PRIMARY CARE
WOMEN'S HEALTH FORUM

NICEr menopause management

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pcwhf.co.uk

Learning Objectives

- To be able to manage common problems arising from the use of HRT, including side effects
- Tailoring regimes to risk profiles

'I feel old Doc'

- *Farah is aged 52. She works at the local school and is struggling to cope with the work because she is so tired and feels so old.*
- *She is emotional on the phone - she has put up with her symptoms for the past 12 months but now she is really struggling*
- *On further questioning she admits that she is waking up several times each night sweating and is wet through.*
- *She finds it hard managing her class of 6 years olds and aches at the end of every day.*
- *She had to take time off last week when she had a panic attack in assembly.*

Farah

- Last period 8 months ago
- Keen to start HRT
- CVD risk – BMI 26, BP 112/66,
- VTE risk – non smoker
- Breast risk – low
- Contraception – sterilised
- FH – dad MI aged 65 years
- PMH – nil no medications

Resources: www.pcwhf.co.uk/resources

Managing the Menopause

- Holistic approach
- Information -
  - www.rockmymenopause.com
  - www.menopausematters.co.uk
- Lifestyle advice opportunities
- PLUS information about options:
  - Complimentary and Alternative therapies
  - Other prescription drugs
  - Vaginal Oestrogens
  - HRT
  - Bisphosphonates/Statins etc

HRT - Individualise care

- Is there a need– symptom/ risk assessment
- Check medical history- rule out contraindications
- Outline potential benefits
- Personalise risk
- Prepare for side effects
- Decide which preparation is required
- Provide information to enable choice

What to consider

- Gynae/menstrual issues
- Contraceptive needs
- Breast history
- CVD risk
- VTE risk
- Endometrial risk
- Bone risk

Resources: www.pcwhf.co.uk/resources

Absolute contraindications – BNF

- Breast cancer – current/past
- Oestrogen sensitive tumour – endometrial cancer
- VTE – current/past
- Liver disease – abnormal LFT
- Thrombophilic disorders
- Active arterial thromboembolic disease
  - MI
  - Angina
  - Stroke

Resources: www.pcwhf.co.uk/resources

Which HRT?

- Which hormones?
- Which regimen?
- Which route?
- Which dose?

