BACKGROUND TO THE MENOPAUSE: ITS CONSEQUENCES AND MANAGEMENT

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Topics

- Background
- Symptoms
- POI
- Non Hormonal
- HRT
  - *Routes*
  - *Types*
  - *Combination*

Topics

- Breast
- Osteoporosis
- Cardiovascular
- Stroke/Hypertension
- VTE
- Dementia
- GSM
- Contraception

The Menopause
-Definition

- The last menstrual period

  – *i.e. only diagnosed in retrospect 12 months later*

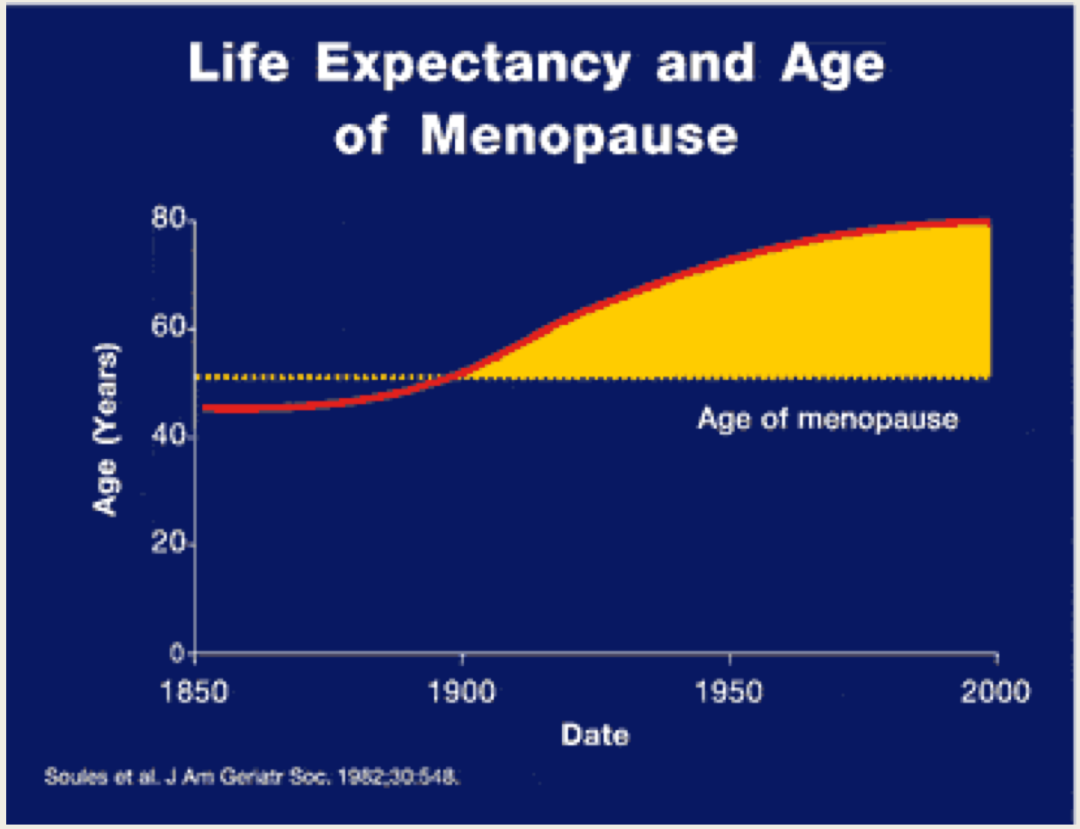
Demographics

1850

- Age of **menopause** - 45 yrs
- Life expectancy - 45 yrs.

2016

- Age of **menopause** – 51/2 yrs.
- Life expectancy - 83 yrs.
- Today > 30% life = postmenopausal



Age at menopause

- Average age at menopause 51-52 (UK)
  - *Normal range 45-55*
    - *No FSH - >45yrs with menopausal symptoms*

- Early menopause
  - *before 45*
  - *Consider FSH; age 40-45, with meno symptoms*
  - *10%*

- Premature Ovarian Failure/Insufficiency
  - *before age 40*
    - *Must do FSH - < 40 when menopause suspected*
  - *1%*

Testosterone

- T levels do NOT fall rapidly at the menopause
- T levels fall steadily from age 20
- There is no significant change at menopause but the ratio between estrogen and testosterone changes and SHBG levels may fall

What are the known causes of POI?

- Idiopathic - ?90%

  - *10–15% of women with POI will have a first degree relative with POI*
  - *Early menopause six-times more likely if mother or older sister also experienced early menopause*

- Chromosomal (10-12%)
  - *E.g. Turner Syndrome*
  - *More often primary amenorrhoea*
- Genetic
  - *E.g. Fragile X premutation (10% of familial POI)*
  - *Autosomal gene mutation e.g. galactosaemia*
- Autoimmune
- Infections
  - *E.g. Mumps oophoritis*

Iatrogenic menopause

- Iatrogenic
  - *Hysterectomy / Bilateral oophorectomy*
  - *Chemotherapy*
  - *Radiotherapy*
- The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process for that treatment.
- Consider leaving ovaries in situ if possible, unless
- Risk-reducing prophylactic surgery e.g. BrCa1/2 carriers

POI - Treatment

BMS/IMS :

“Women with a premature menopause should be recommended hormone therapy until the average age of menopause (unless CI)”

Quality standard

PREMATURE OVARIAN INSUFFICIENCY DIAGNOSIS

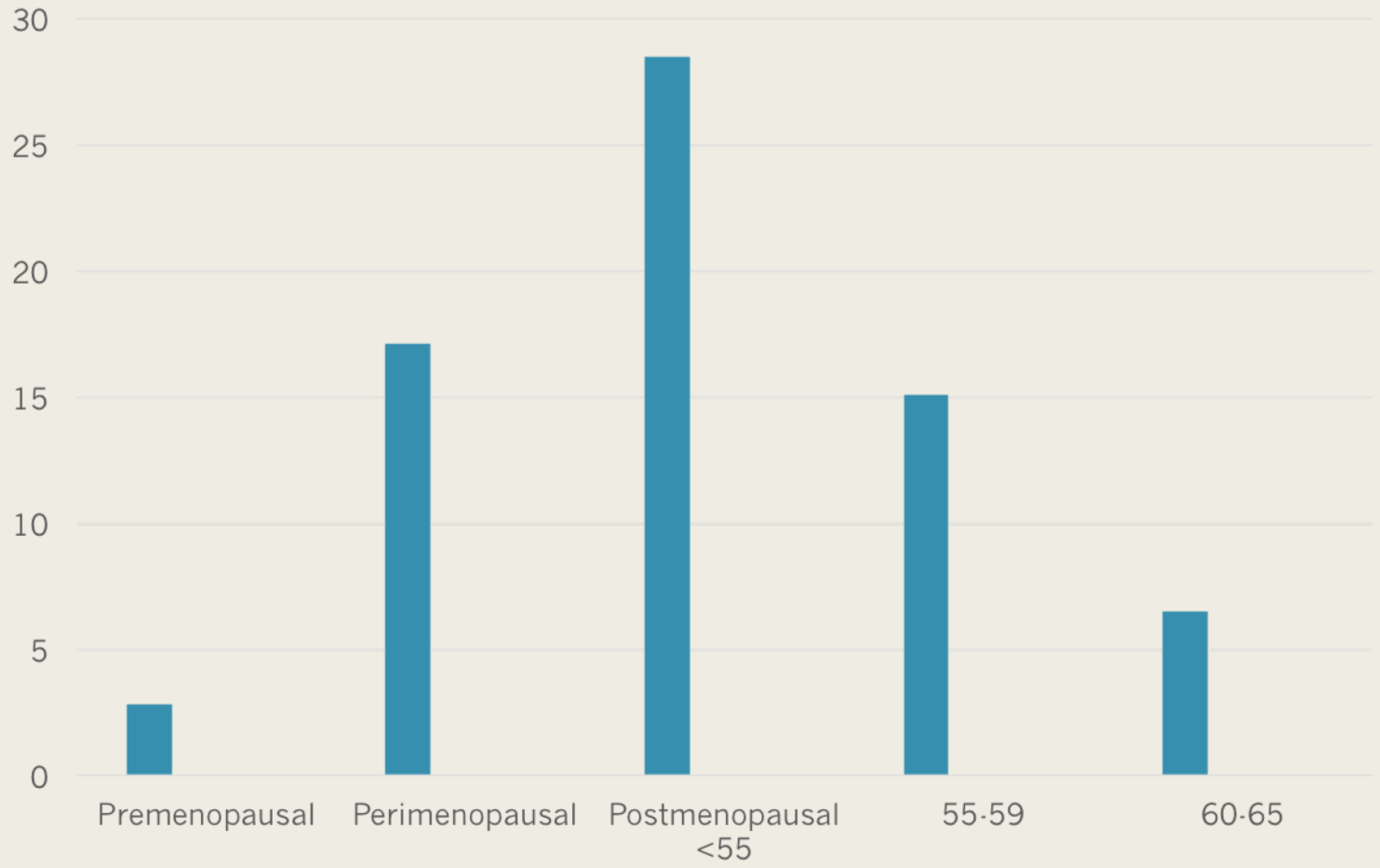
Diagnosis NICE 2015
Menopause symptoms, including no or irreg periods
and

2 x raised FSH 4-6 weeks apart (>25 – ESHRE)

Take into account clinical history

“If diagnosis is in doubt – refer to specialist”

Prevalence vasomotor symptoms



Gartoulla 2015

Estrogen withdrawal does not explain the aetiology of hot flushes

- There are no correlations between hot flush occurrence and plasma, urinary and vaginal levels of estrogens
- Nor are there differences in plasma levels between asymptomatic and symptomatic women
- Clonidine reduces hot flush frequency without changing circulating estrogen levels
- ? Role of neurokinins

Estrogen withdrawal is necessary to explain the occurrence of hot flushes but is not, by itself, sufficient to do so

