HRT & Menopause
Where Do We Stand Now?

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Discussion Points

- Discuss Recommendations made by the British Menopause Society and Women's Health Concern 2016 on HRT in Menopausal women
  - Guidance on the changes in clinical practice Post WHI
  - Cardiovascular “timing hypothesis” and “window of opportunity”

- Routes and Regimens

- Life style changes

- Summary
Health Implications

- Late nineteenth century only 30% survived
- Life expectancy has increased to 80yrs
- 10 million postmenopausal women in UK
- Short term effects
- Long term metabolic problems
Vasomotor symptoms

- Occurs in 75%, 1/3rd being severely affected
- Lasts 7.4yrs
- Estrogen replacement is the most effective Rx
- 32 RCT’s on interventions for Vasomotor symptoms have reported beneficial effect
- Cochrane database in 24 placebo controlled study showed clear benefit
- Nice Menopause guideline group undertook meta-analysis and reported on cost effectiveness of 5yrs use of HRT
- Optimum dose & duration depends on severity & response and arbitrary limits to duration should not be made.
HRT for Management of Menopausal Symptoms

Mood

- Observational data shows short term use may improve mood & depressive symptoms
- Cognitive behavioral therapy may be beneficial for low mood & anxiety
- Women with severe depression should be referred for Mental Health assessment
HRT for Management of Menopausal Symptoms
Vulvovaginal Atrophy/Genitourinary Syndrome of the Menopause

- Genitourinary symptoms are described by 50% of MP women
- Estrogen effective in Rx of these symptoms
- Reduce risk of frequency & urgency and reduce UTI
- Low dose vaginal estrogen preparations can be used and as long as is required
- No need to combine progestogen for endometrial protection
- Non hormonal bioadhesive moisturisers and lubricants
HRT for Management of Menopausal Symptoms

Sexual Function

- Sexual desire & Libido is improved by systemic estrogen
- Topical estrogen improves dyspareunia
- Systemic testosterone has shown to significantly improve sexual function, desire & orgasm
HRT for Management of Menopausal Symptoms Musculoskeletal Effects

Observational studies have shown

- Estrogen therapy has protective effect against connective tissue loss and may reverse this process in menopausal women receiving HRT
Long-term effects OF HRT Osteoporosis

- Life Style Modification
  - Balanced Diet
  - Adequate calcium & Vitamin D intake
  - Exercise
  - Cessation of smoking
  - Avoidance of excessive alcohol
  - Recommended daily intake of Calcium is 1000 mg
  - Vitamin D is 1000 iu/D
Long term Effect of HRT 1
Osteoporosis

- Assessment should be carried out to evaluate an individual woman's risk for developing Osteoporosis
- Bone mineral density is not cost effective & should be on a selective basis
- Fracture Risk assessment by FRAX tool (WHO) to determine the need for Rx with bone preserving agents.
- HRT is effective in preserving bone density in both Hip & Spines well as reducing risk in osteoporosis related fractures
Long term Effect of HRT 2
Osteoporosis

- HRT should be considered as 1st line therapy for prevention & Rx of osteoporosis in POI & menopause women before 60yrs

- Initiating HRT solely for osteoporosis prevention is not recommended

- Osteoprotective is dose & duration dependant and declines on cessation

- Biphosphonates preserve bone density but theoretical concern of over suppression of bone turnover may result in brittle skeleton
Cardiovascular Disease

- WHI early results suggested increased risk of CVD
- WHI Long term data-2013 No detrimental effect with combined E & P regardless of the age

Recent studies looked at HRT initiation before age of 60 with an aim for primary prevention of CVD

- RCT -Danish Osteoporosis Trial-Reduced incidence of CHD by 50% & reduced overall mortality if commenced within 10 years of the MP
- KEEPS RCT; Neutral impact on CV risk markers Coronary calcium scores, intima media thickness, no effect on BP, lipids & IR
Cardiovascular Disease

- **ELITE study** (Early vs Late Intervention Trial, Hodis et al 2016)
  - Estrogen Rx-with or without Progesterone showed significant lower progression of atherosclerosis in the early group but not in late group

