# HRT: What's more recent

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2018

" 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 ".

-Mirror 06/2010

" HRT opened my eyes, and gave me my life back“ Guardian 2015

“HRT will not shorten lives, women told after new research published ” Guardian 2017

“But 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, as shown below. HRT is only responsible for a very small proportion of cancer cases. ” Cancer Research UK.

# Definition

- Cessation of the menstrual cycle due to ovarian failure.
- Median age: 52years.
- Determined in Utero.
- Other factors:
  - IUGR in late gestation.
  - Low weight gain in infancy.
  - Starvation in child hood.
  - Down`s Syndrome.
  - Smokers.

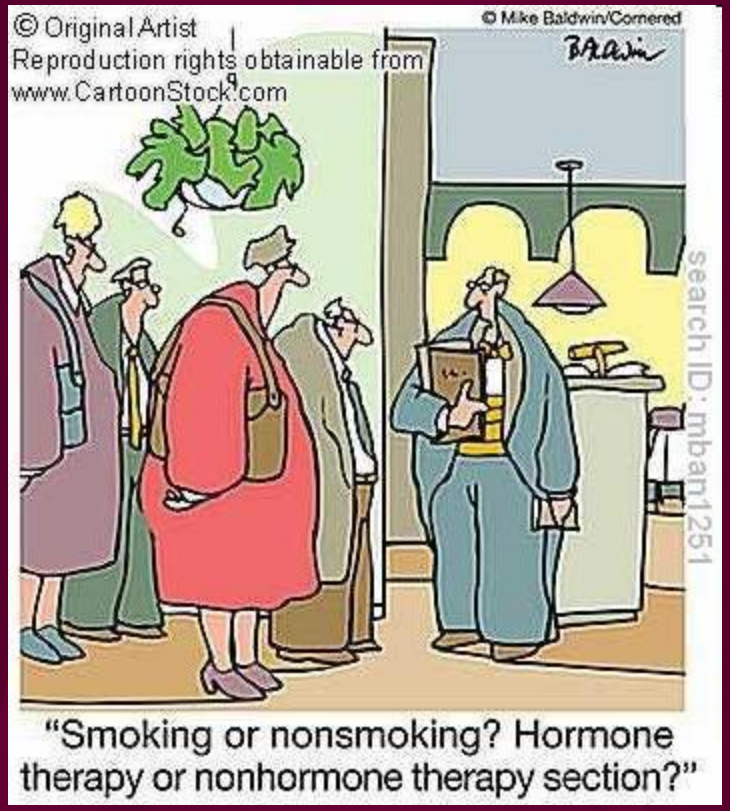
# Terminology to know

- Menopause.
- Perimenopause.
- Premenopause.
- Postmenopause.
- Climacteric.
- Induced menopause.


THE 7 MENOPAUSAL DWARFS
ITCHY
BITCHY
SWEATY
BLOATY
SLEEPY
FORGETFUL
PSYCHO
danc

# Symptoms

- Vasomotor.
  - Hot flushes, night sweats, disturbed sleep patterns, insomnia, irritability, short term memory loss and concentration.
- Sexual dysfunction.
  - Multifactorial.
  - Sexual desire disorders.
  - Sexual arousal disorders.
  - Orgasmic disorders.
  - Sexual pain disorders like Dyspareunia, Vaginismus, genital pain.
- Psychological symptoms.
  - Depressed mood, anxiety, irritability, mood swings, lethargy and lack of energy.
- Urinary symptoms.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search ID: mban1251
"Smoking or nonsmoking? Hormone therapy or nonhormone therapy section?"

# Assessment

- Establish menopause.
- Review symptoms.
- Assess risk for CVD and Osteoporosis.
- Women's view on menopause.
- Patients decision clearly recorded.
- Contraception needs.