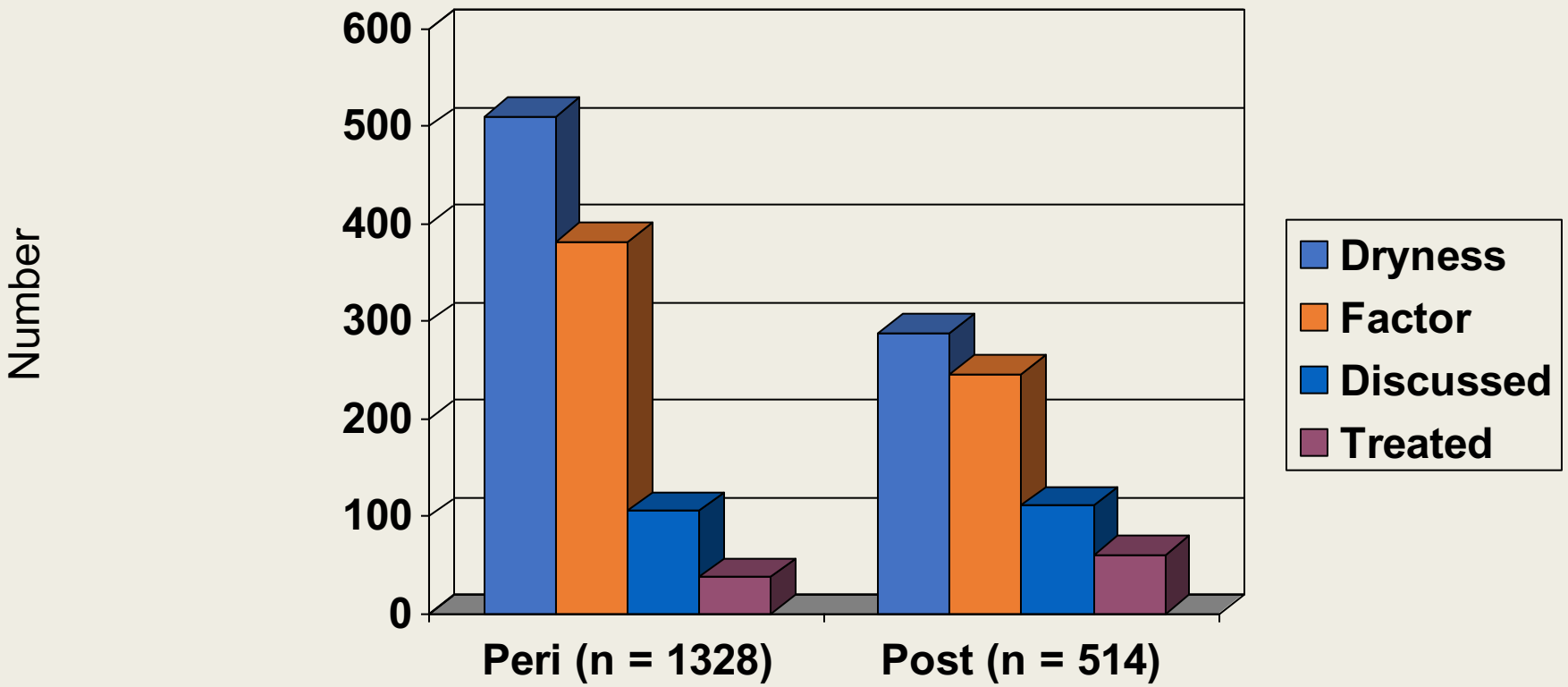
Lower urinary tract atrophy

- Estrogen receptors in bladder trigone, detrusor muscle, urethral sphincter
- Deficiency leads to dysuria, frequency, urgency, urge incontinence, nocturia

Incidence of symptoms of GSM

- 15% premenopausal women
- 10 – 40% postmenopausal
- 10 – 25% women taking systemic HRT
- 2/3 by age 75

Vaginal dryness and libido



Cumming G, Currie H. Web-based survey on the effect of menopause on women's libido in a computer-literate population. Menopause International 2009;15:8-12

Possible reasons

- Embarrassment
- Not seen as serious illness
- Lack of time
- Health professionals’ attitudes
- Unaware of availability of treatments
- Believe symptoms incurable consequence of ageing
- Not asked

Management

Lifestyle advice - symptom control and prevention

- Loose cotton layers
- Fans
- Avoid spicy foods
- Avoid hot drinks
  - *Especially caffeine*
- Diet
  - *Phytoestrogens*
  - *Improve glucose tolerance……*
  - *Calcium/vitamin D*
- Exercise
  - *(Wt and BMD)*

Obesity

- Increased vasomotor and menopausal symptoms in general
- Increased risk CVD, independent of other factors
- Increased risk VTE
- Increased risk cancer

EMAS position statement: Managing obese postmenopausal women
Lambrinoudaki et al. Maturitas 66 (2010) 323-326

Smoking

- Increased menopausal symptoms
  - *(vasomotor, insomnia, psychological)*
- Increased CVD risk
- Increased osteoporosis risk
  - *Mechanisms—toxicity to ovarian follicles, reduced estrogen, earlier age of menopause*

Alcohol

- May worsen vasomotor symptoms
  - *And sleep quality*
- Increased risk osteoporosis
- Increased breast cancer risk
- Calories, contributing to weight gain

Symptom management options … Chillow Pillow / Koolabanda

Phytoestrogens

- Japanese women
  - *Fewer hot flushes*
  - *High soya diet*
- Contains phytoestrogens
  - *Lower risks of*
- Heart disease
- Breast cancer

Phytoestrogens

Soy bean and soy bean products (e.g. tofu), legumes, nuts, whole grain cereals and oilseeds (e.g. flax) are the foods most rich in phytoestrogens.

Plus sesame seeds, wheat, berries, oats, barley, dried beans, lentils, rice, alfalfa, mung beans, apples, carrots, pomegranates, wheat germ, rice bran, soy linseed bread, ginseng, fennel, anise, bourbon and beer!

Red Clover

- Concentrated iso-flavones (phytoestrogens) are found in red clover
- Can be taken in tablet form
  - *e.g. Promensil*

Non-hormonal prescribing for vasomotor symptoms

Some non-hormonal drugs have been shown to reduce the frequency and severity of vasomotor symptoms (<60%)

Clonidine *(licensed)*

- 50 – 100 microg twice daily
  - *side effects include difficulty sleeping, dry mouth, dizziness, constipation, sedation and depression*

Off-label, non-hormonal prescribing for menopausal symptoms

Venlafaxine (SNRI)

- 37.5 – 75mg daily
- higher doses are not more effective and are associated with more side effects
- not licensed

Low dose SSRIs

- eg Fluoxetine/Citalopram 10/20mg, Paroxetine 10mg
- High doses may cause sweats
- Not licensed

NICE 2015: Do not routinely offer first line, no clear evidence for use for mood/anxiety in absence of depression.

More non-hormonal options

Gabapentin

- *300 – 1200mg daily (not licensed)*
  - side effects include dizziness, fatigue, tremor and weight gain

Progestogens

- *evidence suggests breast cancer risk higher with combined HRT than estrogen alone*
- *it is unclear whether progestogens used alone may also increase the risk*
- *it may, therefore, be unwise to prescribe progestogens alone to women with a history of breast cancer*
- *also norethisterone >5mg / VTE risk*

Non-hormonal vaginal options

Moisturisers

- hold moisture on the vaginal walls and only needs to be used 2 or 3 times per week

- Replens
- Regelle
- Hyalofemme

Lubricants

- Sylk
- Yes
- Astroglide
- Durex Play

Petroleum-based lubricants can increase the likelihood of infection and damage latex condoms.

Check the label!

Non-medical options

- Homeopathy
- **Acupuncture**
- Aromatherapy
- Reflexology
- Relaxation therapy
  - *it's all about getting through the menopause as comfortably as we can*
  - *for some it may involve hormones, for many it won't*

Indications for prescribing HRT

- Control of menopause symptoms in peri or post menopausal women
- Treatment of Premature Ovarian Insufficiency (POI)
- Osteoporosis prevention

What are we prescribing?

Estrogens

- *Synthetic* - Ethinyl estradiol
- *Natural* - Estradiol, conjugated equine estrogens,
  Estrone, Estriol

'Natural estrogens' are defined as those found in normal physiology, irrespective of whether they have been prepared by chemical synthesis or extraction from a plant or animal source

What are we prescribing?

Progestogens

Synthetic

- *C19* structurally related to testosterone
  (Norethisterone, Norgestrel, Levonorgestrel)
- *C21* structurally related to progesterone
  (Dydrogesterone, Medroxyprogesterone acetate)
- Spirolactone derived progesterone (Drospirinone)

Natural

- Micronised progesterone (Utrogestan)

Testosterone

Contra indications to HRT use

There are actually very few women who should be advised that they should NEVER use HRT.

Listed contra indications:

- estrogen dependent malignant tumours
- undiagnosed vaginal bleeding
- pregnancy
- active liver disease with abnormal liver function
- active thromboembolic disorder or acute phase myocardial infarction

Precautions with HRT use

- Fibroids
- Hypertension
- Migraines
- Epilepsy
- Endometriosis
- Personal or family history of VTE / stroke
- History of heart disease or recent cardiovascular event
- Starting HRT in the over 60s

- **Family history of breast cancer**

Systemic or local therapy

- Systemic therapy will be required for women who present with a wide range of symptoms

- Local therapy may be needed in addition to systemic therapy or as stand alone therapy:
  - *to treat vaginal symptoms*
  - *prevention of recurrent UTI*

Vaginal estrogens

Advantages

- No/minimal systemic absorption or side effects
- Exerts local effect on vagina and urethra, treats vaginal dryness dyspareunia, may help urinary symptoms of urgency and recurrent UTIs
- No/minimal endometrial stimulation, progestogens unnecessary
- May be acceptable when systemic estrogens are contra indicated
- Some products with long term use licence

Vaginal estrogens - NICE guidance

- Offer low dose vaginal estrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms

- If low dose vaginal estrogen does not relieve symptoms consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause

