HRT VS NON HRT FOR MENOPAUSE

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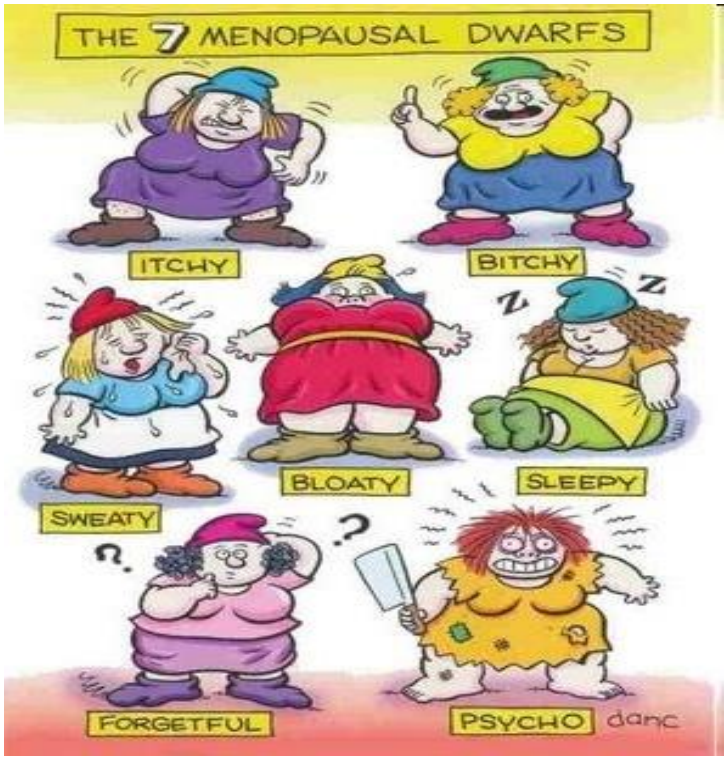
Menopause

- The woman's final menstrual period and the accepted confirmation of this is made retrospectively after 1 year of amenorrhoea. (2017 women's health conference)

- The ovaries stop releasing eggs and stop making hormones estrogen and progesterone

- 95%- 45-55 years of age, Average age 51

Symptoms Of Menopause



- Hot Flashes
- Night Sweats
- Sleep problems
- Vaginal dryness and sexual problems
- Depression , anxiety, mood swings
- Trouble concentrating or remembering things
- Lethargy and luck of energy

- Hot flushes occur in 75 -80% of menopausal women and it may last up to 7-8 years.

- Long term consequences of menopause

  Osteoporosis

  Cardiovascular disease

  Uro-genital atrophy

- Menopause before 40 years are at higher risk for cardiovascular disease and osteoporosis and may also be at increased risk of affective disorders and dementia.

- Most common form of treatment for symptomatic women is Hormone Replacement Therapy

- Goal of therapy is to relieve menopausal symptoms

- More than 50 HRT preparations, which feature different strengths, combinations and route of administrations with potentially different risks and benefits.

- Evidence regarding differences in risks and benefits between different products is limited.

Estrogens- used in HRT include estradiol,estrone and estriol, which chemically synthesized from soya beans or yams.

Routes of administration of estrogen

Oral, transdermal , subcutaneous and vaginal

- **Canonico et al; a meta-analysis of observational studies**, found that oral estrogen was associated with a higher risk of venous thromboembolism than transdermal estrogen:

- Relative risk with oral estrogen- 2.5, 95% CI 1.9–3.4
- Relative risk with transdermal estrogen -1.2, 95% CI 0.9–1.7.

Types of systemic estrogen based HRT

- Estrogen alone in hysterectomized women
- Estrogen +progestrogen in non hysterectomised women and cyclical progestrogen in perimenopausal women
- Continuous combined estrogen-progestrogen in post menopausal women

Progestogens

- Progestogens- used in HRT are almost all synthetic and derived from plant sources.

17 hydroxyprogesterone and 19 nortesterostone derivatives are most commonly used in HRT.