# Other history

- Family history of cancers like breast, bowel, ovarian?
- History of Thrombosis?
- Risk factors for stroke and CVD?
- History of migraines?

| weight (kg) | height (m) 1.38 | 1.42 | 1.46 | 1.50 | 1.54 | 1.58 | 1.62 | 1.66 | 1.70 | 1.74 | 1.78 | 1.82 | 1.86 | 1.90 | 1.94 | 1.98 | weight (st/lbs) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 150 | 79 | 74 | 70 | 67 | 63 | 60 | 57 | 54 | 52 | 50 | 47 | 45 | 43 | 42 | 40 | 38 | 23s 8 |
| 148 | 78 | 73 | 69 | 66 | 62 | 59 | 56 | 54 | 51 | 49 | 47 | 45 | 43 | 41 | 39 | 38 | 23s 3 |
| 146 | 77 | 72 | 68 | 65 | 62 | 58 | 56 | 53 | 51 | 48 | 46 | 44 | 42 | 40 | 39 | 37 | 22s 13 |
| 144 | 76 | 71 | 68 | 64 | 61 | 58 | 55 | 52 | 50 | 48 | 45 | 43 | 42 | 40 | 38 | 37 | 22s 9 |
| 142 | 75 | 70 | 67 | 63 | 60 | 57 | 54 | 52 | 49 | 47 | 45 | 43 | 41 | 39 | 38 | 36 | 22s 4 |
| 140 | 74 | 69 | 66 | 62 | 59 | 56 | 53 | 51 | 48 | 46 | 44 | 42 | 40 | 39 | 37 | 36 | 22s |
| 138 | 72 | 68 | 65 | 61 | 58 | 55 | 53 | 50 | 48 | 46 | 44 | 42 | 40 | 38 | 37 | 35 | 21s 10 |
| 136 | 71 | 67 | 64 | 60 | 57 | 54 | 52 | 49 | 47 | 45 | 43 | 41 | 39 | 38 | 36 | 35 | 21s 5 |
| 134 | 70 | 66 | 63 | 60 | 57 | 54 | 51 | 49 | 46 | 44 | 42 | 40 | 39 | 37 | 36 | 34 | 21s 1 |
| 132 | 69 | 65 | 62 | 59 | 56 | 53 | 50 | 48 | 46 | 44 | 42 | 40 | 38 | 37 | 35 | 34 | 20s 10 |
| 130 | 68 | 64 | 61 | 58 | 55 | 52 | 50 | 47 | 45 | 43 | 41 | 39 | 38 | 36 | 35 | 33 | 20s 6 |
| 128 | 67 | 63 | 60 | 57 | 54 | 51 | 49 | 46 | 44 | 42 | 40 | 39 | 37 | 35 | 34 | 33 | 20s 2 |
| 126 | 66 | 62 | 59 | 56 | 53 | 50 | 48 | 46 | 44 | 42 | 40 | 38 | 36 | 35 | 33 | 32 | 19s 12 |
| 124 | 65 | 61 | 58 | 55 | 52 | 50 | 47 | 45 | 43 | 41 | 39 | 37 | 36 | 34 | 33 | 32 | 19s 7 |
| 122 | 64 | 61 | 57 | 54 | 51 | 49 | 46 | 44 | 42 | 40 | 39 | 37 | 35 | 34 | 32 | 31 | 19s 3 |
| 120 | 63 | 60 | 56 | 53 | 51 | 48 | 46 | 44 | 42 | 40 | 38 | 36 | 35 | 33 | 32 | 31 | 18s 13 |
| 118 | 62 | 59 | 55 | 52 | 50 | 47 | 45 | 43 | 41 | 39 | 37 | 36 | 34 | 33 | 31 | 30 | 18s 8 |