Non Oestrogen prescribable vaginal preparations

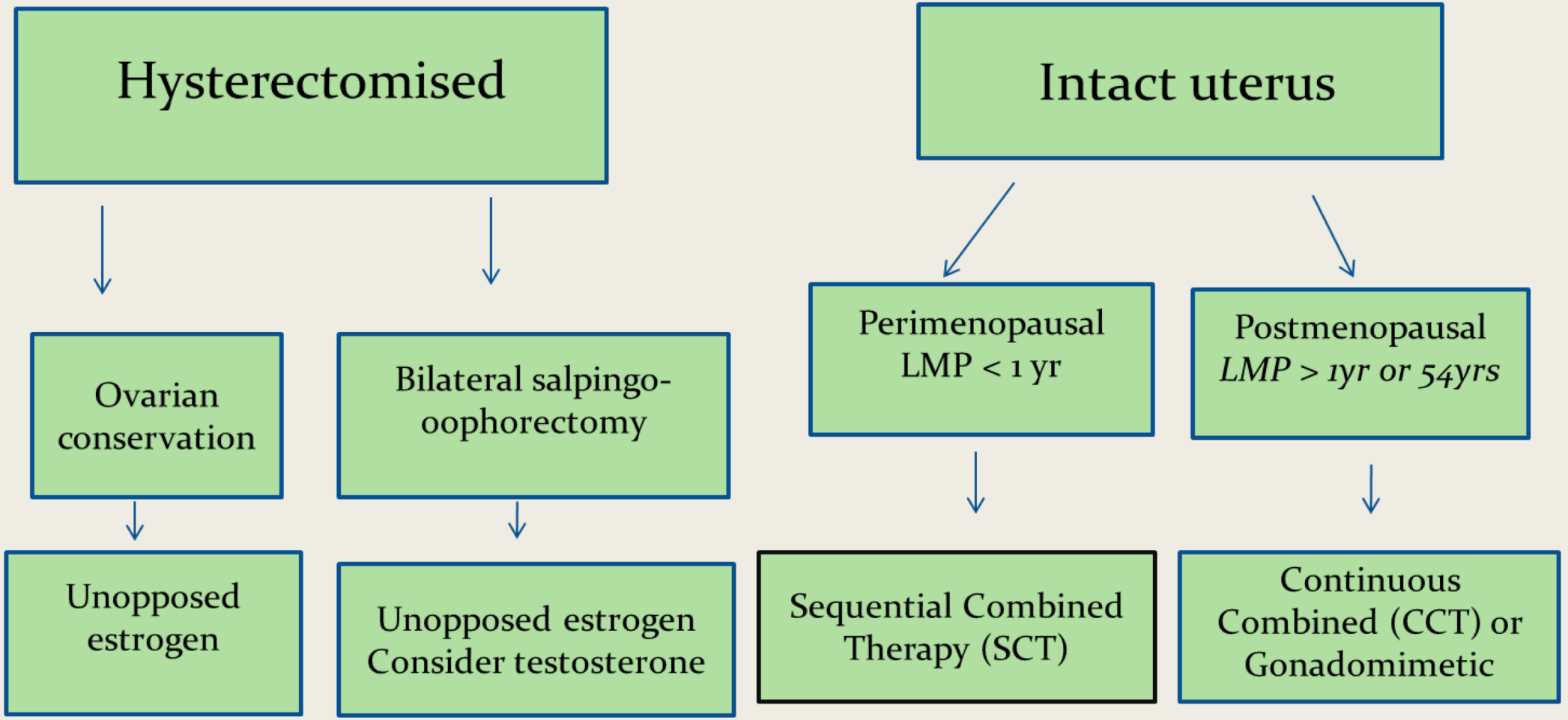
Intrarosa

- 6.5mg pessary.
- Plant derived version of endogenous dehydroepiandrosterone (DHEA)
- Vaginal preparation, acts locally within the vagina.
- Used for the treatment of vulvar and vaginal atrophy in post menopausal women having moderate to severe symptoms.
- Active ingredient Prasterone.
- One pessary each night before bedtime.

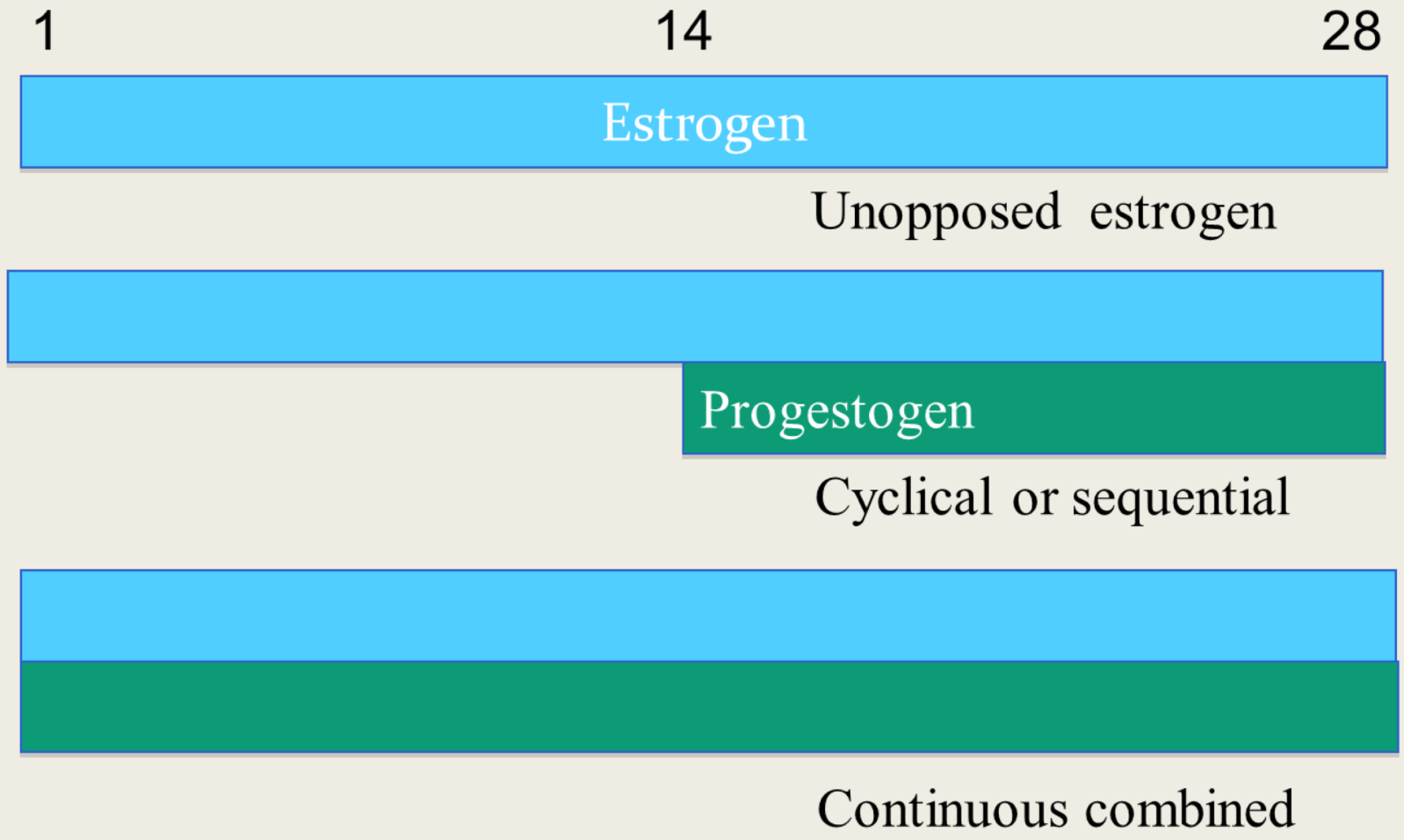
NEW SERM Ospemifene *Osphena (Senshio)*

- Now available in UK
- For the treatment of moderate to severe dyspareunia resulting from vulval and vaginal atrophy
- Oral tablet 60mg
- Side effects include hot flushes
- Avoid concomitant other estrogens or estrogen agonists/antagonists
- Possible increased risk of stroke and thrombosis
- As the endometrium acts as an agonist - possible increased risk in endometrial hyperplasia
- Not studied in women with previous breast cancer

Which regimen?



Regimens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Estrogen
Unopposed estrogen
Progestogen
Cyclical or sequential
Continuous combined

Cyclical or continuous combined?

Cyclical therapy is also known as sequential therapy.

- Peri menopausal women
- Progestogens given for 12-14 days of each cycle for monthly bleed and are mostly combined with estrogen within one tablet
- Adjunctive progestogens including Mirena coil can be given with estrogen only preparations
- Withdrawal bleed in response to progestogens.
- Consider prescribing progestogens to start the same day each month as an aid to remembering!

Cyclical or continuous combined?

Continuous Combined

- Suitable for post menopausal women 12 months since last menstrual period
- Age 53-54yrs
- Daily dose of estrogen and progestogen, maintains an atrophic endometrium
- Consider changing to continuous combined to reduce risk of endometrial cancer after 5 yrs of cyclical therapy

Cyclical preparations - bleeding

- Women should be instructed to commence within a couple of days of the onset of their menstrual cycle if having relatively frequent bleeds
- The withdrawal bleed from the HRT will happen towards the end of one packet and the beginning of the next packet
- Regardless of bleeding, take one packet after the next without breaks

Commencing or swapping to continuous combined therapy

- If not already on HRT may commence immediately

- If swapping from cyclical HRT:
  - *Continue on to new CC HRT straight after the last tablet of cyclical preparation*
  - *May consider waiting for bleeding to finish before commencing CC preparation*

Route of therapy

Oral estrogen therapy dose

- Estradiol 0.5mg 1mg 2mg tablets

- Conjugated equine estrogen (Premarin)
  0.3mg 0.625mg 1.25mg tablets

POI patients may require higher doses

Aiming for lowest effective dose – may not be the lowest dose

COC for Premature Ovarian Insufficiency

COC can be prescribed for young women with premature ovarian dysfunction:

- Controls menopausal symptoms
- Protects against long term health issues from estrogen deficiency
- Offers contraception
- Free
- In keeping with peers
- Zoely and Qlaira offer combined approach but cost often prohibitive

Oral estrogens

- Familiar - easy to take, easy to stop and mostly cheap!
- Different estrogens may be absorbed differently
- Variable absorption, up to 90% may never reach circulation
- Higher doses required than with non oral estrogens - metabolised in liver
- Carry higher risks for thrombosis and stroke.

Non oral estrogens

Patches

- Variation in dose - 25, 37.5, 40, 50, 75, 80, 100mcg
- Some changed twice weekly, some weekly
- Available as estrogen only or combined estrogen and progesterone
- Available as cyclical or continuous combined
- Combined patches only available in one standard dose
- Usually worn below the waist, instruct patients about what to do if patches fall off (particularly important with cyclical therapy)

Non oral estrogens

Gels

- 0.5mg 1.0mg sachets *Sandrena*
- 1- 4 strips / measured doses *Oestrogel*

Available as estrogen only so needs to be combined with separate progestogens if uterus is present.

Should both be applied daily to dry healthy skin free of moisturisers. Mostly applied to inner thigh. Should not be applied close or directly to breast tissue.

Patches and gels

- Avoids first pass metabolism in liver
- Less affect on clotting factors reduces risks for thrombosis.
- Steady absorption over 24 hours
- Reduces trigylcerides
- May not be absorbed well
- Patches may cause irritation or may not stick

NICE Guidance - Venous Thromboembolism

The risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk

Choosing the right dose

Estrogens - use the lowest effective dose.

Likely to start with lowest possible dose if:

- *Previous side effects*
- *At risk patients*
- *Nervous about side effects or using HRT*

Likely to start with higher doses if:

- *Very symptomatic*
- *Previous low doses ineffective*
- *Young*

Estradiol implants

- Estradiol implants - available in 25mg or 50mg dose. Often only available in secondary care or private sector
- Usually reserved for patients in whom other HRT therapies are not suitable or effective
- Minor surgical procedure - inserted under local anaesthetic into subcutaneous fat, mostly on the abdominal wall
- Estradiol levels need to be monitored to avoid taxyphalaxis

Which progestogens?

