HRT-how safe is it now?

Debunking misconceptions and minimising side-effects

Rashna Chenoy MA FRCOG, Oct 2012
Menopause: epidemiology

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<th>Great Britain</th>
<th>Globally</th>
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<td>2009</td>
<td>13million</td>
<td>500million</td>
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<td>2020</td>
<td>25 million</td>
<td>1200million</td>
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Post-menopausal population in 2009 was 18% in UK (expected to double by 2020)
Menopause

- **Average age** = ~51 yrs
- **'Premature'** menopause = ~1% of women <40 yrs
- **'Early'** menopause = 20% of women between 40-45 yrs
- **Life expectancy** in UK, 2012 = 85 yrs
Menopause: treatment

- Hormone replacement therapy (HRT)
- Non-hormonal treatments
HRT

- **If uterus present**: oestrogen + progesterone
- **If uterus absent**: oestrogen alone

Testosterone may be required in some cases
HRT

Routes of Delivery

- Oral
- Patches and gels
- Implants & Injections
- Intravaginal creams, pessaries, rings
- Nasal sprays
Bio-equivalence of available ERTs

- Micronised Oestradiol 2mg
- Conjugated Equine Oestrogens 0.625mg
- Oestradiol valerate 2mg
- Transdermal E2 patch 50 mcg
- Transdermal Estrogel 2 doses (1.5mg)
- Transdermal Sandrena 1mg
Progestogens & Progesterone

- Medroxyprogesterone
- Norgesterol
- Didrogesterone

- Micronised natural progesterone - ‘Utrogestan’
- Drospirenone - ‘Angeliq’
Benefits of HRT

Long-term Benefits

Osteo-protection

- Oestrogen, Tibolone, Raloxifene stop bone loss
- Bone gain is seen in the first 18-24 months only
- Some progestogens also enhance bone gain
- Oestrogen implants give the best results
- Life-long HRT is advised for bone protection
- Smokers & thin women respond poorly
Benefits of HRT

Long-term Benefits

**Cardio-protection**

- **Conflicting data on benefits of HRT**

- **CHD Primary prevention**
  - 40% reduced risk in epidemiological studies
  - No clear evidence to support HRT purely for cardioprotection

- **CHD Secondary prevention**
  - No benefit compared to placebo
  - Survival rates better compared to placebo/no HRT
  - Increased coronary events in first year of treatment
  - Best avoided during an acute CHD event
Benefits of HRT

Long-term Benefits

Cognitive function

- 1 in 10 people develop Alzheimer’s >65yrs

- HRT delays/prevents Alzheimer’s by
  - increasing cerebral blood flow & neuronal function
  - increasing synthesis of neurotransmitters
  - suppressing amyloid deposition
  - other as yet unclear mechanisms

- HRT does not reverse established Alzheimer’s
Contra-indications to HRT

- Active breast cancer or undiagnosed breast lumps
- Undiagnosed vaginal bleeding
- Active or recent endometrial cancer
- Active or recent TED (phlebitis and varicose veins are not CIs)
- Uncontrolled hypertension
- Oestrogen-induced cholestasis
- ? Malignant melanomas
Misconceptions about HRT

Perceived contraindications to HRT

- Hypertension & Heart Valve disease
- Hyperlipidemia, DM, Thyroid disease
- Liver & Gall bladder disease
- Migraine, Epilepsy, Parkinsonism
- Crohn’s, Rheumatoid arthritis, SLE
- Asthma, Otosclerosis, Malignant melanoma
- Renal failure
Misconceptions about HRT

- Weight gain
- Importance of regular withdrawal bleeds
- High risk of Breast & Endometrial cancers
- High risk of DVT
- Exacerbation of fibroids, endometriosis, CIN
- Large number of medical contraindications
Misconceptions about HRT

Weight gain

- 22 studies have looked at the effect of combined & unopposed HRT on BMI

- No increase in weight was found above that which normally occurs at the menopause
Misconceptions about HRT

Regular withdrawal bleeds

- Not necessary
- Investigate irregular bleeding >3 months duration
- Progestogens taken continuously for 10-12 days
- Type & route of progestogens affect duration
- Regulate bleeding by increasing ratio of Progesterone:Oestrogen
Misconceptions about HRT

Breast cancer

- Per year of HRT use the risk increases by <0.1% (<1/1000 women per year of use)
- Combined HRT more risky than oestrogen alone
- Tibolone, SERMs, Mirena IUS + Transdermal Oestrogen, and Long-cycle natural transdermal Oestrogen & natural Progesterone - safer
- Good survival rates in women on HRT
HRT & Breast cancer risk

- HRT confers same or less risk than
  - Delayed natural menopause >55 yrs
  - Nulliparity
  - High BMI >35
  - Alcohol consumption >2u/day
  - Delayed first child birth >35 yrs
  - Family history of breast cancer