| 116 | 61 | 58 | 54 | 52 | 49 | 46 | 44 | 42 | 40 | 38 | 37 | 35 | 34 | 32 | 31 | 30 | 18s 4 |
| 114 | 60 | 57 | 53 | 51 | 48 | 46 | 43 | 41 | 39 | 38 | 36 | 34 | 33 | 32 | 30 | 29 | 17s 13 |
| 112 | 59 | 56 | 53 | 50 | 47 | 45 | 43 | 41 | 39 | 37 | 35 | 34 | 32 | 31 | 30 | 29 | 17s 9 |
| 110 | 58 | 55 | 52 | 49 | 46 | 44 | 42 | 40 | 38 | 36 | 35 | 33 | 32 | 30 | 29 | 28 | 17s 5 |
| 108 | 57 | 54 | 51 | 48 | 46 | 43 | 41 | 39 | 37 | 36 | 34 | 33 | 31 | 30 | 29 | 28 | 17s |
| 106 | 56 | 53 | 50 | 47 | 45 | 42 | 40 | 38 | 37 | 35 | 33 | 32 | 31 | 29 | 28 | 27 | 16s 10 |
| 104 | 55 | 52 | 49 | 46 | 44 | 42 | 40 | 38 | 36 | 34 | 33 | 31 | 30 | 29 | 28 | 27 | 16s 5 |
| 102 | 54 | 51 | 48 | 45 | 43 | 41 | 39 | 37 | 35 | 34 | 32 | 31 | 29 | 28 | 27 | 26 | 16s 1 |
| 100 | 53 | 50 | 47 | 44 | 42 | 40 | 38 | 36 | 35 | 33 | 32 | 30 | 29 | 28 | 27 | 26 | 15s 10 |
| 98 | 51 | 49 | 46 | 44 | 41 | 39 | 37 | 36 | 34 | 32 | 31 | 30 | 28 | 27 | 26 | 25 | 15s 6 |
| 96 | 50 | 48 | 45 | 43 | 40 | 38 | 37 | 35 | 33 | 32 | 30 | 29 | 28 | 27 | 26 | 24 | 15s 2 |
| 94 | 49 | 47 | 44 | 42 | 40 | 38 | 36 | 34 | 33 | 31 | 30 | 28 | 27 | 26 | 25 | 24 | 14s 11 |
| 92 | 48 | 46 | 43 | 41 | 39 | 37 | 35 | 33 | 32 | 30 | 29 | 28 | 27 | 25 | 24 | 23 | 14s 7 |
| 90 | 47 | 45 | 42 | 40 | 38 | 36 | 34 | 33 | 31 | 30 | 28 | 27 | 26 | 25 | 24 | 23 | 14s 2 |
| 88 | 46 | 44 | 41 | 39 | 37 | 35 | 34 | 32 | 30 | 29 | 28 | 27 | 25 | 24 | 23 | 22 | 13s 12 |
| 86 | 45 | 43 | 40 | 38 | 36 | 34 | 33 | 31 | 30 | 28 | 27 | 26 | 25 | 24 | 23 | 22 | 13s 8 |
| 84 | 44 | 42 | 39 | 37 | 35 | 34 | 32 | 30 | 29 | 28 | 27 | 25 | 24 | 23 | 22 | 21 | 13s 3 |
| 82 | 43 | 41 | 38 | 36 | 35 | 33 | 31 | 30 | 28 | 27 | 26 | 25 | 24 | 23 | 22 | 21 | 12s 13 |
| 80 | 42 | 40 | 38 | 36 | 34 | 32 | 30 | 29 | 28 | 26 | 25 | 24 | 23 | 22 | 21 | 20 | 12s 8 |
| 78 | 41 | 39 | 37 | 35 | 33 | 31 | 30 | 28 | 27 | 26 | 25 | 24 | 23 | 22 | 21 | 20 | 12s 4 |
| 76 | 40 | 38 | 36 | 34 | 32 | 30 | 29 | 28 | 26 | 25 | 24 | 23 | 22 | 21 | 20 | 19 | 12s |
| 74 | 39 | 37 | 35 | 33 | 31 | 30 | 28 | 27 | 26 | 24 | 23 | 22 | 21 | 20 | 20 | 19 | 11s 9 |