- C19 progestogens structurally related to testosterone

  Norethisterone

  Levo/norgestrel

  Possible better cycle bleeding control

- C21 progestogens structurally related to progesterone

  Dydrogesterone

  Medroxyprogesterone acetate

  Less androgenic side effects

Natural progesterone

Utrogestan

- Oral micronised progesterone, now only comes in 100mg oral capsules
- Possible fewer progestogenic side effects
- Licensed to be used vaginally in other European countries
- Possible reduced risks of thrombosis than other synthetic progestogens
- MIMS guidance for use:

  200mg daily at bedtime on days 15—26 of cycle or

  100mg at bedtime on days 1—25 of cycle
- Many practitioners prefer using daily without a break to provide continuous combined therapy
- Also used in infertility as 200mg vaginal preparation

Routes of therapy - progestogens

- **Oral therapy**

  Mostly already “teamed” up with Estradiol, a few stand alone preparations available

- **Climanor/Provera 5mg MPA tablets**

  Cyclical 10mg for 14 days each 28 day cycle

  Continuous combined 2.5-5mg daily

- **Utrogestan**

  Cyclical 200mg for 12 days of each 28 day cycle

  Continuous combined 100mg daily /days 1-25 of each 28 day cycle

  Taken on empty stomach at bedtime

Routes of therapy - progestogens

- **Transdermal**

  Patches in combination with estrogen.

  Both cyclical and continuous combined available

- **Intrauterine**

  Mirena coil

  Can be used in both pre and post menopausal women

Protecting the endometrium with Mirena

- Mirena provides targeted delivery of levonorgestrel directly to the endometrium
- With Mirena in situ, menopausal women have the freedom to choose the type, route of administration and dose of estrogen most appropriate to their needs, preferences or lifestyles.
- Added benefit of contraception.

Choosing progestogens

Safety Considerations

- The WHI and other studies suggest that the progestogen component of HRT may be more significant for increase in breast cancer risk (more than estrogen)

- Natural progesterone has specific beneficial effects that could justify its use besides the expected actions on the endometrium.

  Reduced risks for thrombosis and ? Breast cancer

- Dydrogesterone possible fewer risks for breast cancer when combined HRT is being used. Fewer risks for thrombosis but not available as a stand alone progestogen.

  Lancet publication August 2019
  Collaborative Group on Hormonal Factors in Breast Cancer.

Altered sexual function - testosterone therapy

- Very common problem in the menopause
- Often multifactorial and difficult to address
- Will often require several approaches or interventions
- Consider vaginal dryness and psychosexual problems as well

NICE guidance

Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.

Testosterone therapy

- Testosterone implants 50mg 100mg
  given alongside estradiol every four to six months

Unlicensed products:

- *Testosterone gel - Testogel / Testim*

  Usually maximum 1 sachet per week 1/3 to 1/4 (50mg) on alternate days

- *Tostran gel*

  2% gel (10mg per 0.5gmetered application), 60g pump dispenser, 1 pump on alternate days

Given in conjunction with estrogen replacement therapy

Tibolone

Gonadomimetic

- Synthetic steroidal compound
- Estrogenic, progestogenic, and androgenic effects
- Controls symptoms and protects bones
- Initially was licensed for libido problems.
- Similar risks and benefits
- Prescribed for post menopausal women treated as a CCT

Duavive

- Duavive 0.45mg/20mg

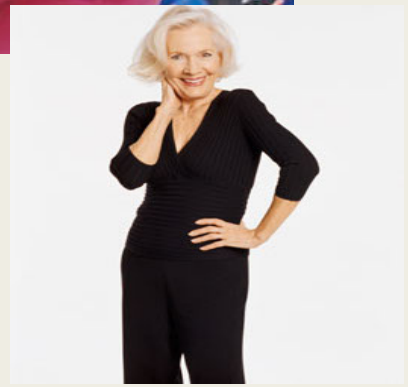
- Conjugated estrogens 0.45mg
- Bazedoxifene acetate equivalent to 20mg bazedoxifene

Modified release tablet, indicated for treatment of estrogen deficiency symptoms in post menopausal women with a uterus in whom treatment with progestin containing therapy is not appropriate

Duavive

- Effect on the risk of breast cancer unknown
- Effect on the risk of ovarian cancer unknown
- Effect on the risk of stroke unknown
- SERMS including Bazedoxifene increase the risk of DVT
- Common adverse reactions include breast tenderness, abdominal pain, constipation, diarrhoea, muscle spasms and increase in blood triglycerides

Different women … different risks



Individual women need individual assessment and individual treatment

Reducing risks with HRT prescribing

- HRT remains the **gold standard** for treatment of estrogen deficiency symptoms in menopausal women
- Estrogen probably adds some cardio protection if initiated prior to or within 10 yrs of menopause
- However this may be obscured by the use of progestogens especially MPA
- Oral HRT is associated with increased risk of VTE, gallbladder disease and possibly stroke
- This increased risk can be prevented by the transdermal route of estradiol

IMS Recommendations 2011

Governing principles:

- HRT should not be recommended without a clear indication for its use, i.e. significant symptoms or physical effects of estrogen deficiency
- Postmenopausal HRT is not a single regimen given to a standard woman
- HRT must be individualised and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations

NICE guidance also recommend an individualised approach

Treatment duration

- Premature ovarian insufficiency: treat until 52yrs then reassess, continue if symptomatic (*endorsed by NICE guidelines).*
- The only way to know if a women is still symptomatic and requires HRT is to stop HRT and assess. Consider reducing dose prior to stopping.
- If indications for HRT include osteoporosis prevention/treatment, may continue for longer
- Guidelines suggest we use the lowest possible dose for the least possible time

Treatment duration

- Risk / benefit analysis
- Patient choice, provided patient aware of potential risks and benefits and has justifiable reasons for staying on HRT
- Often quality of life issue
- Assessed on an individual basis, no arbitrary time limit

Stopping HRT

- No evidence to support weaning off HRT but does seem to be a sensible concept
- Try lower dose for at least 3-6 months before stopping
- Lower dose VS every other day
- Alternatives may prove useful at this time
- Pick right time to give it a try!
- NICE guidance suggests that reducing dose or stopping abruptly does not effect the long term likelihood of symptoms returning

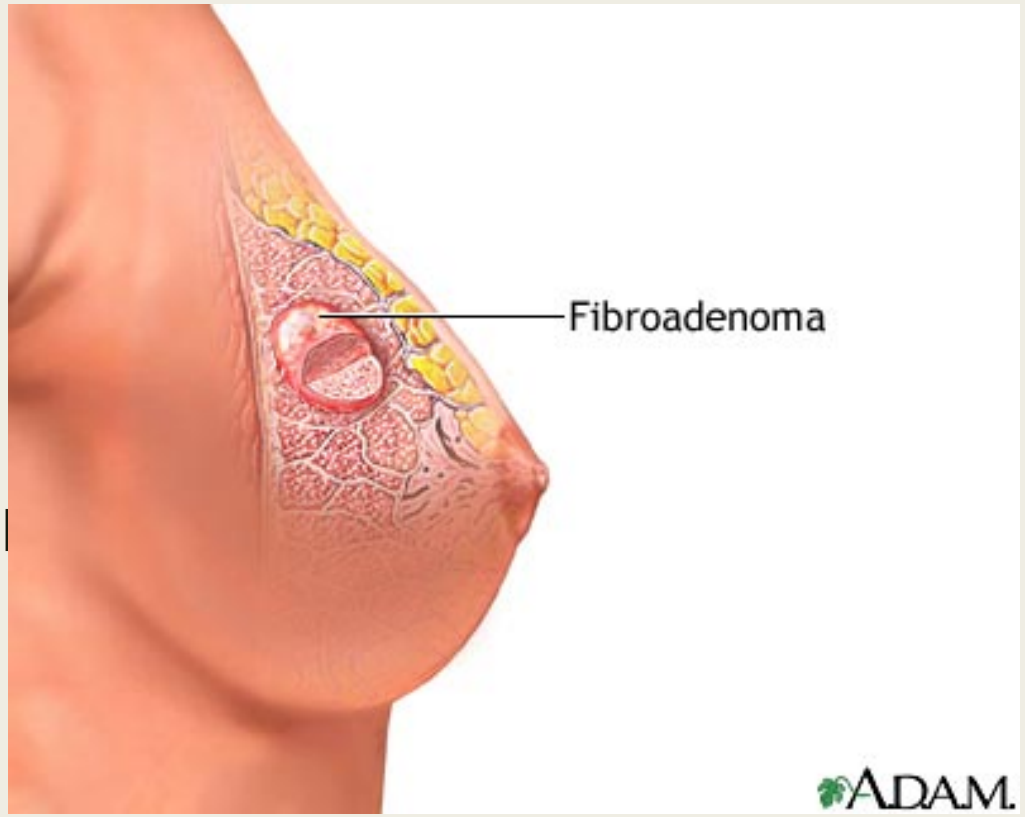
HORMONES AND THE BREAST

Cystic breast disease

- Simple cysts are more prevalent in HRT users
  - *7% in HRT users cf <1% in non-users*
  - *Harvey et al. Am J Roentgenol 1999; 172: 1615-9*
- Simple cysts are not premalignant and do not increase future breast cancer risk
- Not a contra indication to HRT, although they will persist
- No particular HRT type or route more/less preferable

Fibroadenomata

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



Atypical Ductal and Lobular Hyperplasia

- Precancerous conditions
- *Atypia is associated with 5-fold increased risk of cancer*

- Little data on the effect of HRT
- *One study found no increased risk of invasive breast cancer in women taking estrogen with previous histologically defined benign breast disease with atypia*

