11th ASEAN & 8th Perak Health CONGRESS on PRIMARY HEALTH CARE

Menopause: MHT & Other Therapies

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TOPICS OF DISCUSSION

HORMONAL

- **MHT** – ET, EPT

HORMONAL EFFECTS

- **STEAR** - Tibolone
- **SERM** – Raloxifene
  - Ospemifene

NON-HORMONAL

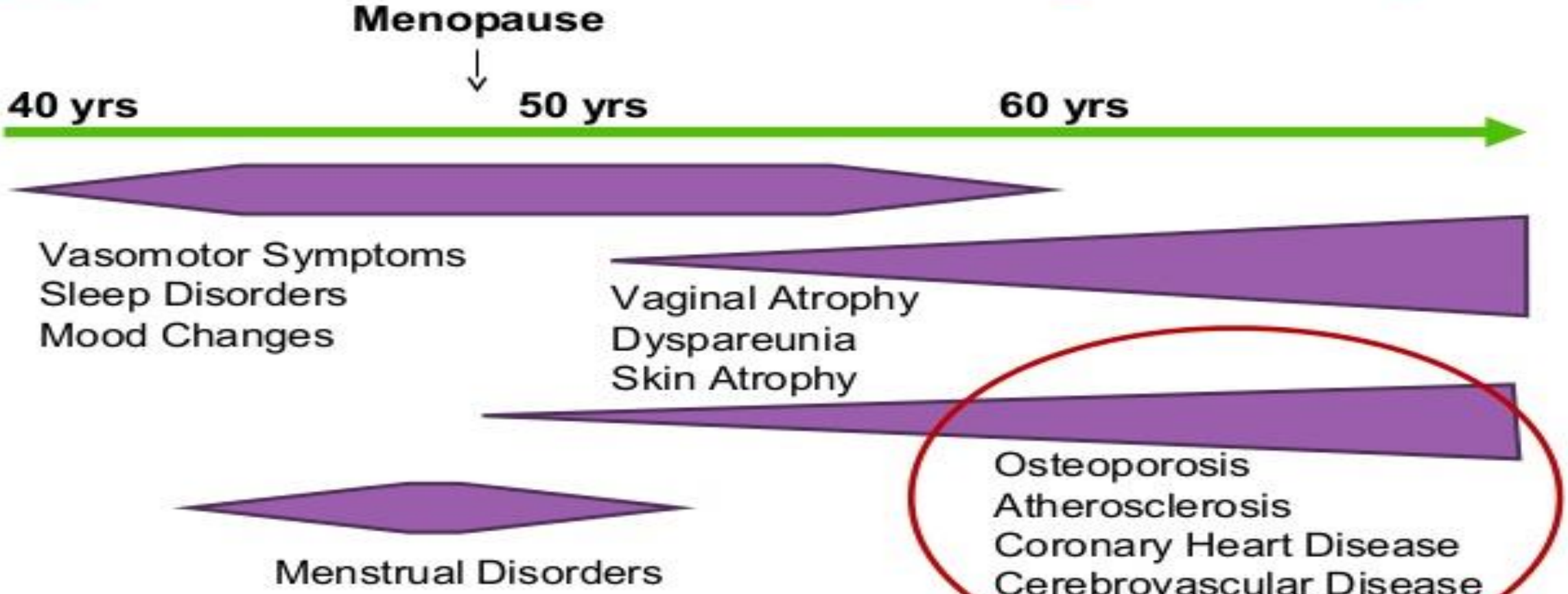
- **NON-PRESCRIPTION:**
  - Black Cohosh
  - Red Clover
  - Soy products
- **PRESCRIPTION:**
  - Anti-depressant
  - Anti-epileptic
  - Anti-hypertensive

By 2025, the number of postmenopausal women is expected to rise to 1.1 billion worldwide.

POSTMENOPAUSAL YEARS

When is Medical Intervention Required?

Symptoms and Disorders in Relation to Age and Menopause



Adapted from Bungay G et al. Br Med J 1980;281:181–3; Van Keep PA et al. Maturitas 1990;12:163–70.