| 72 | 38 | 36 | 34 | 32 | 30 | 29 | 27 | 26 | 25 | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 11s 5 |
| 70 | 37 | 35 | 33 | 31 | 30 | 28 | 27 | 25 | 24 | 23 | 22 | 21 | 20 | 19 | 19 | 18 | 11s |
| 68 | 36 | 34 | 32 | 30 | 29 | 27 | 26 | 25 | 24 | 22 | 21 | 21 | 20 | 19 | 18 | 17 | 10s 10 |
| 66 | 35 | 33 | 31 | 29 | 28 | 26 | 25 | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 18 | 17 | 10s 6 |
| 64 | 34 | 32 | 30 | 28 | 27 | 26 | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 18 | 17 | 16 | 10s 1 |
| 62 | 33 | 31 | 29 | 28 | 26 | 25 | 24 | 22 | 21 | 20 | 20 | 19 | 18 | 17 | 16 | 16 | 9s 11 |
| 60 | 32 | 30 | 28 | 27 | 25 | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 17 | 17 | 16 | 15 | 9s 6 |
| 58 | 30 | 29 | 27 | 26 | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 18 | 17 | 16 | 15 | 15 | 9s 2 |
| 56 | 29 | 28 | 26 | 25 | 24 | 22 | 21 | 20 | 19 | 18 | 18 | 17 | 16 | 16 | 15 | 14 | 8s 11 |
| 54 | 28 | 27 | 25 | 24 | 23 | 22 | 21 | 20 | 19 | 17 | 17 | 16 | 16 | 15 | 14 | 14 | 8s 7 |
| 52 | 27 | 26 | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 17 | 16 | 16 | 15 | 14 | 14 | 13 | 8s 3 |
| 50 | 26 | 25 | 23 | 22 | 21 | 20 | 19 | 18 | 17 | 17 | 16 | 15 | 14 | 14 | 13 | 13 | 7s 12 |
| 48 | 25 | 24 | 23 | 21 | 20 | 19 | 18 | 17 | 17 | 16 | 15 | 14 | 14 | 13 | 13 | 12 | 7s 8 |
| 46 | 24 | 23 | 22 | 20 | 19 | 18 | 18 | 17 | 16 | 15 | 15 | 14 | 13 | 13 | 12 | 12 | 7s 3 |
| 44 | 23 | 22 | 21 | 20 | 19 | 18 | 17 | 16 | 15 | 15 | 14 | 13 | 13 | 12 | 12 | 11 | 6s 13 |
| 42 | 22 | 21 | 20 | 19 | 18 | 17 | 16 | 15 | 15 | 14 | 13 | 13 | 12 | 12 | 11 | 11 | 6s 9 |
| 40 | 21 | 20 | 19 | 18 | 17 | 16 | 15 | 15 | 14 | 13 | 13 | 12 | 12 | 11 | 10 | 10 | 6s 4 |
| 38 | 20 | 19 | 18 | 17 | 16 | 15 | 14 | 14 | 13 | 13 | 12 | 11 | 11 | 11 | 10 | 10 | 6s |
| 36 | 19 | 18 | 17 | 16 | 15 | 14 | 14 | 13 | 12 | 12 | 11 | 11 | 10 | 10 | 9 | 9 | 5s 9 |
| | 4'6[1/2] | 4'8 | 4'9[1/2] | 4'11 | 5'[1/2] | 5'2 | 5'4 | 5'5[1/2] | 5'7 | 5'8[1/2] | 5'10 | 5'11[1/2] | 6'1 | 6'3 | 6'4[1/2] | 6'6 | |