Dupont et al. Cancer 1999; 85: 1277-83

- Current practice is **not to use HRT** where atypia is proven histologically

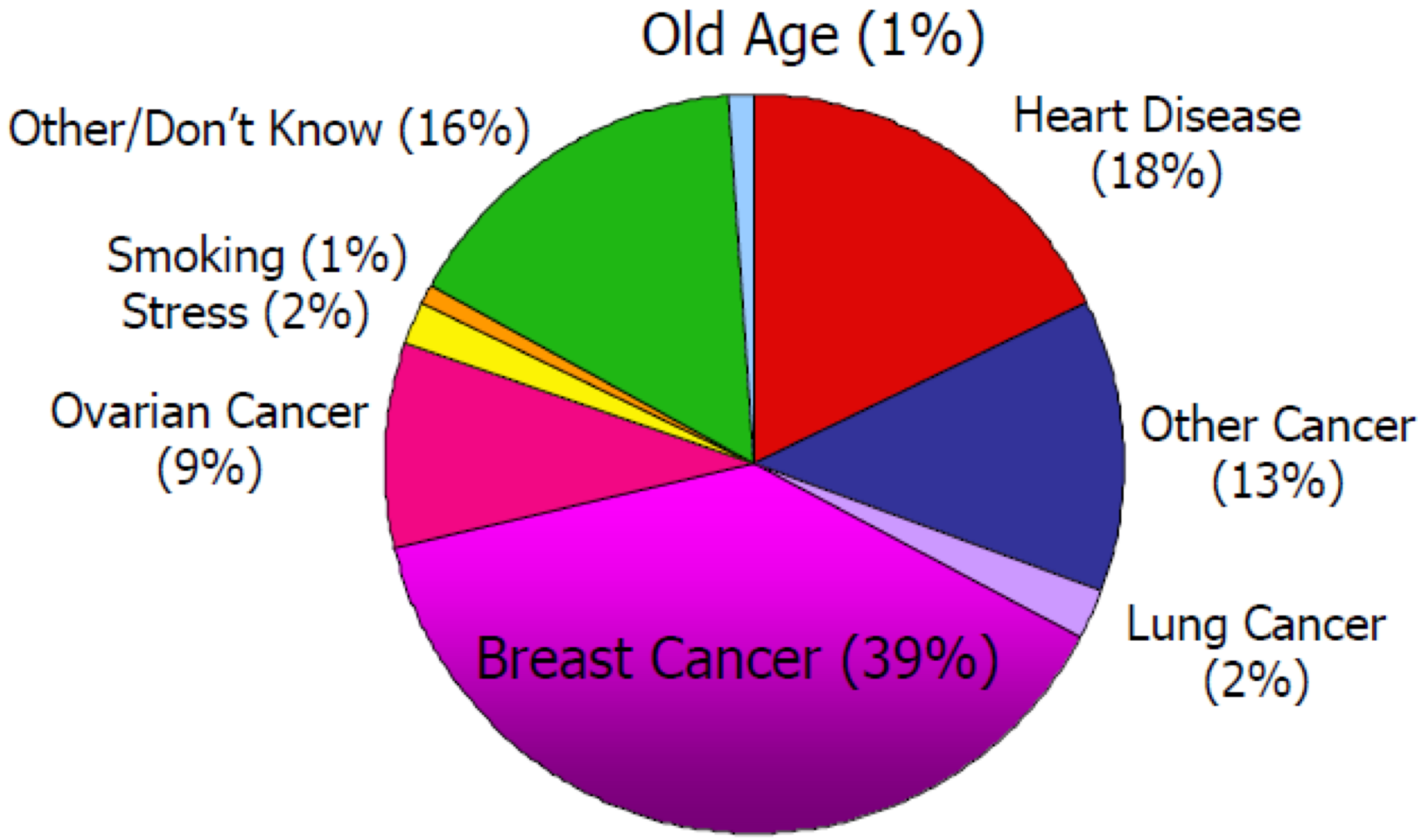
Mastalgia

- V Common with HRT
  - *20-36%*
  - *Common reason for stopping HRT*

- Increased with higher estrogen dose

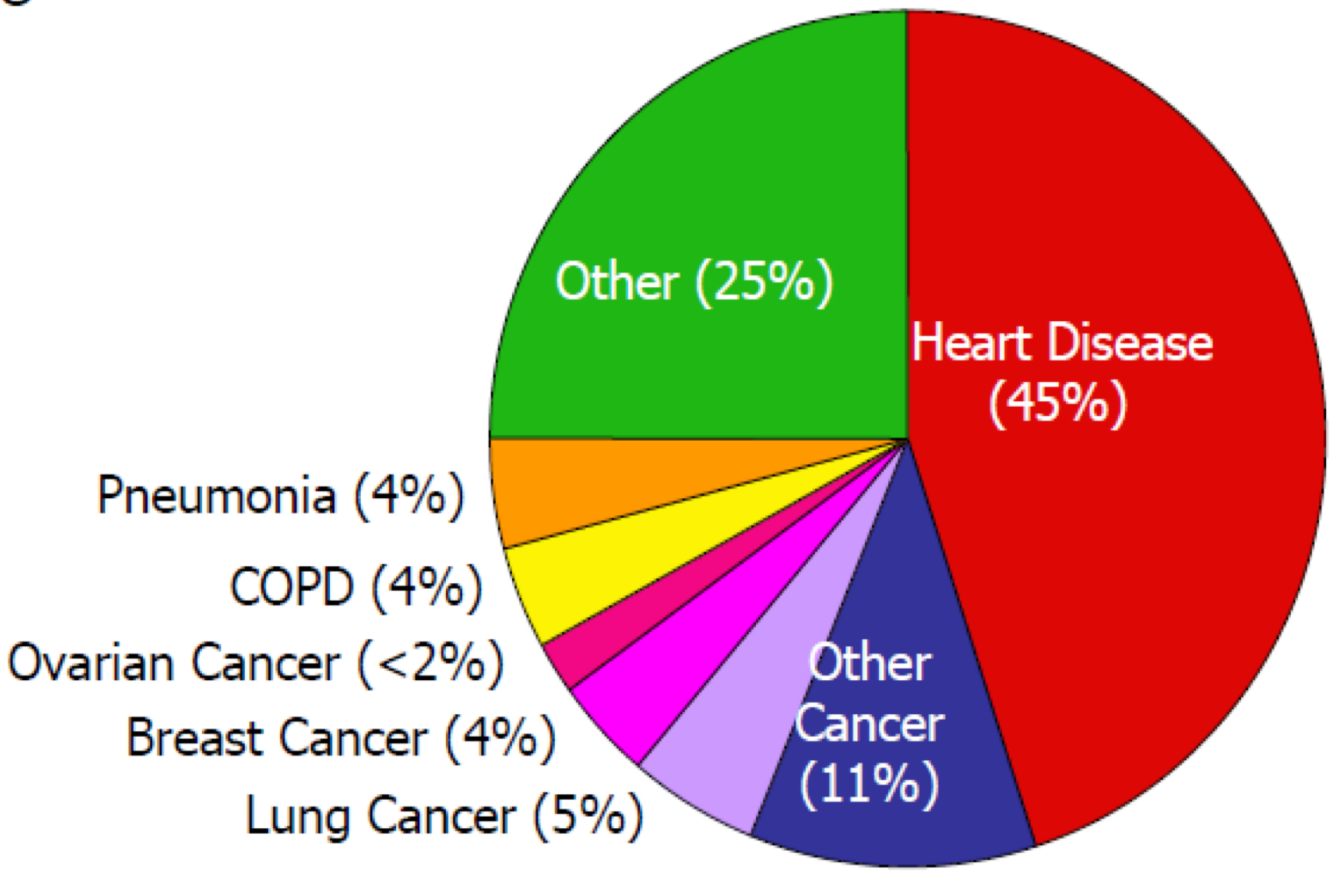
- Can also be associated with progestogen e.g. MPA

Leading Causes of Death Perceived by Women



Gallop Poll

Actual Causes of Death Among U.S. Women



Cancer Research UK statistics

- 1 in 7 UK females will be diagnosed with breast cancer in their lifetime.

- 23% of breast cancer cases in the UK are preventable.

  - *<1% of breast cancer cases in the UK are caused by oral contraceptives.*
  - *2% of breast cancer cases in the UK are caused by HRT.*
  - *8% of breast cancer cases in the UK are caused by overweight and obesity.*
  - *8% of breast cancer cases in the UK are caused by alcohol drinking.*
  - *5% of breast cancer cases in the UK are caused by not breastfeeding.*

WHI

- Combined arm (EE + MPA) of RCT
- *16,608 post menopausal women aged 50 to 79 years*

- *terminated early (5.2 years)*

- ***Numbers of CA Breast exceeding stopping boundary***
- - but not statistically significant

- Estrogen only arm continued

Headline

- **Clinical Alert:** NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit
  - *National Heart, Lung, and Blood Institute (NHLBI)*
    09 July 2002

- *'That headline, pandering to women's greatest fear - the fear of breast cancer - ensured that the word of the study would spread like wildfire. And it ensured that the conversation would be driven much more by emotion and politics than by science.'*

Langer R D. The evidence base for HRT: what can we believe?

Climacteric 2017 ; 20: 91-96

HRT and Breast Cancer – More Bad News

Daily Mail – August 2003

“HRT doubles the risk of breast cancer!”

Million Women Study

Accepted that:

- *HRT increases risk of breast cancer*

Designed to:

- *Assess effects of specific types of HRT on incident and fatal breast cancer*

Million Women Study - results

- RR Ca Br ever users = 1.43 cf never users
- In current users only
  - *RR 1.66*
  - *RR 1.01 in past users*
- slightly increased in 1st year after HRT use
- no different to never users thereafter

Million Women Study - results

- In developed countries the risk of breast cancer in never users = est @ 20/1000 between 50 and 60
  - *Collaborative group figures*

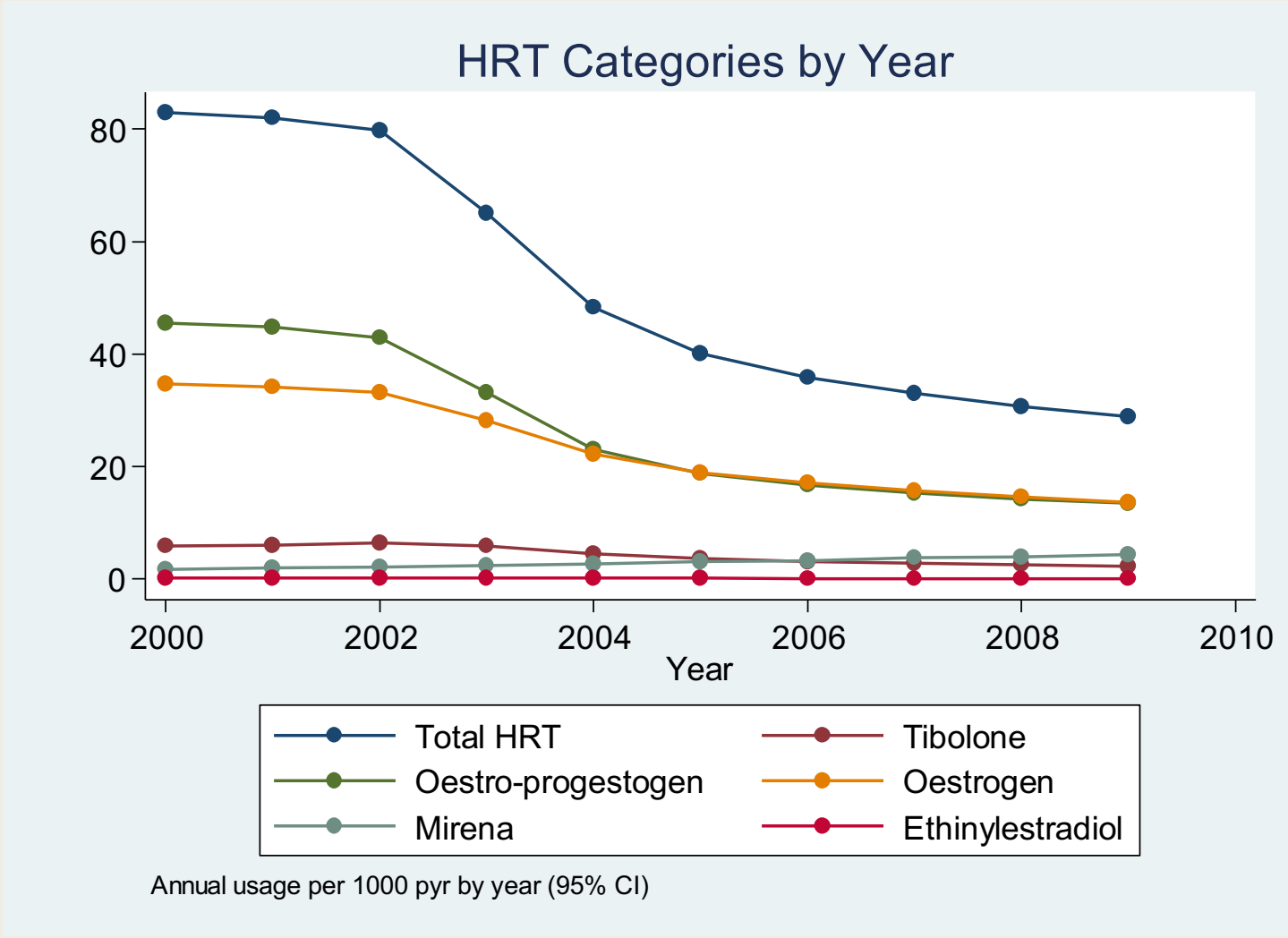
- Using the RR estimates from this study the different patterns of use of HRT would be expected to result in …