Routes of administration of progestrogen:

oral ,transdermal and intrauterine

Side effects of systemic HRT

- Oestrogen related: fluid retention, bloating, breast tenderness or enlargement, nausea, headache, leg cramps and dyspepsia.

- Pregestogen : breast tenderness, headaches, mood swings, depression, acne, lower abdominal pain and backache.

- Combined HRT: irregular break through bleeding
- All type HRT: weight gain

Other hormones used at the menopause

Tibolone

Synthetic steroid compound that on absorption is converted to metabolites with estrogenic, progestagenic and androgenic actions.

It has increased risk of breast cancer recurrence in placebo controlled trial.

Testosterone

Patches and implants are available to use to improve libido.

Contraindications

- Breast cancer
- Coronary Heart Disease
- Previous VTE
- Stroke
- Liver disease
- Vaginal bleeding
- Uterine cancer
- Gallbladder disease

Benefits

- Improve quality of life and reduce vasomotor symptoms
- Estrogen may improve postural balance and reduce falls
  Osteoporosis: fracture at the hip and vertebrae reduced
- Reduced urogenital symptoms and improved sexuality
- Reduction in Colon cancer
- Mortality: 30% mortality reduction in women under 60

Duration of therapy

- Short term, generally not more than 5 years or beyond 60 years of age

- For women experiencing recurrent symptoms – current recommendation is- to try non –hormonal options before resuming HRT.

Women`s health initiative and Million women study

HRT and CVD

- WHI—increased risk in CVD with HRT in Older women only
- Observational studies, RCT and Cochrane reviews 2012 and 2014, women under age 60—benefit of HRT shown in reduce risk of CVD.

HRT and VTE

- Overall baseline VTE risk 1.0 per 1,000 women / year

  Oral HRT- additional 1.5 events per 1,000 women / year, mostly in 1st year

- Risk affected by progestogen type-- Increased with MPA

- No apparent increase with transdermal HRT

  Offer transdermal type if BMI >30

HRT and STROKE

Women on HRT tablets have a 28% higher risk of stroke than none-users, regardless of whether their tablets contain a high or low dose of either or both of the hormones.

HRT and Medical Disease

- **Asthma** – hormonal effect unclear, be prepared to change/stop HRT if symptoms worsens
- **Thyroid** – Control may be affected by HRT, (TBG up) check 3 months after starting HRT
- **Migraine** – not C/I, use transdermal , may worsen or improve

HRT and BREAST cancer

- WHI:
  - Risk of breast cancer in estrogen alone group was 23% lower than placebo group.

- Million women study:
  - Increased risk of breast cancer in all HRT regimen.
  - Greatest risk with combined group.
  - The pattern of progesterone administration did not change the risk.

HRT in women with Family History of breast cancer

Most women with a family history do not fall into a high risk category

- ~ 10% cancers are due to high risk (BRCA1 / BRCA2/ young age at diagnosis)

Observational studies

- No additive effect of HRT with family history. Absolute risk dependent on individual baseline risk conferred by the family history

◦ Known BRCA1 / BRCA2 mutation carriers

- Oophorectomy reduces breast cancer risk (50%).
- Add-back HRT after oophorectomy does not increase breast cancer risk

▸ Studies are inconclusive

- The extra risk of developing breast cancer on HRT does not persist beyond about 5 years after stopping treatment.
- Women taking HRT diagnosed with breast cancer are less likely to have tumours with metastatic spread and therefore have an improved prognosis.
- Regular mammography is indicated for women on HRT after 50 years old.
- There is no indication to arrange mammography routinely for women commencing HRT under the age of 50 years.

HRT and Gynae Cancer

- Endometrial cancer – HRT can be considered with specialist input, generally c/I
- Ovarian cancer –caution with HRT after endometrioid ovarian cancer
- Cervical cancer–no c/I to HRT. If treated with radiotherapy, use continuous combined HRT
  possibility of haematometra if sequential HRT with stenosed cervix
- Vulval, vaginal cancer – no c/I to use of HRT

“ It’s important to remember that the increased cancer risk with HRT is small compared to many other risk factors, like smoking or being overweight.

