Menopause and HRT update

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Scale of the problem

- Global life expectancy for women is 74 years
- Menopausal symptoms affect 70-80% of all women
- 25% describe their symptoms as severe
- Average duration of symptoms is 7 years
- 79% experience vasomotor symptoms
- 22% unexpected sleeping problems
- 20% difficulty with memory and concentration
- 18% unexpected joint aches
- Home life affected in 50%; social life in 36%

(BMS 2016 National Survey results)

Management of menopause

- All women should be able to access advice
- Holistic approach
- HRT most commonly used and most effective intervention
- Decision should be individualized and take into consideration several factors

HRT benefits

Vasomotor symptoms

- HRT is the most effective treatment
- Persists upto 15 years in 20% of women
- Median duration of symptoms is 7 years; starts premenopause
- Oral and transdermal estrogen effective but transdermal more effective and cost effective as symptom severity increases.

Mood

- Short term HRT
- CBT may be helpful
- Micronised progesterone better
- No response/severe depression, psychiatric evaluation may be required

Sexual dysfunction

- Systemic HRT
- Systemic testosterone
- Low FAI not required for diagnosis
- Baseline FAI and at regular intervals.

Vulvovaginal atrophy

- 50% of postmen women
- Topical vaginal estrogens
- For as long as required
- Endometrial protection not required
- Intravaginal DHEA (Intrarosa) .5% daily in dose of 6.5mg daily for 12 weeks)
- Ospemifene 60mg a day

Musculoskeletal effects

- Arthralgia esp small joints is a menopausal symptom
- HRT improves joint ache (WHI study)
- Estrogen deficiency has negative effect on connective tissue metabolism
- First line: Lifestyle modifications
- Sarcopenia :Progressive resistance therapy 2-3 times per week (Cochrane review)
- HRT has no effect on muscle mass (Meta analysis)

Osteoporosis

- 1 in 2 women will sustain a fracture >50
- 2.8% lifetime risk of death related to hip fracture (International Osteo foundation report)
- Significant reduction in risk of any fracture in women on current HRT
- Balanced diet, Adequate Vit D and calcium, exercise, smoking cessation, avoiding excessive alcohol intake
- First line for prevention and treatment of osteroporosis in POI and women <60 years especially those with menopausal symptoms.
- Dose and duration related; effect declines after discontinuation

Cardiovascular disease risk

- Estrogen replacement initiated within 10 years of menopause (the cardiovascular window of opportunity) -Cochrane 2015, prescribed alone or in combination.
- HRT initiated after 10 years: NO increase (Cochrane data analysis and WHI long term follow up study)
- Within 1 year of HRT use (all types), statistically significant reduction coronary heart disease rates
- Likewise reduction with stroke and all cause mortality. Stroke risk reduction 18 to 29%; all cause mortality 12-38% from 1 to 10 years of use

Cognition

- Forgetfulness, difficulty concentrating and brain fog common in menopause
- HRT in early menopause
- HRT unlikely to increase risk of dementia or have detrimental effect on cognitive function in women on HRT before the age of 60

HRT Risks

Breast cancer

Fear of breast cancer is the sole reason for refusing/denying HRT

- HRT use up to 5 years in low risk and high risk
- Count years of exposure from 50
- HRT does not increase risk in Obese women
- Duration dependent risk
- Risk higher with continuous combined HRT compared to sequential HRT
- Absolute risk is low (10 cases/1000 women with 14 years use between ages of 50-59). Balance against significantly LOW risk for endometrial cancer.

(2019 CGHFBC and 2020 Long term follow up of placebo controlled RCT (WHI))

CGHFBC meta analysis results

Type of HRT	Duration of use from age of 50	EXTRA breast cancer cases (developing between 50 to 69 years of age, over 20 years	Background risk
Cont Comb HRT	5 years	1 extra case /50 women	4/50
Cyclical HRT	5 years	1/70 women	4/70
Estrogen only HRT	5 years	1/200	13/200
Cont Com HRT	10 years	2/50	
Cyclical HRT	10 years	2/70	
Estrogen only HRT	10 years	2/200	

CGHFBC meta analysis

- 40% data from MWS
- Data from WHI not included
- French E3N data excluded (pts on mic progesterone)
- When counselling women:

    WHI RCT study which showed increeased risk but not increased mortality

    E3N observational studies showed no increase in risk breast of cancer in users of Micronised progesterone and Dydrogesterone upto 5 years.

    Risk elevated 10 years after discontinuation

    No dosage effect of estrogen on risk; but duration related.
- Modifying effect for obesity:
- Lean and obese women had similar increase in risk of breast cancer with addition of progestogen

Breast cancer and lifestyle risk factors….