- **Mikkola et al 2015 Observational study from Finnish National Registry**
  - 489,105 women using HRT between 1994-2009
  - Risk of CHD related deaths was reduced from 18-54%
  - All cause mortality reduced from 12-38%
  - Women on any regimen who took HRT for 10yrs or more had 19 fewer CHD related death/1000 women

- **Cochrane DB Review 2015- Effects of HRT in context of prevention**
  - HRT within 10yrs of MP- Lower mortality & CHD (RR 0.7; CI 0.52-0.95)
  - Neutral effect was noted if HRT started >10years from MP
Cognition

- Cochrane DB - Observational data
  - If started early in MP possible reduction in Long-term risk of Alzheimer’s disease and all cause dementia

- WHI - No significant improvement or worsening
  - but if started in the older group 65-79 increase in risk of dementia, but not in the Estrogen only arm

- KEEPS Cognitive & Affective Study also showed no difference
Cancer
Breast

- MWS raised concerns over long term safety
- WHI:
  - E2 & P - A small increase after 5yrs in the intervention phase of 1 extra case/1000 per year
  - E2 only arm a small decrease in Breast CA but neutral after 5 years
  - No difference in the cancer deaths in HRT arm
  - No difference in all cause mortality
  - BMI>35 significantly increased risk of invasive breast CA (HR 1.58 CI 1.45-1.79)
Fornier et al 2014
- Micronised progesterone or dydrogesterone not associated with increased Breast cancer risk in short term
- Long term risk slightly increased but non significant on discontinuing
- Other progestogens had slightly increased risks

- Finnish Cancer registry
  - No increase risks with Oral vs Transdermal estrogens
  - Similar risks Oral progestogens vs Levonorgestrel IUS
Cancer Breast

• Jones et al 2016 (39,183 women of whom 775 developed Breast CA)
  • E2 only HRT no increase
  • E2 & P combination-increase significantly and more with longer duration
  • Reduces after stopping
Ovarian Cancer

- Observational data have suggested increased risk
- WHI on RCT which studied this and no increase
- Danish National Cancer Registry a small but significant increase after 8 yrs
- Recent meta-analysis of 52 epidemiological studies significantly increased (1.43;95%CI:1.31-1.56) 1 extra case/1000, 1 extra death/1700
Endometrial Cancer

- Unopposed E2 therapy increases risk but largely avoided by combined HRT
- Long term sequential combined HRT >5yrs may be associated with slight increase
- Continuing combined regimens - Significantly reduced risk
Cervical Cancer

- No association between HRT and Cervical cancer
- WHI study - No significant increase
Colorectal Cancer

- Publish data suggests reduced risk oral combined HRT
- WHI trial reduced in the combined E2 & Progestogen arm, but neutral effect on the E2 only
- No data on the Transdermal HRT and risk of colorectal CA
HRT after Cancer Breast

- Inconclusive on Risk of recurrence
  - Stockholm trial showed no increase and HABITS trial showed an increase

- Based on current evidence systemic HRT should be considered contraindicated

- Non hormonal medications
HRT after Cancer
Endometrial

- Studies have either shown no increase or reduced recurrence rate, the longer the disease free interval
- Mainly early stage disease
- Local Endometrial sarcomas are Estrogen sensitive and is contraindicated
HRT after Ovarian Cancer

- Studies have shown no difference in survival rates or an improvement in survival rates in epithelial ovarian CA
- No adverse effects with germ cell tumours
- No data on granulosa cell tumours, but should be avoided
HRT after Cervical & Vulval Cancer

- Not contraindicated
Venous Thromboembolism

- Risk assessed & Counselling
- Routine thrombophilia screening not required but consider if personal or FH
- Oral E2 increases VTE risk 2-4 fold, highest being in the 1st yr of use
- Personal Hx or FH of DVT, Obesity, >60years, Surgery or hospitalisation
Venous Thromboembolism 2

- Transdermal HRT unlikely to increase risk

- Affected by type of progesterone
  - Increased risk with Norpregnane derivatives & MPA
  - Micronised progesterone & pregnane derivatives such as dydrogesterone have lower risk than other progestogens