# Examination

- BMI.
- BP.
- Assessment of breast and pelvis if clinically indicated.
- Encourage screening for both cervical and breast.

# Investigation

- Diagnosis: FSH >30IU/L(D3-5).
- If amenorrhea early 2 samples in 2/52.
- Other hormones have limited value.
- TFH
- Role of catecholamines.
- Role of 5HIAA.
- Role of testosterone.

# Menopause - Diagnosis

- ? Blood tests (FSH / estradiol)
- NICE no lab tests if 45yr + and symptoms
  - Largely unreliable in perimenopause
  - Depend on stage of cycle
  - Normal levels do not exclude perimenopause as cause of symptoms
  - More helpful when no cycle to monitor e.g. post hysterectomy / IUS, or to investigate secondary amenorrhoea
- History and symptoms

# Investigations for assessment of risk

- Mammography.
- Genetic screening.
- Endometrial assessment.
- Bone assessment.

# Management strategies

- Various preparation available:
  - Different strengths.
  - Combinations.
  - Route of administration.
- “Sequential”.
- “Continuous”.
- Routes: oral, transdermal, subcutaneous, intranasal, Vaginal.
- Can start HRT before amenorrhea begins.

# Routes of Therapy

Non oral route of therapy advantage in

- *VTE*
- *Migraine*
- *Malabsorption diseases*
- *Gallstones*
- *Liver disease.*

Less impact on clotting factors

Steady Absorption over 24 hours

Avoids first pass metabolism in liver

- Hysterectomized women: estrogen only.
- Non Hysterectomized:
  - Estrogen and progesterone as sequential preparations.
  - Progesterone added sequentially for 10-14 days every 4weeks.
  - For 14 days every 13 weeks.
  - Combined and continuous.

- Perimenopausal:
  - Monthly or three monthly cyclical regime.
  - Continuous not used due to irregular bleeding.
- Post menopausal:
  - Predominately combined used and accepted due to lack of bleeding.
  - Other preparation may be used.
  - Irregular bleeding can occur in the 1st 4-6months.
  - Does not warrant investigation unless bleeding is heavier, persists beyond 6 months, occurs after significant amenorrhea.

# Follow up

- 1st visit after start of treatment in 3months.
- Then after evaluation every 1year.
- BP monitoring every 6/12.
- Contraception:
  - Continue contraception for 2 years if women <50years.
  - One year contraception if >50 years.


ANY SIDE EFFECTS FROM THE HRT?
WHAT?
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# Expect side effects

- Estrogen related: fluid retention, bloating, breast tenderness. Nausea, headache, leg cramps, dyspepsia.
- Progesterone related: migraines, headache, fluid retention, depression, acne, mood swings.
- Common to both: weight gain, poor cycle control.

- For vasomotor symptoms: use for/upto 5 years.
- For treatment of osteoporosis: life long
  - Delays risk of fracture 5-10 years.
  - Some women wish to change to other medication like raloxifene, biphosphonates.
- Premature menopause: until 52years.
- Local symptoms treated with vaginal estrogen creams.

# Studies on HRT

- Women`s health initiative and Million women study .
- WHI:
  - Risk of breast cancer in estrogen alone group was 23% lower than placebo group.
  - In combined HRT group increase in risk emerged after 3 years of randomisation.
- 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.

# Benefits

- Vasomotor symptoms.
- Urogenital symptoms.
- Osteoporosis.
- Colorectal cancer.

# Risks/Uncertainties

- Risks
  - Breast cancer
  - Venous thrombo embolism
  - Endometrial cancer
  - Gall bladder disease.
- Uncertainties
  - Coronary heart disease
  - Stroke
  - Dementia

# Other options

- Hot flushes
  - Progestogens, clonidine, SSRI, Gabapentin, propranolol.
- Vaginal atrophy
  - Lubricants, moisturizers.
- Osteoporosis:
  - Bisphosphonates, Alendronate, SERMs like raloxifene, Strontium, para thyroid harmone, calcitonin.
- Others:
    - Clonidine
    - SSRI's / Venlafaxine NICE do not use SSRIs/SNRIs as first line for women in menopause
    - Gabapentin

# Do not forget

- Pytoestrogens
- Herbal products.
- Homeopathy.
- Acupuncture.
- Reflexology.

# Risk factors for osteoporosis

- Family history.
- Low BMI.
- Early menopause(<45years).
- Cigars smoking.
- Alcohol abuse.
- Sedentary life.
- Steroid intake.
- Malabsorption syndrome.
- Hyperthyroid.
- Hypogonadism.

# When to treat

- Be aware of indications for DEXA.
- Assess **risk of fracture** using FRAX and NOGG, rather than treating BMD alone.
- Exclude secondary causes.
- Fracture in postmenopausal women aged >75, can be treated without need for DEXA
- Women with prior fracture have 86% increased risk further fracture.
- Intervention essential to prevent further fracture.

# Treatment options

- Bisphosphonates (consider drug holiday)
- HRT – NOS recommend 1st line in women <age 60 with no c/I to HRT
- Strontium
- Raloxifene
- Denosumab
- Teriparetide
- All should have annual review.