Risk factor	Excess risk per 1000 women over 5 years aged 50-59
Overweight	+4
Obesity	+10
Alcohol	+8 (4-6 units/day) ; +11 (>6units)

Women with increased breast cancer risk

- Non harmonal options always first
- HRT in BRCA1 and 2
- Personal history of breast cancer
- Severe refractory symptoms in breast cancer patients
- Tamoxifen use: Avoid Paroxetine and Fluoxetine
- Vaginal estrogens safe after counselling
- Vaginal HRT not with Aromatase inhibitors; switch to Tamoxifen
- Ospemifene and DHEA

Other cancers

- Endometrial cancer risk:
  - Lower with Continous comnbined HRT
  - Cyclic HRT >5 years causes small increase in risk of endo cancer
  - Change to Continuous regime after 5 years of use or > 55.
- Ovarian cancer: Slight increase in endometrioid and serous epithelial cancers but risk is small.
- Cervical cancer: No association between HRT and Cx cancer
- Colorectal cancer: reduced risk with combined oral HRT. No data on transdermal

VTE

- VTE risk increased in oral HRT takers compared with women not on HRT
- Transdermal estrogen DOES NOT increase risk of VTE above non users
- Micronised Progesterone and dydrogesterone unlikely to increase risk of VTE compared to other progestogens

Stroke

- Oral Estradiol – slight increase in risk
- Progestogens determine risk of stroke.
- Transdermal estrogen
- Women >60 and those with risk factors

Androgens in menopause

- Decline starts 30-40 years and upto 80 years
- In reproductive years
- After menopause
- Female sexual arousal disorder Vs Hypoactive Female sexual desire disorder

Androgens in menopause

- Testosterone therapy benefits increases sexual desire and satisfaction.
- Safety
- Side effects
- Free androgen index
- Baseline FAI
- FAI <1% supports use of androgens. Repeat in 3 months. Maintain <4.5%

Preparations

- Tostran 2% gel (60g pump). 1 pump (.5g) delivers 10mg. Alternate days. Will last 6 months
- Testogel. 5g sachet has 50 mg. Has to last 10 days. So, 1/10 sachet every day

Wont take HRT; Cant take HRT; asked to not take HRT beyond 50

- Life style modification
- Clonidine for hot flushes
- Paroxetine, Fluoxetine, Citalopram, venlafaxine, gabapentin and pregabalin and Clonidine tested in placebo controlled trials shown to be effective
- Paroxetine Best evidence on efficacy
- Venlafaxine if Tamoxifen use
- Isoflavones and soya products
- Black cohosh and St Johns’s wort

Unscheduled bleed on HRT

- Ignore first 6 months
- If persistent, TVS +/- End biopsy
- Irregular bleed on Cont Combined HRT
  - Increase Uterogestan to 200mg daily
  - If Mirena or cont combined preparation
  - Ongoing unscheduled bleed
- Irregular bleed on Cyclical HRT
  - 300 mg micronized Prog for 12 days instead of 200mg
  - 200 mg for 21/28 days
  - Mirena

Unscheduled bleed on HRT

- Switching to combined HRT; switch back for another year
- TVS: ET </= 4mm for Cont combined HRT
- TVS: ET upto 6 mm acceptable with Cyclical
- Endometrial biopsy
- Stop HRT
- Hysteroscopy for recurrent bleeds

Bioidentical HRT
rBHRT Vs cBHRT

- ‘Bioidentical hormones’ are precise duplicates of hormones
- cBHRT Vs rBHRT
- ‘Body identical HRT’ to distinguish regulated hormone therapy from unregulated compounded varieties.
- **cBHRT formulation types:**

  Biest (E2 plus E3 in a 20/80 ratio)

  Triest (E1 plus E2 plus E3 in a 10/10/80

Issues with compounded BHRT

- No evaluation by the MHRA as conventional pharmaceutical products.
- The absence of evidence to support the practice of combining E1 and E3 with E2.
- Dosage of estrogen higher or lower than it needs to be
- Is the dosage of progesterone sufficient?
- The absence of warnings on the products regarding potential risks and side effects
- Transdermal progesterone in cream or gel preparations with variable absorption and fluctuating tissue availability and as a result may not provide sufficient endometrial protection.

HRT practical prescribing

Side effects:

- Fluid retention, breast tenderness and headaches are side effects of both oestrogen and progesterone and cannot be distinguished in continuous combined.
- Mood and PMT changes are due to progesterone. Nausea and bloating are due to oestrogen.
- Side effects decrease in 3 to 4 months.

HRT practical prescribing

- HRT not contraindicated in hypertensive patients.

- Vagifem 10 micrograms twice a week is maintenance dose. Younger patients need upto 5 X 10 microgram pessaries per week
- Mirena now licensed for 5 years for HRT and acceptable.

- 15% patients given cyclical HRT may not bleed and it just means that the oestrogen has not been primed enough for progesterone to make it bleed and that is ok.

HRT practical prescribing

- In POI, COCP better
- All oral HRT contain lactose.
- If high oral doses not working, check estradiol levels. If level low, try patch or gel.
- In patients with migraine, transdermal better and avoids headaches. Gradually increase dose

HRT practical prescribing

- Uterogestan is 200 mg 12/28 days or 100 mg day 1-25 or simply 100 mg everyday
- Progestogenic side effects in second half of cycle
- In women on long term HRT, check if vagifem required.
- In women > 60 years, change to transdermal as age is risk factor
- In patients starting HRT after a gap and high risk patients start in lowest dose; 50 microgram patch can be cut in half .

Thank you!