HRT is only responsible for a very small proportion of cancer cases. ” Cancer Research UK (2010).

KEY RECOMMENDATIONS FOR PRACTICE

- Systemic estrogen, alone or in combination with a progestogen, is the most effective therapy for menopausal hot flashes.
- Because of the potential risks with long-term use of hormone therapy, clinicians should prescribe the lowest effective dosage for the shortest duration necessary to improve symptoms.
- The decision to continue combined hormone therapy for more than three to five years should be made after reviewing the risks, benefits, and symptoms with the patient.

NON HRTs

- Pharmacological alternatives
- Herbals
- Others-Acupuncture
  - Reflexology
  - Magnetic devices
  - Homeopathy
  - Stellate ganglion blockade

Pharmacological Alternatives

- Clonidine, a centrally active alpha-2 agonist for the treatment of vasomotor symptoms.

- A systematic review and meta-analysis confirmed a marginally significant benefit of clonidine over placebo; however, the effects of clonidine were not as great as those of estrogen.

Beta-blockers have a possible option for treating vasomotor symptoms, but the small trials that have been conducted have been disappointing.

Selective serotonin(fluoxetine) and noradrenalin reuptake inhibitors (venlafaxine)

- A significant amount of evidence exists for the efficacy of (SSRIs)and (SNRIs) in the treatment of vasomotor symptoms.
- The main drawback (especially the SNRIs) is the high incidence of nausea, which often leads to withdrawal from therapy before maximum symptom relief efficacy has been achieved.
- These may also be associated with reduced libido and sexual response.

Gabapentin

- The antiepileptic drug has shown efficacy for hot flush reduction compared with placebo.
- RCT of gabapentin 600 mg versus low-dose transdermal estradiol 25 micrograms in women with moderate to very severe hot flushes showed symptom relief in both groups, but estrogen was more effective.
- The adverse effect drowsiness, dizziness, fatigue may restrict use.

Dehydroepiandrosterone (DHEA)

- DHEA was initially used in the USA, where it is classed as a food supplement.
- Some studies have shown benefits on hot flushes, the skeleton, cognition, wellbeing, libido and the vagina dryness.

Antidepressant

- Brisdelle (Paroxetine 7.5 mg) only agent that has received approval by the FDA for treatment of hot flashes.

Vitamins and minerals

- Vitamin E,C and minerals such as selenium, are present in various supplements.

- The evidence that they are of any benefits to postmenopausal women is extremely limited.

Calcium &*Vitamin D supplementation*

- The DRI for vitamin D is 800–1000 IU in the postmenopausal period.

- Vitamin D supplementation has been shown independently to lower the risk of fracture and of falling in elderly patients.

Consider Calcium and Vit D supplements for biochemical insufficiency, dietary deficiency, ?all age >70 yrs, nursing home residents, high dose steroids

Raloxefine

- Selective oestrogen receptor modulator (SERMs)
- Bone protective and reduce cholesterol
- Evidence to suggest that it is protective against breast cancer
- Does not help menopausal symptoms and may worsen them
- No effect on the endometrium
- Slight increase risk of VTE

Bisphosphanate

- Etidronate and Alendronate
- Inhibitors of bone turnover and slow down or prevent bone loss
- Treatment of choice for older women and those with contra-indications to HRT

Non-pharmacological alternatives for vaginal dryness

- Lubricants are used to relieve vaginal dryness during intercourse. They do not provide a long-term solution.

- Moisturisers contain a bio-adhesive polycarbophil-based polymer that attaches to mucin and epithelial cells on the vaginal wall and retains water. They are promoted as providing long-term relief of vaginal dryness .

- The evidence is scant.

Herbals

Most are not FDA regulated

- Phytoestrogen
- Black cohosh
- St John's Wort
- Ginseng
- Chasteberry (Agnus Castus)
- Evening primrose oil

Phytoestrogens

- Phytoestrogens are plant substances that have similar effects to estrogens.
- The most important groups are called isoflavones and soya products.
- Isoflavones are found in soybeans, chickpeas and red clover, and probably in other legumes (beans and peas). Oilseeds such as flaxseed are rich in lignans, which are also found in whole cereals, vegetables, legumes and fruits.

