transdermal remains the mainstay in the treatment of VMS, the duration and the dosage has to be the minimum required. If the duration of treatment of oestrogen exceeds 1-year, it has to be under specific individualized indications with intense follow-up and monitoring.

Genito-Urinary Syndrome (GSM)

Almost all systemic and vaginal ET/EPTs are approved for treating moderate to severe symptoms of vulvar and vaginal atrophy, such as vaginal dryness, dyspareunia, atrophic vaginitis, soreness, recurrent vaginitis and urogenital symptoms such as cystitis, post coital cystitis, nocturia, urinary frequency and urgency (Panay et al., 2013; ACOG, 2014; Villiers et al., 2016). In addition ET/EPT, systemic or local, is likely to improve sexual function in women with dyspareunia secondary to vaginal atrophy (Panay et al., 2013).

The choice of therapy should be guided by clinical experience and patient preference. Progestogen is generally not indicated when low-dose estrogen is administered locally for vaginal atrophy. A systematic review in 2019 supports the use of low-dose vaginal estrogens for treating vulvar and vaginal atrophy in menopausal women without a concomitant progestogen (Constantine et al., 2019). This review did not report an increased endometrial hyperplasia or cancer risk with low-dose, unopposed vaginal estrogens.

For women treated for non-hormone-dependent cancer, management of vaginal atrophy is similar to that for women without a cancer history. For women with a history of hormone-dependent cancer, management recommendations are dependent upon each woman`s preference in consultation with her oncologist.

New recommendation

There has been no new evidence against this recommendation. When ET/EPT is considered solely for this indication, local vaginal ET is generally recommended (ACOG, 2014) (Villiers et al., 2016). Recent evidence shows that there is no excess risk of breast cancer with vaginal oestrogens (Collaborative Group on Hormonal-Factors in Breast Cancer, 2019). Vaginal ET can be continued for women as long as distressful symptoms remain (Constantine et al., 2019).

Sexual function

ET/EPT, systemic or topical, may improve sexual function in women with dyspareunia secondary to vaginal atrophy (Panay et al., 2013). The administration of systemic testosterone has been shown to result in significant improvement in sexual function, including sexual desire, and orgasm (Panay et al., 2013). Androgen replacement therapy will be discussed in a separate guidance.

New recommendation

There has been no new evidence against this recommendation. Recent evidence shows that there is no excess risk of breast cancer with local oestrogens (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). Vaginal ET can be continued for women as long as distressful symptoms remain (Constantine et al., 2019).

Bone health

There is strong evidence of the efficacy of ET/EPT in reducing the risk of postmenopausal osteoporotic fracture. For women who require drug therapy for osteoporosis risk reduction (including women at high risk of fracture during the next 5-10 y), ET/EPT can be considered as an option.

New recommendation

There has been no new evidence against this recommendation. However, if a woman at risk of osteoporosis is prescribed ET/EPT, it must be based on an individual case by case approach with increased surveillance if continued beyond one year.

Premature menopause and premature ovarian failure

A spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years places a woman at a higher risk for cardiovascular disease and osteoporosis in addition to affective disorders and dementia as well. In such women, ET/EPT reduces symptoms and preserves bone density (Villiers et al., 2016).The current recommendation was for women who have an early or premature menopause, ET/EPT was recommended until at least 51 years of age unless there are contraindications (Panay et al., 2013; Magraith, Karen, Stuckey, 2019). Thereafter, a shared decision about whether to continue ET/EPT should be made in the same way as it would be for other women of this age (Magraith and Stuckey, 2019). The mode of delivery and the dose may be adjusted over time.

New recommendation

There has been no new evidence against this recommendation. As the duration of treatment of oestrogen exceeds 1-year, it has to be under specific individualized intense follow-up and monitoring.

Effects of ET/EPT on other health issues

Coronary heart disease

RCTs and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone ET/EPT may decrease the risk of myocardial infarction and all-cause mortality when initiated in women younger than 60 years of age and/or within 10 years of menopause (Villiers et al., 2016). This view was further endorsed by the KEEPS study (Miller et al., 2019).

New recommendation

There has been no new evidence against this information. However, ET/EPT is not indicated as primary or secondary prevention of coronary vascular disease in view of recent evidence on elevated breast cancer risk in women on long-term ET/EPT.

Diabetes mellitus

Large RCTs 17 suggest that ET/EPT reduces new onset of diabetes mellitus. There is inadequate evidence to recommend combined EPT for a sole indication of the prevention of DM in perimenopausal women.

New recommendation

There has been no new evidence against the above information.

Depression, dementia and cognitive decline

HRT should not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women (Panay et al., 2013). It is unknown whether ET has a direct

benefit or harm for treatment of dementia due to Alzheimer`s disease. The KEEPS continuation study results would help to answer this issue. Evidence is insufficient to support the use of ET/EPT for the treatment of depression in general.