EFFECTS OF MENOPAUSAL HYPOESTROGENISM

- Hot flushes, night sweats
- Fatigue, insomnia
- Mood swings, depression
- Vaginal atrophy, dyspareunia, reduce libido, marital discord
- Urinary incontinence (>70: 70%)
- Thinning and sagging of skin, wrinkles
- Sagging breasts
- Weight gain, abdominal fat, **visceral fat**
- Tooth loss & receding gums
- Poor work performance, early retirement
- Heart disease, osteoporosis, dementia

PREVALENCE OF MENOPAUSAL SYMPTOMS IN MALAYSIA

RANK	SYMPTOMS	%
1	Joint & muscular discomfort	73.3
2	Fatigue	59.3
3	Irritability	57.8
4	Hot flushes, sweating	55.0
5	Sleep problems	54.3
6	Anxiety	46.9
7	Depressive mood	44.6
8	Heart discomfort	43.8
9	Vaginal dryness	40.3
10	Sexual problems	34.1
11	Bladder problem	24.8

Bahiyah Abdullah, Burhanuddin Moize, Badrul Aznil Ismail, Mahidah Zamri et al. Prevalence of menopausal symptoms, its effect on quality of life among Malaysian women and their treatment seeking behavior. Published Oct **2016**

IMS & NAMS guidelines on MHT

- **MHT remains the most effective Rx for VMS & GSM**

- **Benefits outweigh risks if MHT is started soon after menopause**

NAMS 2017 and CLIMATERIC 2016, VOL 19, NO.2, 109-150

18 YEARS OF WHI FOLLOW-UP MHT (ET & EPT) TRIALS

AGE (yrs)	MORTALITY (all-cause)
50-59	31% reduction*ss
60-79	No reduction
50-79	No increase

CARDIAC EFFECTS OF MENOPAUSE

- **CVD is the number 1 killer of women > 65**
- **More women die from CVD than from all other causes of death combined. [1]**
- **45% of women will die from CVD & only 3% from breast cancer**
- Autopsy showed that women who go through **early surgical menopause are more likely to have CVD.[4]**
- Early natural/surgical menopause - more likely to develop CVD than age-matched premenopausal women.[2]
- **Women who had BSO & not on MHT have higher risk of CVD.**
- **BSO < 35 increase the risk of heart attack by 7x.[3]**

1. O.M. Reslan and R.A. Khalil, "Vascular effects of estrogenic menopausal hormone therapy," *Reviews on Recent Clinical Trials* 7, no. 1 (February 1, 2012): 47-70.
2. W.B. Kannel et al., "Menopause and risk of cardiovascular disease: the Framingham Study," *Annals of Internal Medicine* 85 (1976): 447-52.
3. L. Rosenberg et al., "Early menopause and the risk of myocardial infarction," *American Journal of Obstetrics and Gynecology* 139, no. 1 (January 1981): 47-51.
4. Cardiovascular diseases, World Health Organization, last modifies January 2015, who.int/mediacentre/factsheets/fs317/en.

CARDIOVASCULAR DISEASE

- The benefits of estrogen initiated within the first few years of menopause far outweigh any potential side-effects.
- A delay of 10 years or more before beginning MHT allows time for adverse changes such as atherosclerosis to develop.
- Once estrogen-deprived arteries become blocked by atherosclerosis, initiating estrogen at this late juncture will not restore what was lost.

MICROVASCULAR HEART DISEASE

- When E was infused into the left coronary arteries of pmw - **most of the benefits of E on the heart were on the microcirculation.**[1]
- Women who have heart attacks typically have disease of the small micro-vessels of the heart rather than the large coronary arteries.
- This is a major reason why **women's symptoms of heart attack often** differ from men's & why the typical tests used to diagnose heart disease in men often aren't helpful in women.[2] - **angiogram 50% false negative**
- Women have 10x more ERs than men, which allows E to dilate their arteries more than can occur in men.
- **Not taking E early deprives women of the dilating effects of E on their heart's microcirculation.**

1. P. Collins et al., "17β-estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease," *Circulation* 92 (1995): 24-30.
2. D.M. Gilligan, A.A. Quyyumi, and R.O. Cannon, "Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women," *Circulation* 89 (1994): 2545-51.

NEW EVIDENCE FOR CARDIAC BENEFIT OF MHT

- New data in USA & Europe indicate that the use of **estradiol-**based MHT regimens does not endanger the heart, but rather, it **significantly reduces the incidence of CAD events & mortality.**
- To get maximal cardioprotective efficacy of MHT, a woman should **initiate MHT as soon as VMS occur**, & preferably within the first 10 postmenopausal years

Mikkola TS, Savolainen-Peltonen H, Venetkoski M, Yikorkala O. New evidence for cardiac benefit of postmenopausal hormone therapy. ***Climateric*, 2017 Feb**;20(1):5-10. doi: 10.1080/13697137.2016.1262839. Epub 2017 Jan 2

EFFECTS OF MENOPAUSE ON CHOLESTROL LEVELS

- Premenopausal women have lower LDL & higher HDL levels than men of the same age.[1]
- **After menopause LDL rise** & often are greater than the levels of age-matched men & LDL **shift to smaller, denser sizes** which are more likely to cause atherosclerosis.
- The **small & dense LDL particles cause plague to grow**, & their smaller size makes it easier for them to penetrate the lining of arteries. **Healthy lifestyle reduces small LDL.**
- The big & fluffy LDL is packed with nutrients & carries fat-soluble vitamins & antioxidants to the cells.

