Update on menopause

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HRT for management of menopausal symptoms

- Most commonly used treatment
- Most effective intervention
- Time , dose , duration - individualised
- No arbitrary limit on duration

Long term effects of HRT

- First line treatment : prevention & treatment of osteoporosis in POI and menopausal women below 60yrs particularly those with symptoms
- HRT started before 60yrs or within 10 yrs of menopause : reduction in atherosclerosis progression , coronary heart disease and death from cardiovascular cause as well as all-cause mortality (Cochrane, ELITE , Finnish observational study)

Long term effects of HRT

- HRT started after 10 yrs of menopause : do not increase cardiovascular events , cardiovascular mortality , all cause mortality
- Timing hypothesis / window of opportunity
- WHI RCT , Danish Oteoporosis Trial , KEEPS RCT , ELITE trial, Finnish observational study
- HRT is unlikely to have detrimental effects of dementia or cognitive function when started before 60 yrs

Long term effects : breast cancer

- Estrogen only HRT : little or no change in risk
- Combined HRT : increased risk which appears duration dependent & may vary with type of progesterone used
- Risk is low in both medical & statistical terms
- Vaginal estrogen : no associated increase in risk
- Micronised progesterone & dydrogesterone : lower risk
- h/o breast cancer : contraindication for systemic HRT

Long-term effect : other cancers

- Serous & endometriod ovarian cancer : slight increased risk (epidemiological studies): risk is small both in medical & statistical terms

- Survival rates with epithelial ovarian cancers : no adverse effect

- Endometrial cancer : > risk with unopposed Estrogen which can largely be avoided with Progesterone

- Recurrence risk with early endometrial cancer : no effect

- Colorectal cancer : reduced risk with combined HRT

Long-term effect : VTE

- Transdermal estradiol : unlikely to increase the risk of VTE or stroke above that in nonusers
- Lower risk compared to oral estradiol
- Micronised progesterone (utrogestan) & dydrogesterone : unlikely to increase risk of DVT
- Utrogestan has selective effect on progesterone receptors and less interaction on androgen & mineralocorticoid : reduction in metabolic & other side effects

Other recommendations

- Persistent unscheduled bleeding beyond 4 to 6 months : USS, pipelle biopsy , hysteroscopy
- POI and early menopause : use HRT at least till average age of menopause
- Testosterone : in distressing low sexual desire & low energy levels particularly on HRT with adequate oestrogen level

HRT & breast cancer

- Most common female cancer in UK
- 11400 die each year in UK
- Life time risk 1 in 7
- 23 % are preventable : OCP < 1% , HRT 2% , overweight & obesity 8 %, alcohol drinking 8% , not breast feeding 5 % (cancer research UK)

The Million Women study

- Observational data: raised concerns of breast cancer
- Flaws in study methodology & findings : limits to establish a causal association between HRT & breast cancer

WHI Estrogen+ProgesteroneRCT

- Intervention phase after 5 yrs : 1 extra case per 1000 women per year (HR 1.24). Not statistically significant after adjusting confounding variable .
- Early post intervention phase (2.75 yrs) : sharp decrease in risk to make risk statistically insignificant(HR1.23)
- Late post intervention phase (5.5 yrs): small increase in risk (HR 1.37)

WHI estrogen-alone trial

- Intervention phase : reduction of risk was not statistically significant (HR 0.79)
- Early post intervention phase (with 2.75 yrs) : statistically significant reduction in risk (HR 0.55)
- Late post intervention phase (5.5 yrs) : risk reduction becomes neutral (HR 1.17)

NICE 2015 guideline

- Oestrogen alone : little or no change in risk of breast cancer
- Estrogen + progesterone : can be associated with increased risk of breast cancer . It’s related to treatment duration & reduces after stopping HRT.