- HRT regimen & duration of use influence risk
HRT & Breast cancer risk

- **WHI study**
  - Risk of breast cancer 23% less in ERT-only group vs placebo
  - 3-7 cases per 1000, directly due to combined HRT use >5yrs

- **MW study**
  - All regimens increased risk (ERT, cHRT, Tibolone)
  - Greatest risk with combined HRT, cyclical or continuous
HRT & Breast cancer survivors

- **HABITS study**
  - increased risk of recurrence, 2004

- **Stockholm study**
  - no increased risk of recurrence, 2004

- **LIBERATE study**
  - Tibolone vs Placebo = 16.7% vs 11.4% recurrence
    
    *Lancet, Feb 2009*
HRT... for breast cancer survivors, when....

- Breast cancer was treated pre-menopausally with uneventful resumption of periods
- Non-hormonal methods have failed to control distressing symptoms
- Successfully treated women are at increased risk of osteoporosis and cardiovascular disease
- Fully informed women insist on HRT to improve negative impact on QOL & sexual function
HRT... for breast cancer survivors

Safe assumptions?

- HRT is safe in ER-ve tumours
- HRT is safe in ER+ve tumours if concurrently on Tamoxifen
- Mirena IUS is safe
- Natural progesterone safer than synthetic progestogens
- Low-dose Vaginal oestrogens are safe
HRT and other Breast concerns

- **Family History of Breast cancer**
  - No additive effect of HRT with family history
  - Risk needs to be individualised
  - Only 10% of breast cancers are due to BRCA 1&2 mutations
  - In mutation carriers -
    - prophylactic oophorectomy + add-back HRT
      - (IUS + TTS Estradiol, does not negate advantage of oophorectomy)

- **Benign Breast disease**
  - HRT increases incidence of benign breast cysts
  - HRT does not increase breast cancer risk in benign disease
  - Ductal and lobular atypical hyperplasia = 5-fold risk of cancer
Misconceptions about HRT

Venous Thrombo-embolism

- Relative risk increases by 2-4
- 2 extra cases / 10,000 users per year
- Usually occurs in first year of use
- Not contraindicated if previous provoked DVT
- May require prior thrombophilia screening
Misconceptions about HRT

Exacerbation of fibroids, endometriosis, CIN

- **Fibroids** – may grow but evidence is poor, c-c HRT preferred
- **Endometriosis** – may be reactivated, c-c HRT best
- **CIN** – no effect
HRT and Fibroids

- HRT can cause fibroids to become enlarged resulting in heavy and painful withdrawal bleeds

- Treatment option:
  - *Mirena IUS* + *Transdermal Estradiol*
HRT and Endometriosis

- ERT can cause reactivation of endometriosis with risk of endometrioid carcinoma in a small number of cases

- Treatment options:
  - Mirena IUS + Transdermal estradiol
  - Continuous combined HRT / Tibolone
  - Progestogens only
HRT and Gynaecological cancers

- **CIN and Cervical cancer**
  No contraindications to using HRT

- **Ovarian Cancer**
  No contraindications for use except in endometrioid ovarian cancer where continuous combined HRT is advisable

- **Endometrial cancer**
  No observed risk of recurrence with ERT in treated cases
  No advantage to using combined HRT after early stage endometrial cancers

- **Vulval cancers**
  No contraindications to using HRT, except in malignant melanomas where risk is controversial
HRT and Cardiovascular Disease

- Menopause is a risk factor for cardiovascular disease
- HRT is beneficial for prevention & treatment of CHD & CVD
- HRT has a beneficial additive effect with Statins, Fibrates and Aspirin
HRT and Cardiovascular Disease

• Hypertension is reduced by HRT—especially ‘Angeliq’

• Dyslipidemia – route of delivery & progestogen dependent
  • **Oral HRT**: drop LDLs & Lipoprotein a, raise HDLs & Triglycerides
  • **TTS HRT**: drop LDLs, Lipoprotein a, & Triglycerides, but HDL neutral
  • **Tibolone**: drops HDLs, LDLs, Triglycerides and Lipoprotein a
  • **Oral androgenic HRT**: drop LDLs, Lipo-a, & Triglycerides, but HDL neutral
HRT and Thromboembolic Disease

• DVT / PE affect approx 5/10,000 women on HRT and most commonly occur in the first year of use

• Hx of unprovoked VTE is a relative contraindication
  • Check for thrombophilia, underlying malignancy & collagen disorders
  • Transdermal route preferable, +/- low-dose Warfarin
  • High dose Progestogens & Raloxifene increase risk - best avoided
  • Tibolone - no data
HRT and Thromboembolic Disease

- **Women on long-term anticoagulation**
  - HRT, Progestagens, SERMs can be used safely with anticoagulation

- **Peri-operative VTE risk**
  - continue HRT and use adequate VTE prophylaxis
HRT and Diabetes

- HRT reduces incidence of Type 2 Diabetes
- Oral estradiol enhances Insulin action and improves glycaemic control
- Avoid Conjugated equine oestrogens and androgenic progestagens due to their insulin resistance effect
HRT and Thyroid disease

- Hyperthyroidism is associated with increased risk of osteoporosis. HRT is not a contraindication.