1. V. Guetta and R.O. Cannon III, "Cardiovascular effects of estrogen and lipid lowering therapies in postmenopausal women," *Circulation* 93 (1996): 1928-37.
2. R.A.Lobo, "Effects of hormonal replacement on lipids and lipoproteins in postmenopausal women," *Journal of Clinical Endocrinology & Metabolism* 73, no. 5 (1991): 925-930.

ORAL vs TRANSDERMAL ESTROGEN

- **Oral E ↑HDL2 (big & able to remove LDL) & ↓LDL, which are positive in terms of preventing CVD.[1]**
- **Oral E also have beneficial effects on blood glucose levels.**
- The first-pass effect of oral E can increase the concentration of blood-clotting factors that are made in the liver, therefore can increase the risk of blood clots & stroke.
- **TD E has little effect on LDL or HDL but slightly ↓TG & produce larger LDL (resistant to oxidation)[2]**
- **Any non-oral route of taking E avoids the first-pass effect, so it has little effect on LDL & HDL levels but it doesn't increase the risk of blood clots.[3]**
- **Estradiol or CEE 0.45mg or less, are less likely to cause blood clots.[4]**

1. A. Paganini-Hill, R. Dworsky, and R .M. Krauss, "Hormone Replacement Therapy, Hormone Levels, and Lipoprotein Cholestrol Concentration in Elderly Women," *American Journal of Obstetrics and Gynecology* 174, no.3 (March 1996): 897-902.
2. A. Wakatsuki et al, "Different Effects of Oral CEE and Transdermal Estrogen Replacement Therapy on Size and Oxidative Susceptibility of Low-Density Lipoprotein Particles in Postmenopasal Women," *Circulation* 106, no.14 (October 1,2002): 1771-76.
3. B. W. Walsh et al, "Effects of Premenopausal Estrogen Replacement on the Concentrations and Metabolism of Plasma Lipoproteins," *New England Journal of Medicine* 325 (1991): 1196-1204.
4. . N.L. Smith et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens," *JAMA Internal Medicine* 174, no. 1 (2014): 25-34

TRANSDERMAL ESTROGEN

- **TD E2 is associated with a lower risk of VTE, stroke & ↑TG, than oral E.**
- Baseline risk of both VTE & stroke is very low in healthy, young pmw.
- If a patient prefers an oral preparation over a TD one (cost or personal preference), **oral E is considered to be safe.**
- All routes of E administration appear to be equally effective for symptom relief & bone density, but their metabolic effects differ:
- **Oral E has more favorable effects on lipid profiles**, but there is no evidence that this results in long-term clinical benefit. On the other hand, oral E are associated with increases in Se TG & CRP.

ESTRADIOL & VASODILATION

- In lab studies done with arteries taken from menopausal women not taking E, the arteries were found to function poorly.
- When E was added to the culture dishes, the function of the arteries improved.[1]
- In a study involving E given to women after menopause, the women's **blood vessels responded to E_2 with the most dilation & improved blood flow if the women were within 5 years of menopause.[2]**
- The earlier E_2 is initiated the greater the benefit.

1. K. Kublickiene et al., "Small Artery Endothethelial Dysfunction in Postmenopausal Women: In Vitro Function, Morphology, and Modification by Estrogen and Selective Estrogen Receptor Modulators," *Journal of Clinical Endocrinology & Metabolism* 90, no. 11 (November 2005): 6113-22.
2. C. Vitale et al., "Time Since Menopause Influences the Acute and Chronic Effect of Estrogens on Endothelial Function," *Arteriosclerosis, Thrombosis, and Vascular Biology* 28, no. 2 (February 2008): 348-52.

EARLY INITIATION of ESTRADIOL-BASED MHT

- 489,105 women given ET or EPT
- Traced from nationwide reimbursement register in Finland
- Follow up for 15 years (1994 – 2009)
- The estrogen used was almost entirely **E_2 1-2 mg OD**
- **With early initiation of MHT:**
  - **The risk of dying from CHD was ↓ by 19/1,000 women**
  - **The risk of dying from stroke was ↓by 7/1,000 women** [1]

1. T.S. Mikkola, P. Tuomikoski, H. Lyytinen et al., "Estradiol-Based Postmenopausal Hormone Therapy and Risk of Cardiovascular and All-Cause Mortality," *Menopause* 22, no. 9 (September 2015): 976-83.