Collaborative Group on Hormonal Factors in Breast Cancer 2019

- January 1992 to January 2018
- 58 studies ; 24 were prospective
- 108647 post menopausal women with breast cancer
- 55575 (51 %) had used HRT
- No data on breast cancer mortality

Collaborative Group meta-analysis

- Continuous combined HRT : For taking HRT for 5 years from the age of 50 yr , the risk of developing breast cancers goes up by 1 extra case in 50 over 20 yrs (from background risk of 3 in 50 to 4 in 50).
- Sequential combined HRT : 1 extra case in 70 over 20 yrs (from background risk of 4 in 70 to 5 in 70)
- Estrogen only HRT : 1 extra case in 200 over 20 yrs (from background risk of 13 in 200 to 14 in 200)
- No dosage effect for oestrogen
- Vaginal estrogen - no adverse effect

Collaborative group Meta-analysis

- > 40 % cases included were from MWS which had significant methodological limitations
- Data form placebo controlled WHI study were not included
- Very small number of women on micronised progesterone (MP) included
- French E3N cohort study which demonstrated lower breast cancer risk with MP - not included

BMS view on meta-analysis

- The meta-analysis provide important additional informations
- Findings are consistent with NICE
- Needs to be discussed in the context of overall risk & benefits

WHI long term RCT : JAMA 2020

- 27000 women enrolled between 1993-1998 & followed up through 2017
- Estrogen only : significant decrease in breast cancer diagnosis (HR 0.78) & breast cancer mortality (HR 0.60, p<0.001)
- Combined HRT : increased risk of breast cancer (HR 1.28) but no significant difference in breast cancer mortality (HR 1.35, p=0.11)
- Subgroup analysis : BMI > 35 : significantly increased risk of invasive breast cancer (HR 1.58); increase in oestrogen & progesterone receptor positive cancer (HR 1.86) ; increase in breast cancer mortality (HR 2.11).

French E3N cohort study 2014

- Large observational study between 1992 to 2008
- 3678 invasive cancer among 78353 women
- Estrogen + MP / dydrogesterone : no increased risk with short term use upto 5 yrs (HR 1.11); slight increase risk with long term use > 5yrs (HR 1.15); risks no longer statistically significant following discontinuation (HR 1.15).
- Estrogen + other progesterones : slightly elevated risk with short term use < 5yrs (HR 1.7) and long term use > 5yrs (HR 2.02) ; slight ongoing risk on discontinuation (HR 1.36) .

E3N Cohort & Finnish Cancer Registry

- Estradiol oral / transdermal : no difference in risk for invasive breast cancer
- Mirena / oral progesterone : no difference in risk for invasive breast cancer

BRCA1 & BRCA2 with BSO

- Meta-analysis & systematic review
- No increase in the risk of breast cancer in women with BRCA1 & 2 mutations using HRT following risk reducing BSO

Summary ….

- Estrogen only HRT : little or no change in risk of breast cancer
- Combined HRT : can be associated with increased risk which appears duration dependent & may vary with the type of progesterone
- Risk is low in both medical & statistical terms particularly compared to other modifiable risk factors (eg obesity)
- Should be taken in the context of overall benefits of HRT
- MP / dydrogesterone : likely to be associated with a lower risk (large observational studies)

HRT after breast cancer

- Systemic HRT is contraindicated
- Non-hormonal options : first choice
- No response to non-hormonal treatment : vaginal oestrogen can be considered . Switch to tamoxifen if they are on aromatase inhibitors.
- Ospemifene : contraindicated during active treatment
- Vaginal DHEA : further research needed .

HRT & VTE

- Traditional oral HRT : 2 to 4 fold increase in VTE
- Risk is more with higher dose & Conjugated equine
- Transdermal estradiol : does not increase risk of VTE above that in non-users ; lower risk than oral(observational , meta-analysis , lab studies)
- Risk assessment for VTE prior to HRT
- Routine thrombophilia screen is not necessary

Meta-analysis on VTE risk 2018 Scarabin

- 4 case control + 3 cohort studies : oral / transdermal
- Oral estrogen only / non users : RR 1.48
- Transdermal estradiol / non users : RR 0.97
- Transdermal estradiol + utrogestan : RR0.93
- Nonpregnane derivative (normegestrol) : RR 2.42
- Pregnane derivative (Medroxyprogesterone) : RR 2.77

Women with high risk for VTE

- Transdermal estradiol + micronised progesterone
- Unlikely to significantly increase their intrinsic risk

HRT & Stroke

- HERS study : no increase in incidence of stroke with HRT
- WHI study : 13 yrs cumulative follow up data
- 2015 Cochrane analysis : no significant increase in risk for stroke when started before 10 yrs on menopause or below 60 yrs

Summary …..

- Risk of stroke is age related & overall is low <60 yr
- Oral estradiol : small increase in risk & dose related
- Transdermal : unlikely to increase the risk above baseline risk
- Progesterone : May have an effect on the risk. Use micronised progesterone / dydrogesterone