- ERT increases production of TBG, therefore dose of thyroxine replacement may have to be increased in women being treated for hypothyroidism.
HRT and Migraines

- HRT may reduce migraines caused by fluctuations in oestradiol level at the menopause
- Transdermal route is preferred to ensure steady serum levels
- Avoid sequential HRT to prevent progestogen-induced cyclical migraines – use continuous combined patches or Mirena IUS
- No reported interactions between HRT and migraine medications
HRT and Epilepsy

- Anticonvulsants pre-dispose to osteoporosis due to adverse effects on calcium and Vitamin D metabolism

- Transdermal route is preferred as hepatic enzyme induction by anti-convulsants may require higher doses if oral HRT is used
HRT & Long-term corticosteroid therapy

- Collagen disorders, Inflammatory bowel disease, Asthma, COPD, Chronic active hepatitis

- Corticosteroid-induced osteoporosis is a major concern

- HRT does not exacerbate rheumatoid arthritis and can be used as adjunct to anti-rheumatic therapy

- HRT is not contraindicated in SLE but there is an increased risk of VTE and may require low-dose anticoagulation in addition to TTS
HRT and Liver disorders

- Transdermal HRT is preferred in gall bladder & chronic liver disease
- Avoid HRT in acute conditions
- Primary biliary cirrhosis is not a contraindication for HRT
HRT and Rarer conditions

- **Otosclerosis**
  - no data to show that HRT exacerbates the condition

- **Immunosuppressive therapies** - eg after transplantation
  - no reported interaction between tacrolimus and cyclosporin
  - transdermal route preferred

- **Renal failure**
  - no data on use of HRT
HRT and the older woman

- HRT can be started in women after age 65 with good results and lower side-effect profile.
- Ultra low-dose patches (14 µg/day) and oral HRT (Premique 0.3mg/day) available.
- Mini-Mirena (10mcg/day) - awaited.
- ‘Critical window’ benefit for dementia may be lost.
Summary

- Individualised risk assessments
- Holistic approach
- Safest route and formulation of HRT
- Shortest effective duration of treatment
HRT protocols

If confirmation of menopause is required (women <45 yrs with symptoms suggestive of the menopause; following hysterectomy with ovarian conservation; women using COCPs), FSH and oestradiol levels should be measured within the first 5 days of the menstrual cycle. In about a third of perimenopausal women on the combined oral contraceptive pill, vasomotor symptoms occur during the pill-free week. Diagnosis of the menopause is possible by checking the FSH level on the 7th day of the pill-free interval. If the FSH level is >30 U/L it should be repeated after 3 months and if the level is again >30 U/L, menopause is considered to be established.

Indications for HRT:
- Treatment of vasomotor symptoms
- Treatment of urogenital symptoms and sexual dysfunction
- Treatment and prevention of osteoporosis

Other benefits:
- Prevention of coronary heart disease
- Reduction of cerebrovascular accidents
- Delay the onset and progression of Alzheimer’s disease
- Prevention and treatment of mood swings and depression
- Protection against colon cancer
- Prevention of dental caries

Contra-indications to HRT:
- Active breast cancer or undiagnosed breast lumps
- Undiagnosed vaginal bleeding
- Active or recent endometrial cancer
- Active or recent TED (phlebitis and varicose veins are not contraindications)
- Uncontrolled hypertension
- Oestrogen-induced cholestasis
- ? Malignant melanomas
Which Route?

Depends on symptoms and side-effects to be avoided.

In general -

**Oral**: for vasomotor symptoms, reduction of low density cholesterol, patch allergy or irritation, eczema/psoriasis, hot climates

**Transdermal / Nasal**: for smokers, triglyceridemia, nausea on oral preparations, family or past history of TED, obesity, gall bladder disease or stones, hypertensives, diabetics, epileptics or those on hepatic-enzyme inducing medications

**Vaginal**: for urogenital symptoms - vaginal dryness, dyspareunia, dysuria & urinary urgency (but not stress incontinence)

Which Regime?