SURGICAL MENOPAUSE & DIABETES RISK

- Although not all prospective studies have observed an association between natural menopause & diabetes risk, **surgical menopause has been strongly linked to an ↑ DM risk** [1]
- The ↑risk associated with surgical menopause may be attributable to the more **abrupt loss of sex steroids**, compared with the slower decline that occurs during the natural menopause transition, supporting the notion that **ovarian hormone loss is the major driver of metabolic dysfunction after menopause.**
- Large RCTs consistently support a benefit of **E-based MHT on reducing fasting glucose, insulin level & incidence of new-onset T2DM after menopause** [2]

1. Lejskova M , Pitha J , Adamkova S , Auzky O , Adamek T , Babkova E , Lanska V , Alusik S . Bilateral oophorectomy may have an unfavorable effect on glucose metabolism compared with natural menopause. Physiol Res . 2014;63(Suppl 3):S395–S402.
2. Szmuilowicz ED , Stuenkel CA , Seely EW . Influence of menopause on diabetes and diabetes risk. Nat Rev Endocrinol . 2009;5:553–558.

METABOLIC EFFECTS OF MHT

- WHI – women receiving continuous-combined **CEE+MPA** had a statistically significant **19% ↓** in the incidence of T2DM translating to **16 fewer cases / 10,000** person-years of therapy.[1]
- In the **CEE-alone** cohort, there was a **↓ of 14%** in new diagnoses of T2DM translating to **21 fewer cases / 10,000** person-years.
- Meta-analysis of published studies found that combined EPT **↓**T2DM incidence almost 40%, with lower fasting glucose levels & Hb A_{1C}.[2]
- **The benefits reverses when MHT is discontinued.**

1. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013; 310: 1353-1368.
2. Xu Y, Lin J, Wang S, Xiong J, Zhu Q. Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus. *Kaohsiung J Med Soc* 2014; 30: 350-361.

OSTEOPOROSIS – A Silent Killer

- Preventable & Treatable
- MHT prevent post-menopausal osteoporosis & fractures
- 30% of women >65 who do not take MHT will suffer from an osteoporotic fracture
- 20% die within 1 year of hip fracture
- Mortality is greater for hip fracture than breast cancer in elderly women
- Any Rx, esp MHT, which ↓ the risk of osteoporosis will result in a lessening of premature death among pmw

ESTROGEN PREVENTS BONE LOSS

- When **estrogen was replaced immediately after surgical menopause, there was no bone loss over the next 12 years**
- **Delay of 3 years** before starting estrogen, women already lost 10% of their bone density - but if given estrogen at that time, the bones were **able to regain the lost density**
- **Delay of 6 years before starting estrogen - unable to regain lost bone - but no further bone loss**

R. Lindsay and F.Cosman, "Estrogen," in The Aging Skeleton, ed. C.J. Rosen, J. Glowacki, and J.P. Bilezikian (Waltham, MA: Academic Press, 1999), 495-505.

Dementia & Alzheimer's is Now an Epidemic in America

1:3 seniors will die with a form of Dementia

Women > 65: 1:6 has Alzheimer

"The American Academy of Anti-Aging and Preventative Medicine, 25th September 2017, www.WorldHealth.net

ALZHEIMER'S DEMENTIA

- **Begin 10-15 years after menopause.**
- Estrogen reduces toxic damage to all body cells, but in particular it helps protect brain cells.
- **Early initiation of E helps to control the release of enzymes that may result in a reduction in Alzheimer's dementia by 30%.**
- Estrogen Rx started 10 or more years after the menopause may actually increase the incidence of dementia.

Impact of long-term systemic MHT use on Alzheimer disease risk

- 8,000 women followed up for 25 years in Finland
- 227 cases of AD (mean age 72)

MHT (years)	Hazard Ratio	Risks of AD
5 or less	Not associated	Nil
5-10	0.89	11% reduction
> 10	0.53	47% reduction*

Imtiaz B, Tuppurainen M, Rikkonen T, et al. Post-menopausal hormone therapy and Alzheimer disease: a **prospective cohort study**. ***Neurology*, 2017;** 88 (11): 1062-1068.