# Calcium and Vitamin D

- Check levels in:
- all with confirmed osteoporosis or fracture at baseline
- if on treatment for osteoporosis and new fracture
- malabsorption
- Vitamin D deficiency common
- Consider Ca and Vit D supplements for :
- Biochemical insufficiency, dietary deficiency, ?all age >70, nursing home residents, high dose steroids

# Benign breast issues

**Breast cysts**

- more prevalent in HRT users
- not premalignant and do not increase future breast cancer risk
- not a contraindication to HRT, although they will persist.
- no particular HRT type or route more/less preferable

**Fibroadenoma**

- Benign breast tumours
- 50% reduced risk with OCP
- May be stimulated by estrogen replacement
- No malignant potential
- Not a contraindication to HRT

# Benign breast Issues continued…

**ATYPICAL DUCTAL AND LOBULAR HYPERPLASIA**

- Precancerous conditions
- Atypia is associated with 5-fold increased risk of cancer
- Little data on the effect of HRT
- Current practice is not to use HRT where atypia is proven histologically.

**MASTALGIA**

- V Common with HRT, especially higher estrogen dose / progestogen e.g. MPA
- Cyclical –
  - Reduce caffeine consumption
  - Reduce fizzy drinks
  - Supporting bra
  - Gamma Linoleic Acid e.g. EPO
  - Simple analgesics
  - Refer if severe
    - ? For Danazol / Bromocriptine / Tamoxifen
- Non-cyclical
  - Local – refer
  - Diffuse – Rx as for cyclical
    - Refer if persists

# Breast Cancer

- Increased risk Ca Br with longer term use of combined HRT (CEE and MPA)
- NICE--RR 1.24 —baseline 23 per 1000, combined HRT—extra 5 cases over 7.5 years
  - NO increased risk with E alone (RR 0.77)
  - Individual baseline risk most important