New recommendation

There has been no new evidence against the above information.

Complications of ET/EPT

Breast cancer

This was discussed under the section "New evidence on breast cancer in ET/EPT users"

Venous thromboembolism

Oral ET/EPT increased the risk of VTE two- to four-fold, with the highest risk in the first year of use. The risk of VTE was increased by smoking, age, obesity and oral ET/EPT (Panay et al., 2013). The use of transdermal ET/EPT has not been associated with increased VTE risk (Olié et al., 2011). Observational studies and a meta-analysis show a lower risk of VTE with transdermal therapy (0.05mg twice weekly or lower) compared to oral therapy (Villiers et al., 2016). Transdermal treatment was the safest type of hormone replacement therapy when risk of venous thromboembolism was assessed (Mohammed et al., 2015).

New recommendation

There is no new evidence to warrant a change in practice.

Stroke

The WHI study revealed an overall increased incidence of stoke in women using estrogen and progestogen therapy or estrogen alone (Panay et al., 2013). A smaller increase in the incidence of stroke was seen in women who commenced HRT between the ages of 50 and 59 (Panay et al., 2013). Both ET and EPT appear to increase the risk of ischemic stroke in postmenopausal women (Villiers et al., 2016). Women with prevalent cardiovascular disease (CVD) have a high baseline risk of stroke. It is advisable that ET/EPT should be particularly avoided for women who have an elevated baseline risk of stroke.

New recommendation

There is no new evidence to warrant a change in practice.

Endometrial cancer

Unopposed oestrogen replacement therapy increases endometrial cancer risk. Most studies have shown that this excess risk is not completely eliminated with monthly sequential progestogen addition, especially when continued for more than 5 years. This has also been found with long cycle HRT. No increased risk of endometrial cancer has been found with continuous combined regimens.

New recommendation

Local vaginal oestrogen preparations were not shown to increase endometrial cancer, and as such progestogen supplementation is not required (Collaborative Group on Hormonal Factors in Breast Cancer, 2019).

Ovarian cancer

Most data are related to the replacement with oestrogen alone with increasing risk in long term therapy (>10 years). However with continuous combined therapy, this increase does not seem apparent. This issue is unresolved and requires further examination and there is currently insufficient evidence to recommend alterations in ET/EPT prescribing practice.

New recommendation

There is no new evidence to warrant a change in practice.

Colorectal cancer

Results from the oestrogen progestogen arm, but not the oestrogen alone arm, of the WHI study were consistent with data from case control and cohort studies that indicate that ET/EPT reduces the risk of colorectal cancer by about a third (Women's Health Initiative, 2002). However little is known about colorectal cancer risk when treatment is stopped. There is no information about ET/EPT in high risk populations and current data do not allow prevention as a recommendation.

New recommendation

There is no new evidence to warrant a change in practice.

Gallbladder disease

WHI confirmed the observation of the Heart and Estrogen/progestin Replacement Study published in 1998 that HRT increases the risk of gallbladder disease. Gallbladder disease increases with ageing and with obesity, and as confounder HRT users may have silent pre-existing disease.

New recommendation

There is no new evidence to warrant a change in practice.

Conclusion

It is well accepted that ET/EPT offers benefits for menopausal symptoms. However, except for vaginal estrogen, ET/EPT use beyond one year seems to confer a steadily increasing risk of breast cancer related to the duration of use. Therefore the lowest effective dose should be used for the shortest time. Extended treatment beyond 1 year has to be individualized and should be under strict surveillance.

Future research

Despite short-term benefits of ET/EPT from the KEEPS study, the Lancet evidence necessitates a closer review of ET/EPT use and recalculation of all-cause mortality figures. Furthermore in view of the recent damning evidence there needs to be a revisit on the implications of current ET/EPT use in premature menopause in relation to breast cancer and also of the possibility of breast cancer following blanket administration of combined oral contraceptive pills and long-acting reversible contraception (LARC) for women of reproductive age.

The following guidance was considered in the preparation of this text.

- 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy
- 2014 Practice Bulletin of the American College of Obstetricians and Gynecologists
- 2014 Statement on Management of the menopause by the Royal Australian and New Zealand College of Obstetricians & Gynaecologists
- 2015 European Menopause and Andropause Society Position statement
- 2015 Endocrine Society Clinical Practice Guideline on Treatment of Symptoms of the Menopause
- 2016 International Menopause Society Recommendations on women's midlife health and menopause hormone therapy
- 2016 Revised Global Consensus Statement on Menopausal Hormone Therapy
- 2017 hormone therapy position statement of The North American Menopause Society
- 2018 Australasian Menopause Society Information sheet on Combined Menopausal Therapy
- 2019 Menopause Guidelines of Royal Australian College of General Practitioners.

Adopted from Position statement of Sri Lanka menopause society of Sri Lanka 2009

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