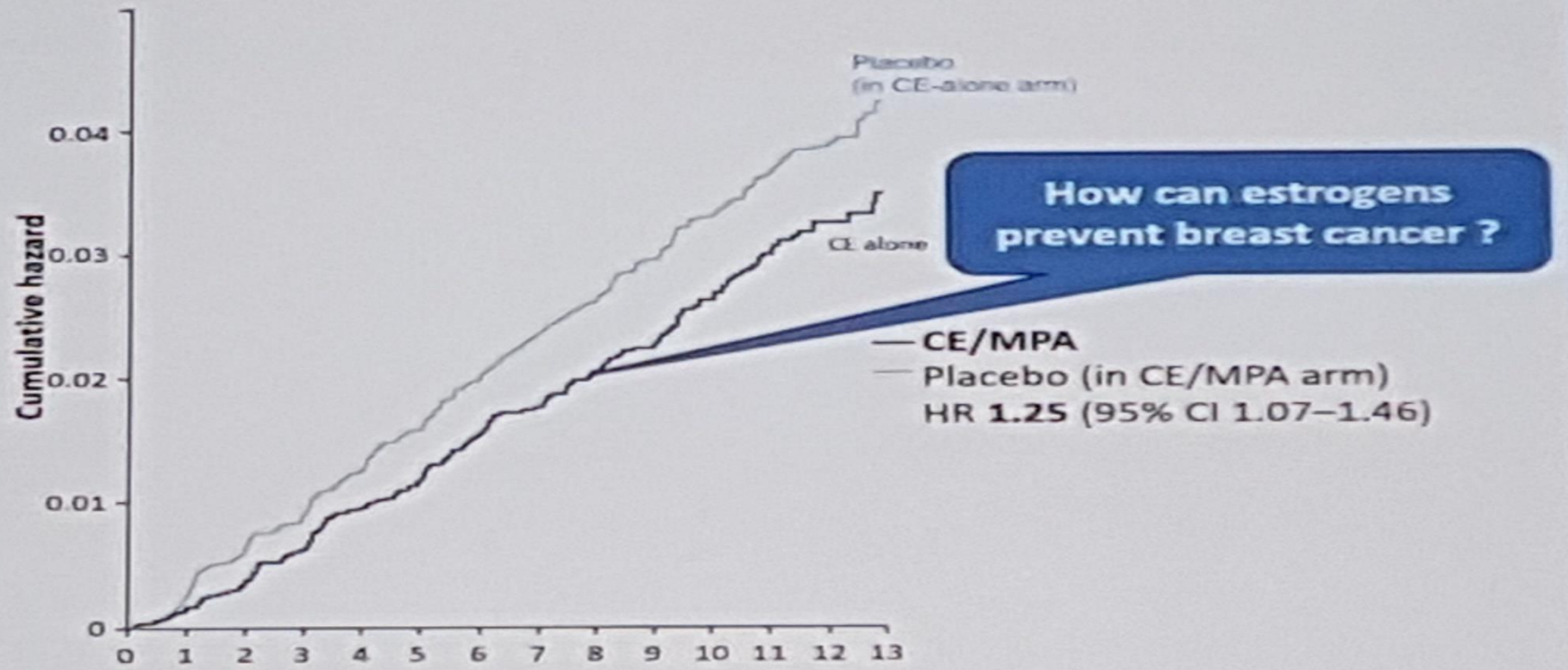
THE UNNECESSARY FEAR OF BREAST CANCER

- **Heart disease is 10 times more likely than breast cancer to kill pmw.**
- **Worry about breast cancer is the major reason why women say NO to estrogen.**
- WHI: <1 additional case of breast cancer diagnosed per 1,000 women who had formerly used EPT.
- **EPT does not increase the risk of dying from breast cancer.**

ET lowers the risk of breast cancer

Variations in Associated Breast Cancer Risk Between CE alone and CE/MPA

Cumulative hazards, adjusted for age and race/ethnicity, for invasive breast cancer by randomization assignment in the WHI CE-alone and CE/MPA trials



UAB

Anderson GL, et al. *Lancet Oncol*. 2012;13(5):476–486.

BREAST CANCER

- Etiology is **multifactorial** - c**aused by an accumulation of up to 200 abnormal mutation of genes within the cell & the majority of these mutations probably occur prior to menopause.**
- It develops in about **12% of women who live to 90.**
- The large majority are **sporadic** in nature.
- 25% are diagnosed in pre-menopausal women.
- **Over 80% of breast cancers in pmw occur in women who have never taken hormone therapy.**

Nick Panay, Paula Briggs, Gab Kovacs, Managing the Menopause. 21st Century Solutions 2015

RISK FACTORS FOR DEVELOPING BREAST CANCER

- Family history 3-5x
- Age >50 - risk double every 10 yrs
- Dense tissue in breasts 2x
- Smoking 10/> cigarettes daily 2x
- 2/> alcoholic drinks daily 2x
- Obesity 1.5x
- Sedentary lifestyle 1.5x
- EPT 1.3x (<1:1000)

- Never pregnant 1.2x
- Early menarche +/or late menopause 1.2x.

BREAST CANCER

- The increase risk of breast cancer is primarily associated with the addition of a **progestin** to estrogen therapy & the **duration** of use.