**Women who have had a hysterectomy**: Unopposed oestrogen
oral tablets /transdermally/aerosol spray/implant/vaginal pessaries,ring,cream

**Women who have a uterus or who have had an endometrial ablation**: Continuous oestrogen combined with with sequential (12 days every month/14 days every 3 months) or continuous progestogen /SERMs

**Women who cannot tolerate oestrogen with or without an uterus**: Progestogens

**Women who wish to avoid HRT**: Phytoestrogens / Herbal treatments / Homeopathy/ Non-hormonal treatments
Unopposed Oestrogen: aim to start with oestrogen dosage equivalent to 1mg of oral oestradiol (CEE = 0.625mg or E2 transdermal = 50 µg) daily and reduce down to the lost required dose after 6-12 months.

i) Tablets
- Elleste Solo - E2, 1mg; od/ad
- Premarin - CEE, 0.625mg; od/ad

ii) Patches
- Evorel - E2, 25, 37.5, 50, 75, 100 µg; twice weekly
- Elleste - E2, 40, 80 µg; twice weekly
- ProgynovaTS - E2, 50, 100 µg; once weekly
- Femseven- E2, 50, 100 µg; once weekly

iii) Gels
- Sandrena - E2, 1 or 2mg; od/ad
- Oestrogel - E2, 1-2 mtd doses; od/ad

iv) Vaginal
- Orthogynest - E3 0.01% - 1 applicatorful or 1 pessary 500 µg; od / ad x 3/6wks, and then once every 7-10 days x 6 months
- Ovestin - E3 0.1% - 1 applicatorful or 1 pessary 500 µg; od / ad x 3/6wks, and then once every 7-10 days x 6 months
- Premarin - CEE, 0.625mg -1 applicatorful; od / ad x 3/6wks, and then once every 7-10 days x 6 months - not advised for longterm use as greater systemic absorption compared to other vaginal oestrogens
- Vagifem - E2, 25 µg; od x 2wks then one every 3 days x 2wks, then once every 7-10 days x 6months - best for longterm use, as least likely to have systemic side-effects due to minimal absorption.

Sequential Combined HRT:

Oral:

i) Elleste Duet - E2 + NET - od/ad

ii) Femoston 2/10, 2/20 - E2 + didrogesterone -od/ad

Transdermal:

i) Any of the above E2 only patches/gels + Dydrogesterone 10mg od x 14 days/NET 1mg od x 14 days every month (or every 3 months in long cycle regimes)
ii) Nuvelle TS sequential combined patches - E2 50 μg daily + Lng x14 days

**Continuous Combined HRT:**

Oral:

i) Elleste duet conti
ii) Femoston conti
iii) Premique low dose -0.3mg for women >60yrs
iv) Tibolone - 2.5mg od/ad (esp if low libido or osteoporosis or mastalgia)
v) Raloxifene -60mg od/ad (not useful for vasomotor s/s )

Transdermal:

i) Evorel conti patches
ii) Oestrogel/Sandrena + Mirena IUS (particularly useful for pms-like symptoms, migraines, obesity, patch irritation)

**Continuous Progestogen-only HRT:** useful for controlling vasomotor symptoms and protection from osteoporosis for women who cannot tolerate oestrogen

i) Norethisterone oral - 5-15mg od
ii) Medroxyprogesterone -5 mg od
iii) Didrogestosterone -10-20mg od

**Testosterone HRT:** for low libido and extreme lethargy

i) Intrinsa patches x2/week
ii) Sustanon injections - 100,250,500 mg at monthly, 3-monthly or 6-monthly intervals
iii) Testosterone pellet - 50 or 100 mg sc at yearly intervals
iv) Tibolone - 2.5mg od/ad
Alternatives to HRT:

i) Soya Isoflavones - 40mg bd/td (Estroven)
ii) Clonidine
iii) Black Cohosh
iv) Red Clover (Novogen’s preparation has been through clinical trials)
v) Sepia
vi) EPO and Omega oils

Side-effects:

i) Nausea, fluid retention, bloating - usually settles in a few weeks; switch to non-oral route. If no improvement, check LFT and gall stones.
ii) BTB - Usually seen on CC - HRT - if does not settle in 3 months, change progestogen to more androgenic type ie Lng or NET, or switch to sequential HRT. Will need investigation if persists after 6 months of commencing HRT or starts after previous normal treatment cycles.
iii) If migraines or headaches start while on HRT, stop treatment and review.
iv) If persistent mastalgia change to more androgenic HRT and try a non-oral route or switch to Tibolone.

Contraception:

i) If menopause attained < 50 – continue contraception for 2 yrs after last period
ii) If menopause attained > 50 – discontinue contraception after 1 year following last period.
iii) If HRT started before cessation of menstruation, ensure x2 FSH readings 3 months apart = >30u/l, then continue contraception for a further 12 months.

Cessation of HRT:

i) Gradually wean off HRT over 2-3 months, substituting with natural, weaker alternatives eg isoflavones, if necessary.
ii) Aim to cease HRT after 5 years of use, if not sooner.