Estimated extra cases of breast cancer per 1000 women by 60y

■ 5 years E from 50y	1.5 extra cases
■ 10 years E	5 extra cases
■ 5 years E+P	6 extra cases
■ 10 years E+P	19 extra cases

Non-users – 20 cases per 1000 women 50-60 yrs
Collaborative group figures

HRT usage in the UK



MHRA 2011

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

Women with, or at high risk of, breast cancer - NICE

For advice on the treatment of menopausal symptoms in women with breast cancer or at high risk of breast cancer, see NICE guidelines on

- *early and locally advanced breast cancer and*
- *familial breast cancer*

Offer menopausal women with, or at high risk of, breast cancer:

- *information on all available treatment options*
- *information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen*
- *referral to a healthcare professional with expertise in menopause*

- *No good evidence re HRT after breast cancer +/- Tamoxifen*
- *HRT may be offered in exceptional cases*

Vaginal estrogen after breast cancer

- Post menopausal breast cancer patients and age-matched controls
- Vaginal atrophy in 32% taking Tamoxifen

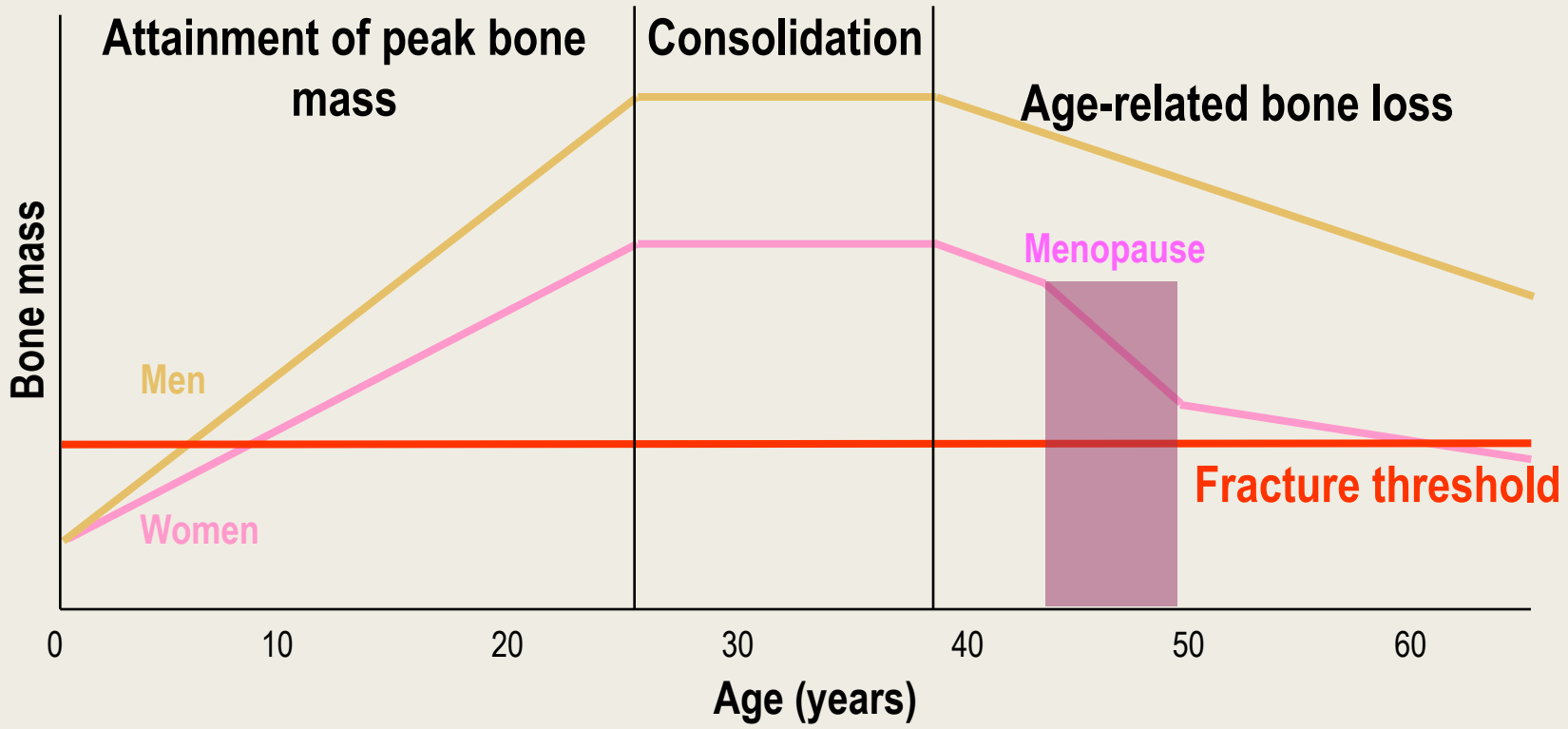
  57.6% aromatase inhibitors
- No RCTs
- Cohort study 1472 women breast cancer, 69 (4.7%) used vaginal estrogen
- Small numbers, no increased recurrence

A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer.

Dew JE, Wren BG, Eden JA. Climacteric 2003 Mar;6(1):45-52

OSTEOPOROSIS

Age-related changes in bone mass



*Compston JE. Clin Endocrinol 1990; **33**: 653–682.*

Lifestyle Advice

- Give up smoking
- Reduce alcohol
- Exercise (tailored to individual)
- Balanced diet
  - *Calcium*
  - *Vitamin D*
- Avoid falls

Osteoporosis Treatment: Calcium and Vitamin D

- Calcium
- Fewer than half adults take recommended amounts
- Usually 700 mg/day standard; 1000 mg/day in postmenopausal women/osteoporosis

(NICE 2015 CKS)

- Vitamin D
- 400 IU day at least;
  - *Frail older patients with limited sun exposure may need up to 800 IU/day*
  - *(2016 – consider in all DoH)*

Guidelines - HRT

- For women in late postmenopause (HRT).. is as effective as bisphosphonate therapy for preventing early postmenopausal bone loss and increasing bone mass. *Endocrine Society Statement 2010*

- HRT is an effective treatment for menopausal symptoms that also offers protection against fractures at both hip and spine……HRT has a role to play in the management of osteoporosis in postmenopausal women below the age of 60 years" *NOS Statement 2011*

- HRT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause *Global Consensus Statement 2013*

Bone-sparing doses of estrogen

- Dose dependent response
- “Standard” doses:

  estradiol 1-2mg

  conjugated equine estrogen 0.625mg

  transdermal 50mcg patch
- Increasing evidence that even lower doses may be bone protective, particularly in older women.
- Age 60+ 14mcg/24hr patch effective (Ettinger et al Obst Gyn 2004)
- 65+ 0.25mg estradiol increased BMD (Prestwood JAMA 2003)
- Early postmenopause 0.3mg Premarin (Lindsay Osteoporosis Int 2005)

Hormone replacement therapy

- HRT reduces risk of fragility fracture--vertebral and hip
- Maintained during treatment
- May continue longer when HRT taken longer
- Provides other benefits

- Not usually suitable for starting many years after menopause (but will protect bones at any age)
- Thrombosis risk with tablets
- Small increase in breast cancer risk with long-term use if progestogen required

What about progesterone?

- Increasing evidence that progesterone is active in bone health
- Prevention—anovulatory cycles??
- Does not on its own prevent bone loss
- Complementary bone actions with estrogen as anti resorptive

Progesterone and Bone: Actions promoting bone health in women. J Osteoporosis 2010. Seifurt-Klauss et al.

SERMS

- Currently only raloxifene
- Daily tablet

- May have some benefits of estrogen, e.g. for heart
- Thrombosis risk
- Strong protection against breast cancer

- Reduces vertebral fracture – possibly not hip

Premature menopause

- HRT recommended 1st line
- No evidence for bisphosphonates or other Rx in this age group