- **The risk may be lower with micronized progesterone or dydrogesterone than with other progestogen.**

Baber R.J, Panay N, Fenton A. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy, Climateric 2016, Vol 19, No 2, 109-150

REDUCED RISK OF BREAST CANCER MORTALITY IN WOMEN USING MHT

- **489,105 women using MHT (estradiol)**
- **Traced from nationwide reimbursement register in Finland**
- **Follow up for 15 years (1994 – 2009)**
- **From MHT initiation (3.3 million cumulative exposure years) to breast cancer death (n= 1,578 women)**
- **The observed deaths were compared with those in the age-standardized background population.**

Mikkola TS, Savolainen-Peltonen H, Tuomikosi P, Hoti F, Vattulainen P, Gissler M, Yikorkala O. Reduced risk of breast cancer mortality in women using MHT: **a Finnish nationwide comparative study. *Menopause,* 2016 Nov**;23(11):1199-1203.

RESULTS OF THE FINLAND STUDY

- **Breast cancer mortality was reduced in all MHT users with exposure for 5, 10 and >10 years**
- **A significant larger risk reduction was detected in the 50-59 years age group**
- The death risk reductions in ET users are better than EPT users - in all age groups.
- In the Finnish unselected population, breast cancer is fatal in 1 of 10 patients, but in MHT user the **mortality risk is reduced by 50%** (1 in 20)

Mikkola TS, Savolainen-Peltonen H, Tuomikosi P, Hoti F, Vattulainen P, Gissler M, Yikorkala O. Reduced risk of breast cancer mortality in women using MHT: a Finnish nationwide comparative study. ***Menopause*, 2016 Nov;**23(11):1199-1203.

IMS: PREMATURE MENOPAUSE

- Women experiencing spontaneous or iatrogenic menopause before 45 & particularly before 40 are at higher risk for CVD & osteoporosis & may be at increased risk of dementia.
- MHT may reduce symptoms & preserve bone density & is advised at least until the average age of menopause.

CLIMATERIC 2016, VOL 19, NO.2, 109-150

NAMS & IMS RECOMMENDATION

MHT should not be recommended without a clear indication for its use, i.e. significant symptoms or physical effects of estrogen deficiency.

1. NAMS 2107 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 2017; 24 (7): 728-753.

FDA-APPROVED
4 INDICATIONS FOR MHT

1. Vasomotor symptoms
2. Prevention of osteoporosis
3. Premature menopause
4. GSM

Menopause: The Journal of The North American Menopause Society, Vol.24, No. 7, pp. 728-753 (June 2017)

CONTRAINDICATIONS to MHT

1. Known past or suspected **breast or endometrial cancer**
2. Progesterone-dependant meningioma
3. Undiagnosed genital bleeding
4. Previous/current venous **thromboembolism**
5. Known thrombophilic disorders
6. Active or recent **heart attacks/angina**
7. Acute/history of **liver disease**
8. Known hypersensitivity

LOCAL VAGINAL ESTROGEN

- **When GSM is the sole symptom, local vaginal E is the 1st choice.**
- Local E Rx minimizes the degree of systemic absorption &, although vaginal administration can ↑ plasma levels of E during chronic administration, the observed levels are not above the normal range of 20 pg/ml for pmw.
- **Additional progestogen is not indicated** when appropriate low-dose, local E is used, although long-term data (>1 year) are lacking.
- If E is ineffective or undesired, vaginal lubricants & moisturizers can relieve symptoms due to dryness, & sexual activity should be recommended on a regular basis.

STEAR (TIBOLONE)

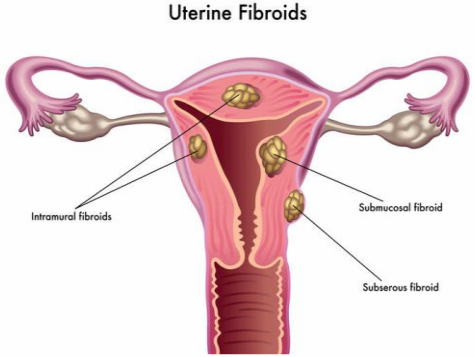
- Selective Tissue Estrogenic Activity Regulator
- **Weak estrogenic, progestogenic & androgenic activity**
- **Suppresses VMS & improves mood & libido**
- Improves vaginal atrophy but it does not affect the endometrium.
- Protective effect on bone mass
- ↓ proliferation of breast epithelial cells, does not increase mammographic density & ↓ cyst diameter of fibrocystic mastopathy
- Rx of choice for women with unwanted side effects of MHT & history of **endometriosis**
- Prolonged use in women >60 has been associated with an ↑ risk of stroke
- Could slightly ↑ the risk of recurrent breast cancer

Effect of tibolone on postmenopausal women with myomas

- 40 naturally pmw with at least 1 uterine fibroid measuring > 20 mm. All were scanned by transvaginal ultrasonography. Randomized into two groups. Group A (n = 20) were treated with Tibolone **2.5 mg daily for 1 year** and group B (n = 20) did not received therapy. The size of the uterine fibroids was reevaluated on the end of the treatment.