- Increased BMI women advised Transdermal HRT as unlikely to increase risk

- Consider referral to haematologist if high risk woman
Stroke

- HERS (Heart & Estrogen Replacement Study)
  - No increased incidence

- WHI- 13 year cumulative FU increased risk for entire group but not in woman 50-59yrs

- Cochrane analysis No significant increase if commenced before 60 or within 10yrs of MP

- Current recommendations is not to be used for Primary or secondary prevention
Stoke 2

- Evidence Transdermal is unlikely to increase risks above that of non-users
- Lower risk of Transdermal vs Oral
- Canonino et Al 2016
  - Progesterone, pregnanes & nortestosterone, no association
  - Increased risk with Pregnanes
POI

- 1% under 30, 0.1% under 30 and 0.01% under 20
- HRT is strongly recommended
  - Maintain Sexual function
  - Minimise risk of CVD, Osteoporosis and cognitive impairment
- HRT Should continue until natural age of MP and then individualise
The Seven Dwarves of Menopause

Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful & Psycho
Routes & Regimens

- Transdermal, Gels & Patches, Subcutaneous
  - Do not alter coagulation cascade
  - Unlikely to increase VTE
  - Lower risk than oral

- Progestogens is required for non hysterectomised women
  - 12-14 days in women if still bleeding or <1yr MP
  - Continuous if >1 year
Routes & regimens

- Continuous combined low grade progestogenic effects
- Ultra low dose but may cause bleeding problems
- Unregulated compounded Bioidentical hormones not recommended as lack of safety data
- Regulated non-compounded body-identical estradiol, progesterone & testosterone produce from plant extracts
• Mirena IUS adequate protection now allowed 5yrs in UK

• Cochrane DB reviews suggests
  • minimum 0f 0.1mg NET, 100mg Micronised progesterone daily orally
  • 1mg NET 10 days if sequential HRT or 200mg for 12 days if sequential
  • Vaginal micronised progesterone 10/7 per month 45mg/10 (4%) or 100mg every other day for 3-5yrs
Routes & Regimens 4

- Vaginal estrogenic creams, rings, tablets, pessaries with symptoms of Urogenital atrophy
- Indefinite usage is sometimes required, progestogenic cover is not required
- Can be used in conjunction with oral/systemic HRT
- Off-label use of vaginal estrogens may be considered in women with Breast CA, in conjunction with MP specialist
Sexual Function/Androgens

- Testosterone implants & Patches have been withdrawn for commercial & not safety reasons
- Tibolone has weak Androgenic effect
- Testosterone gels 1 sachet use quarter on alternate days or 0.5 to 1ml/day
- Some studies have shown benefit on skeleton, cognition & well being of vagina
Life Style

- Optimisation of diet
- Advice on bone, calcium and Vit D intake
- Exercise
- Smoking cessation
- Avoidance of excess alcohol
Alternatives to HRT

- Clonidine
- SSRIs
- SNRI
- Antiepileptic drug
- Black cohosh
- St John worts
- Phytoestrogens: some benefits for symptom relief, 60% reduction but as yet no hard data on major outcome measures, CHD, Fractures or long term endometrial safety
Key Points 1

- All women should be able to access advice on how to optimise menopause transition
- Holistic & individualised approach re lifestyle
- Decision to take HRT should then be made by each woman after given sufficient information
- HRT Dosage, regimen & duration should be individualised and annual evaluation should be performed
Key Points 2

- Transdermal estradiol
  - unlikely to increase risk of DVT or CVA above that in non users
  - lower risk than Oral
  - should be 1\textsuperscript{st} choice in women with Risk factors
- Micronised progesterone & dydrogesterone may be associated with lower risk of Breast CA, VT
- Arbitrary limits of duration of HRT should not be set, if symptoms persist, benefits outweigh risks
- HRT before 60 has favourable Benefit/Risk profile
Key Points 3

- HRT before 60 or within 10yrs of MP likely to be associated with reduction in CHD & CV mortality
- If HRT over 60, start with lower doses & transdermal
- POI women encourage to use HRT at least until MP age
- HRT & COCP should be both suitable for HRT in POI
- HRT more favourable improvement in bone density & CV markers