Early PM: 1º prevention

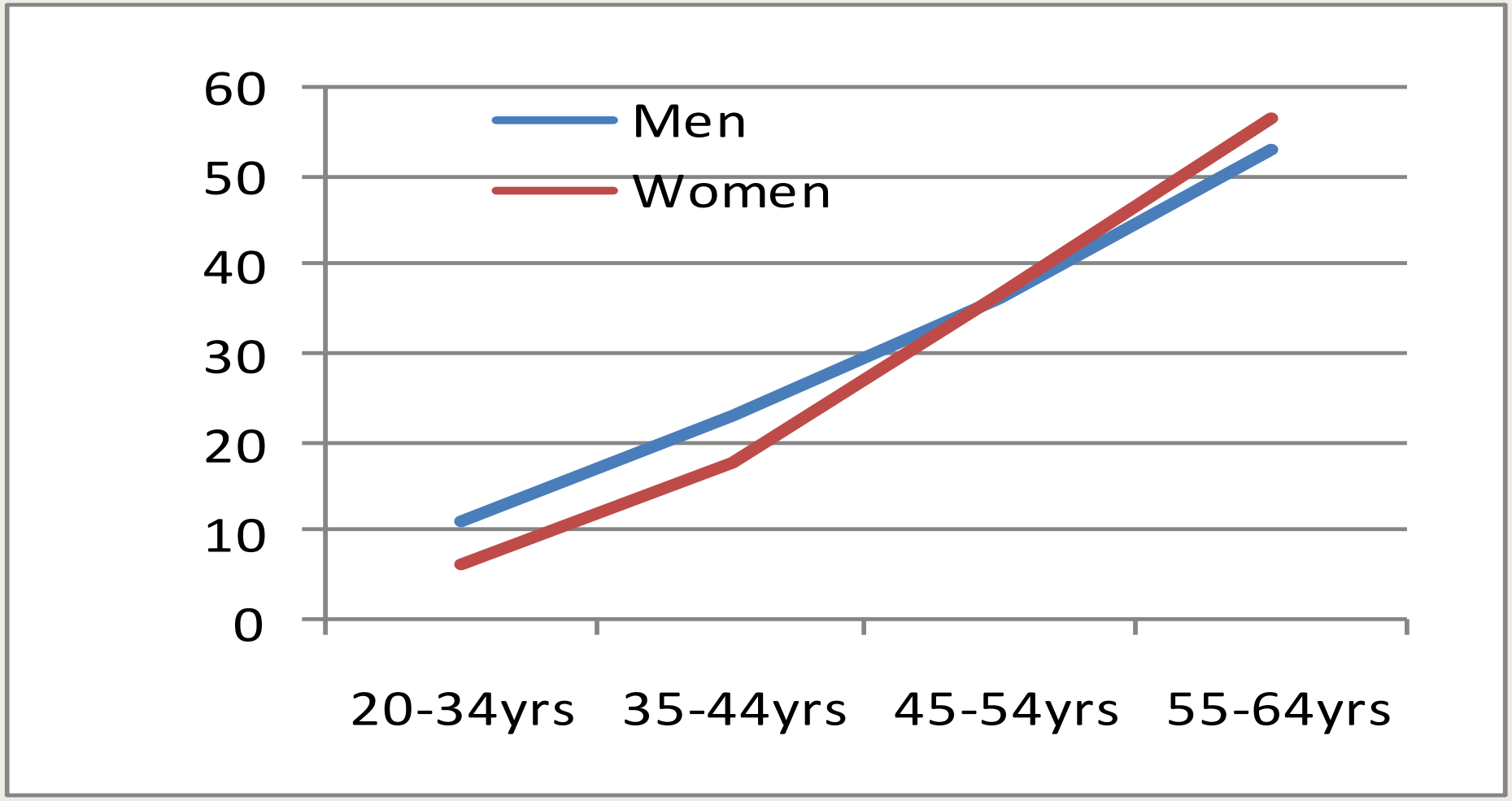
- HRT, especially if menopausal symptoms
- Bisphosphonates
- SERMs – if no menopausal Sx and low hip fracture risk

Late PM: 2º prevention

- Bisphosphonates, raloxifene, denosumab, PTH all licensed in UK for Rx
- HRT – low/ultra-low dose, transdermal if symptomatic

Cardio-vascular Disease

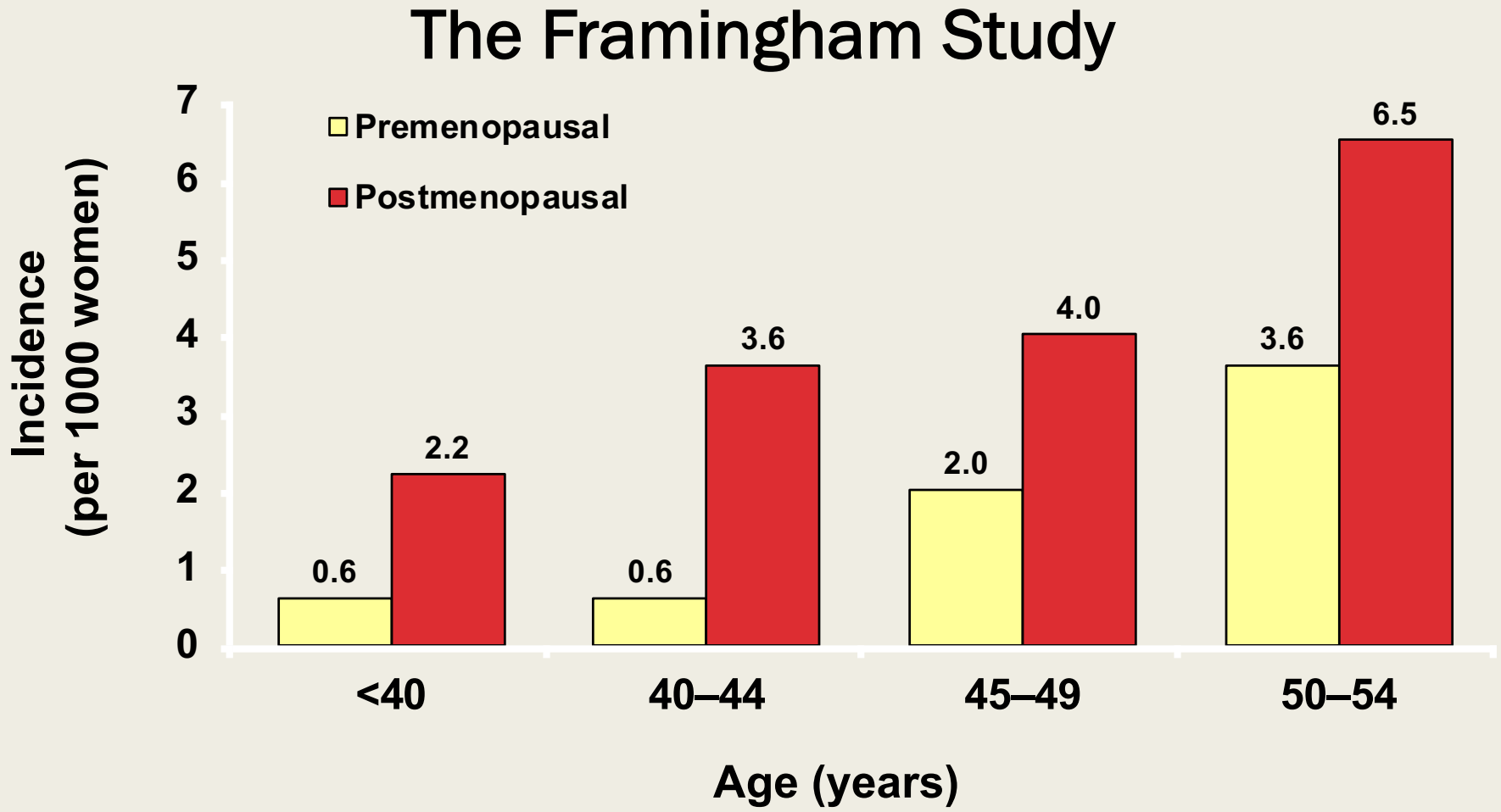
CVD in women



Hypertension

- Generally under-diagnosed and undertreated
- Prevalence in post menopause >2x cf premenopause
- High normal still a risk factor—increased CVD events cf men with Bp 140/90 and above
- 30-50% of menopausal women have high normal or high blood pressure
- NB history of hypertensive pregnancy disorders

Incidence of CVD: relation to menopause status



n = 2873

Kannel WB, et al. *Ann Intern Med.* 1976;85:447-52

What about HRT?

- Should be good!
- Favourable effects of estrogen on:
- BMI
- Lipids—total cholesterol, LDL, lipoprotein(a), HDL
- P may modulate effects on HDL and TGs
- Clearance of small dense LDL, postprandial lipid clearance, LDL oxidation at vessel wall
- Vascular function—calcium channels, ACE activity, smooth muscle proliferation
- Atheroma formation, vascular remodelling (dose dependant)

- Conflicting findings—observational studies and randomised trials

Further analyses of WHI

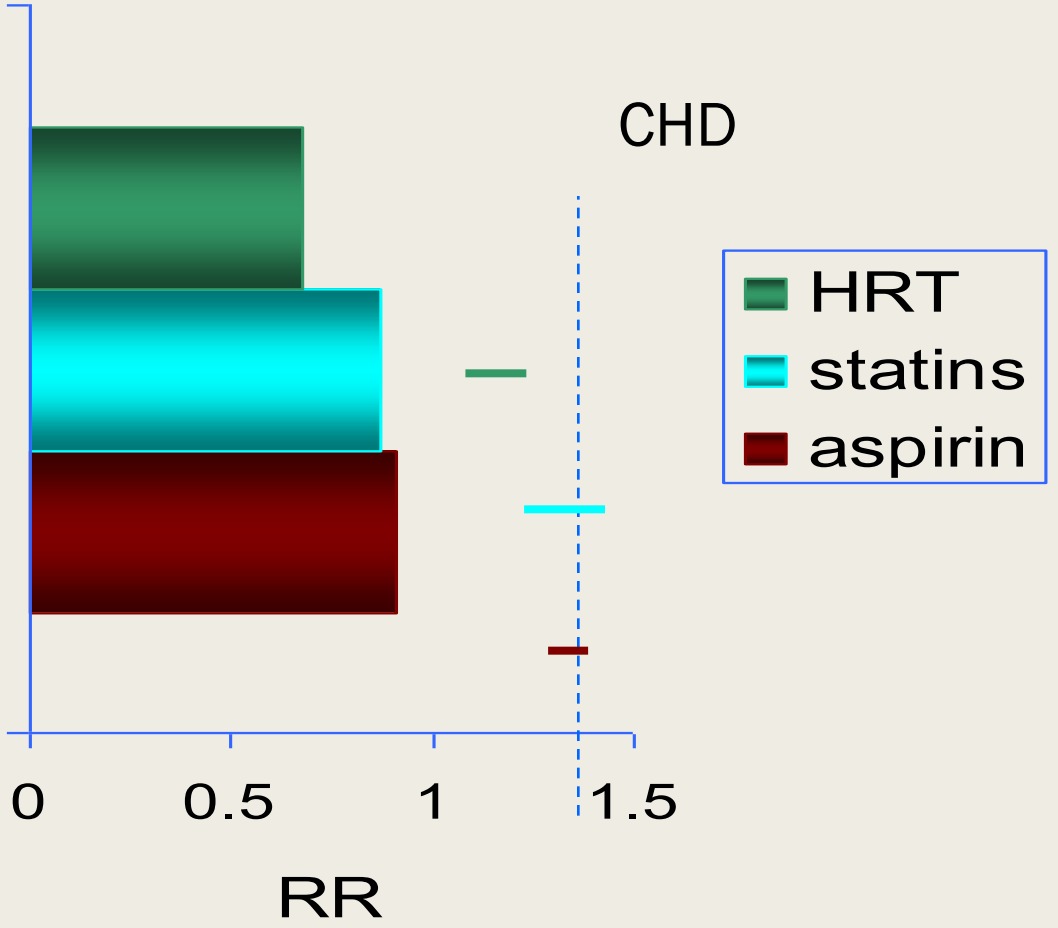
- Starting HRT within 10 years of menopause
  - *24 % reduction in CHD*
  - *30 % reduction in overall deaths*
- Slight increase in stroke risk at all ages
- Coronary artery calcium
  - *Mild-to-moderate 40% reduced*
  - *Severe 60 % reduced*

Timing

- Majority of women over 60
- Starting HRT under 60 per 1000 women over 7 years:
  - 6 fewer deaths
  - 8 fewer heart disease
  - 5 extra blood clots
- Staring HRT over 60
  - No significant reduction
  - No significant increase in cardiovascular events or mortality