- Area of potential concern is phytoestrogens have both estrogenic and anti-estrogenic effects.

- Experts recommend that dietary soy is okay in women with breast cancer but to avoid supplements until their safety has been established.

Black cohosh

- Black cohosh (Actaea racemosa, formerly known as Cimicifuga racemosa) is a herbaceous perennial plant native to North America used widely to alleviate hot flushes but does not help with anxiety or low mood.

- Little is known about the long-term safety of black cohosh. Liver toxicity has been reported.

St John's wort

- St John's Wort (*Hypericum perforatum)* has been shown to be efficacious in mild to moderate depression because of its SSRI-type effect.
- It interacts with many other medications ; cyclosporin, midazolam, tacrolimus, amitriptyline, digoxin, indinavir , warfarin, phenprocoumon and theophylline.
- It may cause breakthrough bleeding.
- In a recent RCT, women on St John's wort reported improved menopause-specific quality of life and non significant improvement in hot flushes.

Ginseng

- Ginseng is a herb native to Korea and China .
- *Studies have* focused on its effects on quality of life issues in menopausal women. It has not been found to be superior to placebo for vasomotor symptoms.
- Case reports have associated ginseng with postmenopausal bleeding and mastalgia; interactions have been observed with warfarin (leading to a reduced INR), phenelzine and alcohol.

Chasteberry (Agnus Castus)

- Limited data exist for the effect of Agnus Castus (*V. agnus-castus) on menopausal symptoms.*

  A combination herbal product that includes chaste tree along with black cohosh, red clover and American ginseng: reduced vasomotor symptoms in a RCT.

Evening primrose oil

- Evening primrose oil is rich in gamma-linolenic and linolenic acid.
- One small randomised placebo-controlled trial has shown it to be ineffective for treating hot flushes.

Other Herbs

- Ginkgo biloba, hops, sage leaf, liquorice and valerian root are popular, but there is no good evidence that they have any effect on menopausal symptoms.

- Recent some encouraging data regarding the safety of traditional hormone replacement therapy (HRT), continue to be concerned about the purported risks, particularly to the breasts and cardiovascular system.

- The choice of treatment remains confusing and the evidence for efficacy and safety for many of these preparations remains limited.

Other treatment methods

- Acupuncture
- Reflexotherapy
- Magnetic devices ,homeotherapy and stellate ganglion blockade

Acupuncture

- The evidence from randomised trials that acupuncture helps menopausal symptoms is conflicting.

Reflexology

- Reflexology aims to relieve stress or treat health conditions through the application of pressure to specific points or areas of the feet, hands and ears.

- One randomised trial in which 67 women aged 45–60 years with vasomotor symptoms were randomised to receive reflexology or nonspecific foot massage.

  There was a reduction in symptoms in both groups, but no significant.

Magnetism

- Magnets are marketed in various forms such as bracelets and insoles.
- There is no known mechanism of action for magnet therapies for the treatment of hot flushes.
- There is no evidence of benefit at present.

Homeopathy

The mechanisms that underlie the biological response to ultra-molecular dilutions are scientifically unclear.

Data from case histories, observational studies and a small number of randomised trials are encouraging.

Larger randomised trials are required to confirm these effects.

Stellate ganglion blockade

Stellate ganglion blockade, which involves local anaesthetic injection into the stellate ganglion, has recently emerged as a new technique against hot flushes and sweating refractory to other treatments or where HRT is contraindicated, such as in women with breast cancer.

- Preliminary studies report encouraging efficacy with minimal complications.

- Despite further research into alternative preparations, their efficacy continues to be lower than with traditional HRT (maximally 50–60% symptom reduction compared with 80–90% with traditional HRT).

- The trials on alternatives on the whole remain small and of short duration and are therefore of limited value in determining efficacy and safety.

Final recommendations

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

- HRT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations.

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ANY SIDE EFFECTS FROM THE HRT?
WHAT?
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