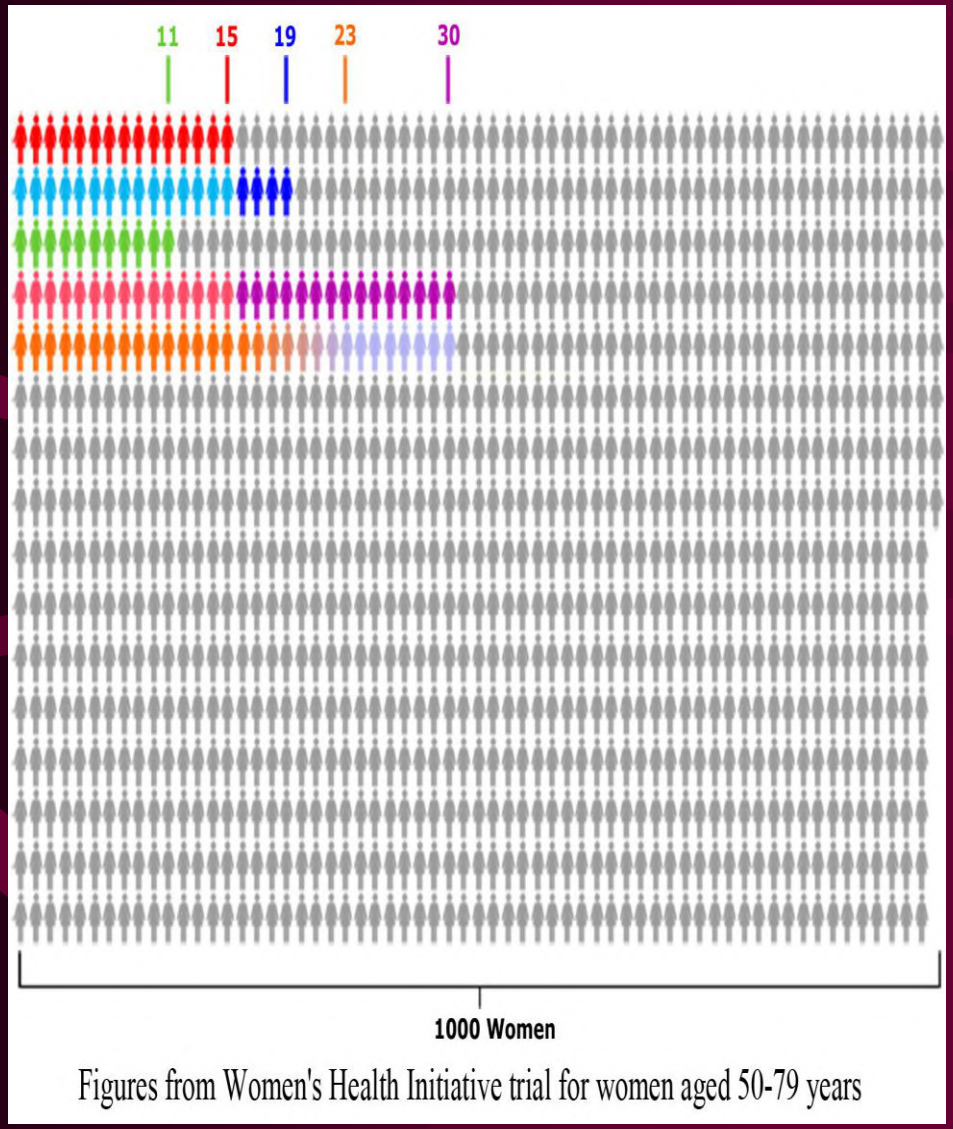
Current hypothesis

- No evidence that HRT initiates new breast cancers. It may increase the likelihood of breast cancer diagnosis by accelerating the growth of pre-existing tumours.
- Risk returns to same as non-users within 5 years of stopping HRT.
- No evidence of increased risk in HRT users under 50
- Mortality is not increased in HRT users.
- Other lifestyle risk factors may be more significant

# BREAST CANCER RISK FACTORS

| Risk Factor | Relative Risk |
|---|---|
| Female | 183 |
| Age < 11 yrs at menarche | 3 |
| Age > 55 yrs menopause | 2 |
| **Lifestyle factors** | |
| Age > 35 yrs first full-term pregnancy | 3 |
| Postmenopausal BMI > 35 kg / $m^2$ | 2 |
| Alcohol (> 2units / day) | 2 |
| **Current use of HRT** | |
| - combined HRT 5 years (WHI) | 1.24 |
| - unopposed conjugated oestrogen (WHI) | 1 |
| - combined HRT (MWS) | 2 |

# www.menopausematters.co.uk/downloads.php




Figures from Women's Health Initiative trial for women aged 50-79 years

| KEY | Relative risk of breast cancer | Number of women developing breast cancer over the next 5 years, per 1,000 women | Number of extra (*or less) cases of breast cancer over the next 5 years, per 1,000 women |
|---|---|---|---|
| No HRT | 1 | 15 | 0 |
| Combined HRT (estrogen plus progestogen) | 1.26 | 19 | 4 |
| Estrogen only HRT | 0.73 | 11 | - 4 * |
| Obese, older than 50 years (BMI greater than 35) | 2 | 30 | 15 |
| Alcohol - 2 or more units/day | 1.5 - 2 | 23 - 30 | 8 - 15 |

# High risk women

- **Family History** (www.NICE.org.uk)

  - Most women with a family history do not fall into a high risk category and do not develop breast cancer
    - ~ 10% cancers are due to high risk (BRCA1 / BRCA2 - young age at diagnosis, clustering of cancers)
  - 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
- **Personal history of breast cancer**
  - Studies inconclusive – QOL to be considered
  - Avoid SSRIs with Tamoxifen. Venlafaxine safest
  - Caution re vaginal estrogen and AIs

# HRT and CVD

- Favourable effects on lipids, w/h ratio, lipid clearance, vascular function, vascular remodelling
- Conflict between studies
- 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
- Window of opportunity

# VTE and HRT

- Overall baseline VTE risk 1.0 per 1,000 women per year
- Oral HRT- additional 1.5 events per 1,000 women per year, mostly in 1st year
- Risk affected by progestogen type--? Increased with MPA
- No apparent increase with transdermal HRT
- Offer transdermal if BMI >30
- If risk factors for VTE, no concern re vaginal estrogen, systemic HRT—discuss and if HRT indicated, use transdermal

# Other medical issues

- **Diabetes**—no c/I to HRT, route dictated by lipids (if increased TGs, use transdermal)
- **Asthma** – hormonal effect unclear, be prepared to change/stop HRT if worsens, may improve
- **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

# Gynae cancers

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

# Useful websites

www.thebms.org.uk

www.menopausematters.co.uk

www.mapofmedicine.com

- Thanks!!
- Any Questions?