CHD: primary prevention

- low-dose aspirin reduces CVA risk
- no reduction in CHD risk with low-dose aspirin
- no reduction in CHD mortality with statins
- reduction in CHD risk with HRT



Hodis and Mack. Menopause 2007; 14: 1-14

CVD--IMS

- *In women <60 years old, who are recently menopausal and with no evidence of cardiovascular disease, the initiation of estrogen-alone therapy reduces CHD and all-cause mortality*
- *The daily cc oral estrogen-progestogen data are less robust but other combined therapy regimens appear to be cardioprotective, as shown in Danish and Finnish studies*

2016 IMS Recommendations on Women's midlife health and menopause hormone therapy. Baber R et al. Climacteric 2016. Vol 19;2:109-150

Take Home Messages – Estrogen and the heart

- Estrogen is strongly cardioprotective in premature menopause
- Estrogen appears to protect the heart in women in their 50s who do not have established cardiovascular disease-Window of opportunity
- Women in their 60s with menopausal symptoms can safely be treated with HRT but if starting consider cardiovascular risk factors and use transdermal route
- Don’t stop HRT unnecessarily , especially before age 60
- Do stop HRT following a heart attack ??-No apparent increase adverse effect with HRT after MI (BMJ April 2012)

Risk of stroke with various types of menopausal hormone therapies

- Cohort Study
- 980,003 women aged 51-70
- 20,199 strokes (78% ischaemic)

- Risk increased with oral only (RH 1.16 , 1.12-1.22)
- No risk with transdermal at standard doses

Lokkegaard et al 2017

VTE risk & HRT

- Baseline risk for VTE 1.0 per 1,000 women per year (@50)
- Oral HRT – additional 1.5 events per 1,000 women per year
- May be different effect from doses and progestogen types – MPA higher risk, progesterone and dydrogesterone lower

- No significant increase with transdermal
- NICE recommends transdermal if BMI >30
- Transdermal over age 60

HRT and Dementia

- Women are more at risk of dementia than men
- HRT has no effect on the progress of established disease

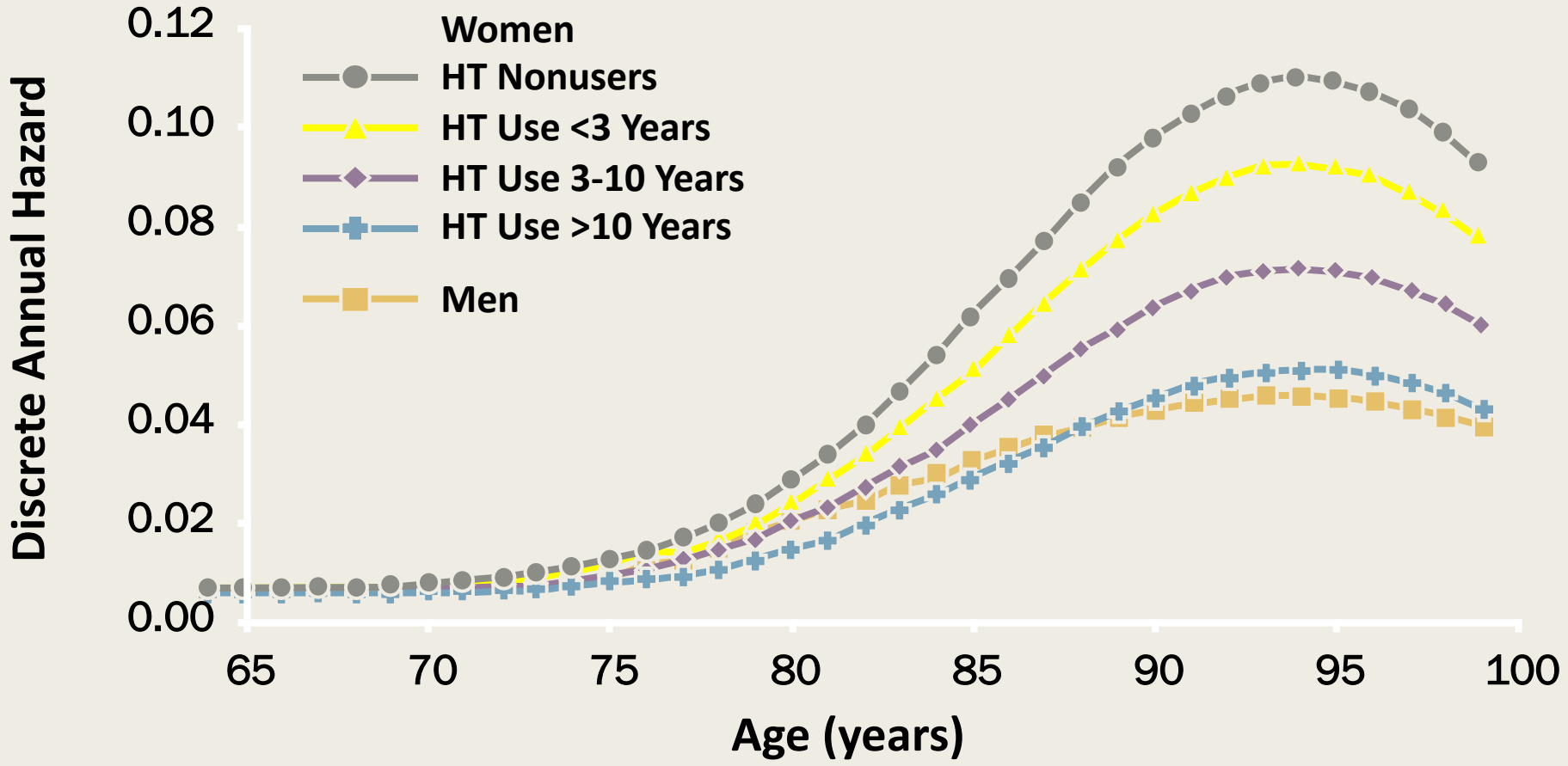
Can HRT prevent it?

– *Obs studies – suggest 'yes'*

– *RCTs (WHIMS / WHISCA) – say 'no'*

– *?? Related to timing of treatment*

Annual risk of AD for HT Users and Nonusers



Zandi PP, et al. *JAMA*. 2002;288:2123-9.

HRT and Dementia

■How does E affect the brain?

-GnRHa – leads to markedly reduced cognitive ability

– *Affects the cholinergic, serotonergic and dopaminergic systems*

- ■ Effects on memory and mood
- ■ E modulates brain function particularly around the menopause.

■BSO at an early age is assoc with an increased risk of AD and Patrkinson's disease

- ■ Rocca, 2007 Neurology

■Earlier use of HRT is associated with a reduced risk of developing AD

Estrogens and bladder

- Systemic HRT—mixed results
- Vaginal estrogen
- Will not cure stress incontinence when used alone
- Best effect on sensory symptoms - urgency, nocturia, frequency, dysuria
- Consider use in conjunction with diet and lifestyle, pelvic floor exercises, bladder training, anti-muscarinics

NICE Guideline NG123 2019

- Offer the anticholinergic medicine with the lowest acquisition cost to treat OAB or mixed UI in women.
- If the first medicine for OAB or mixed UI is not effective or well-tolerated, offer another medicine with a low acquisition cost.
- Offer a transdermal OAB treatment to women unable to tolerate oral medicines.
- Offer intravaginal oestrogens to treat OAB symptoms in postmenopausal women with vaginal atrophy.
- Do not offer oxybutynin (immediate release) to older women who may be at higher risk of a sudden deterioration in their physical or mental health.
- Do not offer flavoxate, propantheline or imipramine to treat UI or OAB.

Pelvic floor atrophy

- Estrogen deficiency leads to changes in collagen in pelvic floor
- Bulging of vaginal walls
- Descent of cervix
- Dragging sensation
- Shortened urethra
- UTIs and stress incontinence

Topical estrogen and prolapse

- ? Preventive role
- Restores thickness, elasticity and pH of vagina
- Improved strength and function of pelvic fascia, ligaments and muscles
- Use with pessaries
- Prior to surgery

Contraception

When to stop contraception

- Two years following the last spontaneous menstrual period if aged under 50
- One year following the last spontaneous menstrual period if aged 50 or over
- By age 54yrs - 80% are 1yr postmenopausal
- By age 55yrs - 96% are 1yr postmenopausal
- FSH >30 – suggest allow an extra year reserve for the over 50s.

Stopping contraception

- **If wanting to stop hormonal contraception before age 50,** switch to non-hormonal methods

- Stop once amenorrhoeic for 2 yrs
- Or 3 yrs if on DEPO due to potential delay in resumption of ovulation

Stopping contraception

Combined hormonal methods

UKMEC does not give an upper age limit but CEU does not recommend using >50yrs

- May have menopausal symptoms at end of pill free week or hormone free interval
- FSH measurement unreliable even at end of pill free week
- Alternative contraception needs to be considered

Stopping contraception

- Amenorrhoea not reliable indicator
- FSH measurements ? restricted to over 50yrs
- If needed, women over 50 using progestogen only contraception including DMPA can have FSH levels undertaken to check menopausal status *FSRH guidelines*
- If level >30 IU/L – contraception can consider stopping after 1 yr.

What about women with Primary Ovarian Insufficiency?

Points to consider:

- Is contraception needed or desired? Is ovarian function ever likely to return?
- Time since ovarian failure, age and causes are relevant
- All methods of contraception are potentially available
- CHC may be used as replacement therapy as well as contraception - free and in step with peers
- Sexual health likely to be in step with own age group, need to be advised accordingly

Which CHC may be a suitable option?

Qlaira

- The first COC to deliver estradiol valerate
- Potential for ↓ metabolic impact than COCs containing EE
- Good cycle control with high patient satisfaction
- Missed pill advice complicated due to the pill being tri phasic.
- 2 placebo pills

Zoely

- Estradiol 1.5mg daily monophasic COC pill.
- 4 placebo tablets.

Both products licenced only as contraceptives and NOT as HRT

So - when to start HRT?

- Women using COC methods will be protected from developing menopausal symptoms apart from during pill free week. FSH cannot be measured.

- Women on non hormonal contraception can commence HRT but if FSH not measured prior to starting contraception will need to be considered up until age 55

- Women on progestogen only contraception who develop menopausal symptoms can be commenced on HRT. Choice of sequential or continuous combined will depend on age and if she has amenorrhea. Consider FSH prior to commencing HRT.

HRT + contraception: summary points

- HRT is not contraceptive – ovulation may still occur
- COC use often masks onset of menopause
- If on HRT – impossible to assess if menopause has occurred (FSH unreliable)
- IUS is the only progestogen that provides contraception + progestogen element of HRT

Finally

- Thank you
- Any questions?

Resources

- British Menopause Society www.thebms.org.uk
- Menopause Matters www.menopausematters.co.uk
- www.bladdermatters.co.uk