- **No statistically significant difference was found in the mean volume of fibroids before & after Rx with Tibolone**

- **Tibolone does not affect preexisting asymptomatic uterine fibroids.**



Gregoriou O[1], Vitoratos N, Papadias C, Konidaris S, Costomenos D, Chryssikopoulos A. Effects of tibolone on postmenopausal women with myomas. *Maturitas* 1997 Jun; 27 (2): 187-91.

RALOXIFENE (EVISTA)

- Selective estrogen receptor modulator (SERM)
- Estrogen agonist/antagonists
- Mimics the action of E on bones – ↓ bone resorption & turnover - **prevents osteoporosis**
- Blocks the effect of E on endometrium & breast
- **Approved for the prevention of invasive breast cancer in postmenopausal women at high risk**
- Hot flushes are a common side effect – start 3 years pm
- May not be suitable for people with a history of TE, CVD, liver or kidney disease, high triglycerides, or who take warfarin
- Temporarily discontinued prior to surgery or inactivity

OSPEMIFENE (SERM)

- **First FDA-approved non-estrogenic oral medication for the Rx of VVA & dyspareunia**
- Significantly improves the structure & pH levels of the vagina & ↓dyspareunia
- Women who dislike vaginal administration or on-demand use of nonprescription lubricants & moisturizers would likely prefer this oral tablet
- **Estrogen agonist action on the bone**
- **Estrogen antagonist on the breast** - reducing the cell proliferation of ductal carcinoma in an *in situ* model.
- Studies evaluating the safety of Rx for up to 52 weeks have shown that ospemifene is a safe medication with minimal impact on the endometrium.
- CI - TE

TYPES of MENOPAUSE Rx used in MALAYSIA

No.	TREATMENT	FREQUENCY (%)
1	Vitamins	40.6
2	Jamu / Akar kayu / Traditional herbs	21.9
3	Hormones	20.3
4	Massage	18.7
5	Evening primrose oil (EPO)	17.2
6	Vaginal lubricant cream	7.8
7	Exercise	4.7
8	Counselling	1.6

Bahiyah Abdullah, Burhanuddin Moize, Badrul Aznil Ismail, Mahidah Zamri et al. Prevalence of menopausal symptoms, its effect on quality of life among Malaysian women and their treatment seeking behavior. Published Oct 2016

MENOPAUSE MANGEMENT IN MALAYSIA

- Many Malaysian women experienced menopausal symptoms, particularly musculoskeletal aches & fatigue.
- It affect the QOL of 52.4% of postmenopausal women.
- **The majority of these women (75.2%) did not seek any treatment to alleviate the symptoms.**
- Only 20.3% used MHT.
- There is a need to improve awareness among the menopausal women & healthcare providers on the variety of intervention ranging from lifestyle modifications to pharmacological therapies

Bahiyah Abdullah, Burhanuddin Moize, Badrul Aznil Ismail, Mahidah Zamri et al. Prevalence of menopausal symptoms, its effect on quality of life among Malaysian women and their treatment seeking behavior. Published Oct 2016

NONHORMONAL THERAPIES

- Numerous alternatives to hormone therapy have been studied, many in RCT, over the past decade.
- The MsFLASH network of collaborating centres, for example, have studied anti-depressants, yoga, mindfulness and other interventions [2, 3, 4].
- One difficulty cited in determining effectiveness in VMS treatment trials has been the **placebo improvement rate between 20 to 60%** [5].

2. Sternfeld, B., Guthrie K.A. et al. Efficacy of exercise for menopausal symptoms: a randomized controlled trial. Menopause 21 (4):330 (2014). (View with CPSBC or UBC) DOI: 1097/GME.0b013e31829e4089

3. Newton, K.M., Reed, S.D. et al. Efficacy of yoga for vasomotor symptoms: a randomized controlled trial. Menopause 21(4): 339 (2014). (View with CPSBC or UBC) DOI: 1097/GME.0b013e31829e4baa

4. Cohen, L.S., Joffe, H. et al. Efficacy of omega-3 for vasomotor symptom treatment: a randomized control trial. Menopause 21(4): 347 (2014). (View with CPSBC or UBC) DOI: 10.1097/GME.0b013e31829e40b8

5. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of the North American Menopause Society. Menopause 22(11): 1155-74 (2015). (View with CPSBC or UBC) DOI: 10.1097/GME.0000000000000546

NONHORMONAL THERAPIES

- A low-dose **paroxetine salt (7.5 mg/d) is the only nonhormonal pharmaceutical approved by the FDA for the Rx of moderate to severe menopausal VMS**, with improvements found in VMS frequency & severity up to 24 months & improvements in sleep disruption without negative effects on libido or weight gain
- Selective serotonin reuptake inhibitors **SSRIs (paroxetine, citalopram, escitalopram)**, serotonin-norepinephrine uptake inhibitors **SNRIs (venlafaxine, desvenlafaxine**), gabapentinoids **(gabapentin and pregabalin)** and **clonidine** have all been shown to have efficacy in reducing VMS.
- Onset of action is rapid, usually within 2 weeks.

The North American Menopause Society (NAMS). 2015;22(11):1155-1174

NONHORMONAL THERAPIES

- **Recommended Rx** to ease distressing menopausal symptoms include **cognitive-behavioral therapy, and to a lesser extent clinical hypnosis**, which have been shown to decrease VMS.
- **Recommended with caution** include weight loss, mindfulness-based stress reduction, the S-equol derivatives of soy isoflavones & stellate ganglion blockade; further studies are warranted.
- **Not recommended** at present are cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, OTC supplements & herbal products, acupuncture & chiropractic interventions. There were negative, insufficient or inconclusive data on these Rx to permit their recommendation as proven Rx for VMS management.
- Despite lack of specific recommendation for the Rx of VMS, the **benefits of a healthy diet, with weight loss if necessary & regular exercise are well known & recommended for everyone.**

BLACK COHOSH

- A 2016 systematic review & meta-analysis of RCT examined 4 studies of herbal & plant-based therapies that included black cohosh to treat menopausal symptoms[1]. The trials randomized a total of 511 women to a daily dose of various formulations of 6.5 to 160 mg/day black cohosh extract or placebo. **There were no significant associations between supplementation with black cohosh & reduction in the number of VMS.**
- There is currently insufficient evidence to support the use of black cohosh for hot flushes. The effect of black cohosh on other important outcomes, such as health-related QOL, sexuality, bone health, night sweats & cost-effectiveness is not yet established.
- **There were originally reports of liver toxicity, but these have not been seen in larger studies & appear to be due to contaminants, though the longest study was only for 6 months.**

1. Franco OH, Chowdhury R, Troup J, Voortman T, Kunutsor S, Kavousi M, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. JAMA 2016;315:2554-63. [PubMed abstract]

SOY SUPPLEMENTS

- 2012 analysis of 19 studies - soy isoflavone supplements **↓ the severity of hot flashes by 26% compared to a placebo.**
- Cochrane review (2013) - no firm evidence that dietary soy or isoflavone supplements eased hot flashes. But it did find a **benefit from supplements that were high in genistein**, one of the main isoflavones in soy.
- A 2015 analysis of 10 studies found that plant isoflavones from soy & other sources **reduced hot flashes by 11%.**
- Soy isoflavones **take more than 13 weeks to reach just half of their maximum effect**. MHT takes 3 weeks to show the same benefit
- NAMS position statement 2015 - the most recent clinical trials have found them to be no more effective than a placebo.

RED CLOVER

- *Trifolium pratense* (Swiss Red clover) extr (equiv to isoflavones 40 mg)
- Isoflavones are changed in the body to phytoestrogens
- So far, there isn't enough scientific evidence to determine whether it is effective for controlling hot flushes
- In 5 controlled studies, **no consistent or conclusive evidence was found that red clover leaf extract reduces hot flashes.**
- As with black cohosh, however, some women claim that red clover has helped them.
- Studies report few side effects & no serious health problems with use.
- But studies in animals have raised concerns that red clover might have harmful effects on hormone-sensitive tissue.

CONCLUSION

- **Individualize treatment**, symptoms relieve or long-term health
- Short term symptoms relieve – non-hormonal Rx
- Premature menopause – MHT
- PERIMENOPAUSE – OCP, cyclical-MHT
- I year after menopause – continuous-MHT, Tibolone
- 3 years after menopause – continuous-MHT, Tibolone, Evista
- Estradiol better than CEE. Route – oral, transdermal, vaginal
- Micronized progesterone (oral/vaginal) or dydrogesterone are safer
- **Early initiation of MHT** ↓risk of CVD by 50%, & ↓all-cause mortality by 30%
- The sooner estrogen is replaced, the sooner symptoms resolve, & the better protection for long-term health – bones, brain, skin, vagina, urinary tract, QOL
- **MHT can be continued >65 if no contraindications**

CARMEN DELL 85

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