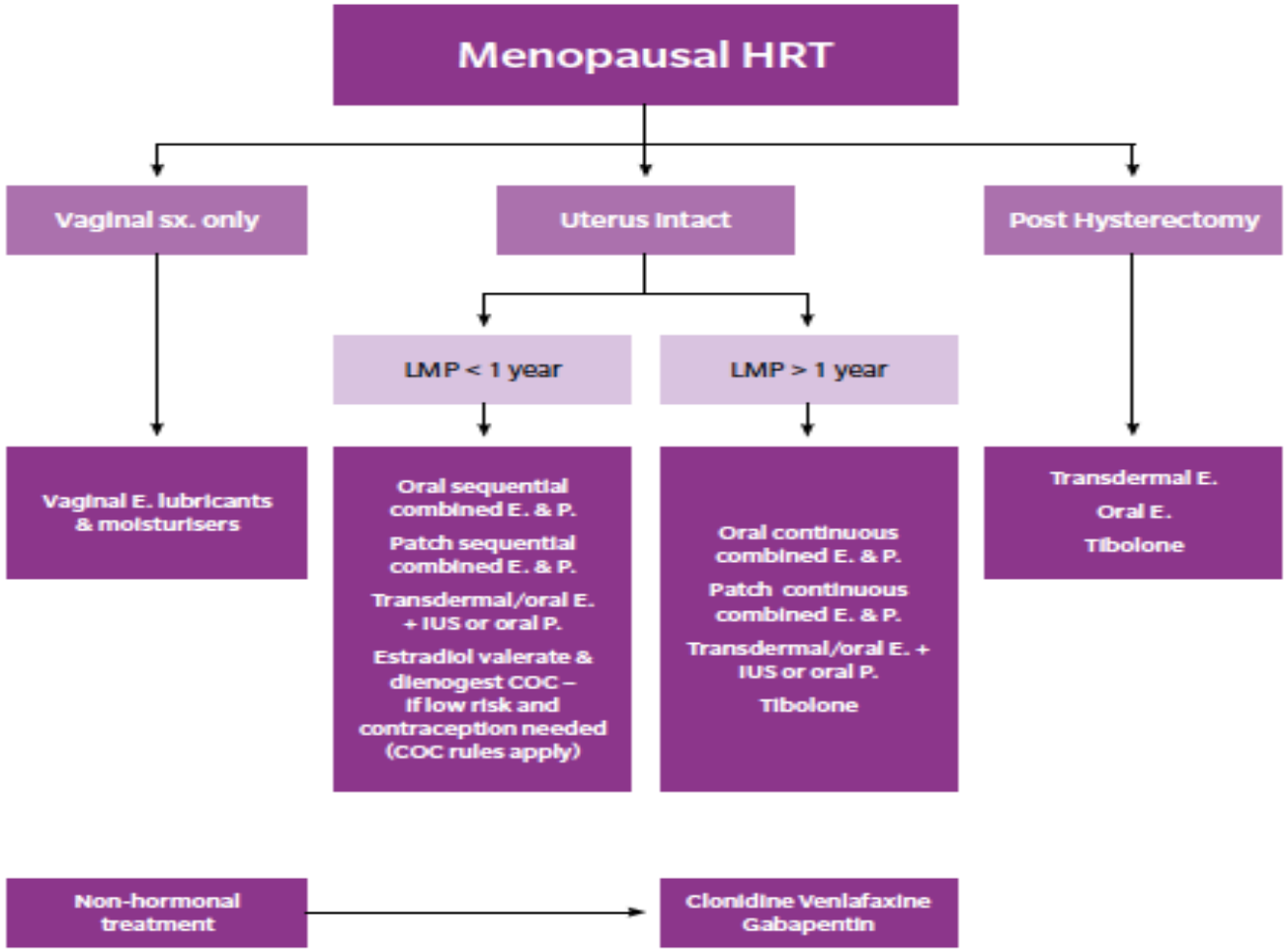
Resources: www.pcwhf.co.uk/resources

Farah

- What HRT is your first choice?
  - Sequential HRT
  - Continuous combined HRT

Resources: www.pcwhf.co.uk/resources

Which Regimen?



Which hormones?

HRT	TABLETS*	2ND LINE*	TRANSDERMAL*
SEQUENTIAL PREPARATIONS For patients with: • Intact uterus • perimenopausal-under 1yr or amenorrhoea	**Estradiol 1mg + Norethisterone sequential** **Estradiol 2mg + Norethisterone sequential**	**Estradiol + Dydrogesterone 1/10mg sequential** **Estradiol + Dydrogesterone 2/10mg sequential** (Non-androgenic)	**Estradiol 50mcg + Levonorgestrel 10mcg SEQUI patch** **Estradiol 50mcg + Norethisterone 170mcg SEQUI patch**
CONTINUOUS COMBINED Bleed free HRT use if: • Over 1yr since last period • >54y • >3yrs on sequential HRT	**Estradiol 2mg + Norethisterone 1mg CONTI** **Estradiol 0.5mg + Dydrogesterone 2.5mg CONTI** **Estradiol 1mg + Dydrogesterone 5mg CONTI**	**TIBOLONE 2.5mg** Can be useful if: • Bloating on oestrogen • Poor libido • Endometriosis	**Estradiol 50mcg + Levonorgestrel 7mcg CONTI patch** **Estradiol 50mcg + Norethisterone 170mcg CONTI patch**
UNOPPOSED OESTROGEN Post hysterectomy	**Estradiol 1mg tablets** **Estradiol 2mg tablets**		**ESTRADIOL PATCH** 25mcg, 37.5mcg, 50mcg, 75mcg, 100mcg **Estradiol 0.06% gel** **Estradiol 500mcg or 1mg gel sachets**
TOPICAL VAGINAL OESTROGEN			**Estradiol 10mcg** vaginal pessaries **Estriol 0.1% CREAM** Estradiol vaginal ring
PROGESTOGEN ADJUNCT TO TOPICAL OESTROGEN IF NO HYSTERECTOMY	**Medroxyprogesterone** 10mg d14-28 or 2.5-5mg daily~ **Micronised progesterone** 200 mg d14-28 or 100mg daily~	**Levonorgestrel intrauterine system 52mg** Replace after five years as per FSRH guidance	

NICE Guidelines: REVIEW AND REFERRAL

- At 3 months to assess efficacy and tolerability
- Annually thereafter unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events).

Resources: www.pcwhf.co.uk/resources

Farah: 3 month review

- BP is now 135/76
- BMI 27
- C/o headaches and breast pains– keen to try another HRT
- Currently taking HRT containing 2mg EE and 1mg NE

What are your options?

Resources: www.pcwhf.co.uk/resources

HRT side effects

Oestrogen:

- Headache
- Nausea/indigestion
- Bloating/fluid retention
- Breast tenderness
- Leg cramps

Options:

- Reduce dose
- Change route
- Change type

Which dose?

	Ultralow	Low	Medium	High
Oral	0.5mg	1mg	2mg	3-4mg
Patch	Half 25	25	50	75-100
Gel - pump	Half pump	1 pump	2 pumps	3-4 pumps
Gel - sachet	Half x 0.5mg sachet	0.5mg	1-1.5mg	2-3mg
Spray	1 spray	2 sprays	3 sprays	

HRT side effects

Progestogen:

- Headache
- Fluid retention
- Breast tenderness
- Acne
- Depression
- PMS type symptoms

Options:

- Change type
- Change route
- Reduce dose (if possible)
- Change duration

TYPE OF PROGESTOGEN	GOOD FOR	WATCH OUT FOR	PRESCRIBED AS
SYNTHETIC: C19 TESTOSTERONE DERIVATIVES			
Norethisterone	Cycle control Androgenic – good for libido	Some degree of estrogenic effect caution if VTE risk ++	E2/Net fixed combined tablet/patch or as stand alone
Levonorgestrel As IUS	Cycle control Low systemic absorption Excellent contraception Good for HMB	Androgenic effects (acne, mood) PMS	52mg LNG IUS Or In combined patch
SYNTHETIC: C21 PROGESTERONE DERIVATIVES			
Medroxyprogesterone acetate	Cycle control	Caution if VTE risk +	SCHRT – E2 plus 10-20mg cyclically CCHRT- E2 plus 5mg conti Or fixed dose in oral
Dydrogesterone	Non-androgenic so good if PMS type side effects	Only available with oral oestrogen	Oral fixed dose Sequential (including low dose) or combined
Natural progesterone: Micronised progesterone	Fewer progestogenic side effects No androgenic or glucocorticoid activity No impact on lipids	Less effective cycle control Take at night as may cause sedation	Sequential – 200mg cyclically Or Continuous 100mg daily

Farah: 12 month review

- Symptoms are better but she is fed up with periods

- BP 133/67, BMI 30 – no other changes

What are your options?

Resources: www.pcwhf.co.uk/resources

Farah: Next Annual Review

- BP 142/67
- Non smoker
- BMI 33
- Side effects settled
- She asks about her breast cancer risk.

Resources: www.pcwhf.co.uk/resources

What do you say?

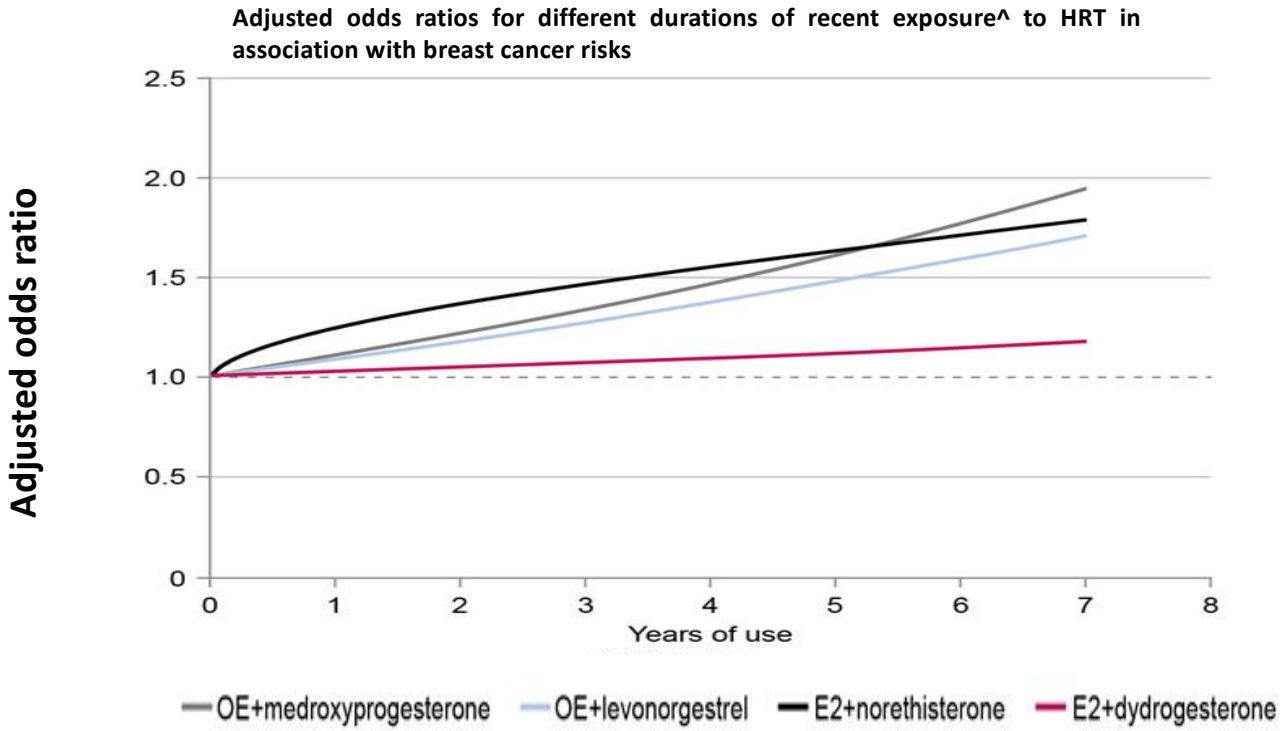
So what about breast cancer?

- Most common female cancer
- Lifetime risk is one in nine (up to 85 years)
- 80% diagnosed in women older than 50 years
- HRT with oestrogen and progestogen is associated with an increase in risk of breast cancer
- **No** increased risk of death from breast cancer
- Other life choices higher risk including alcohol and obesity

Breast Cancer Risks - NICE

www.thebms.org.uk

Breast cancer risk over time

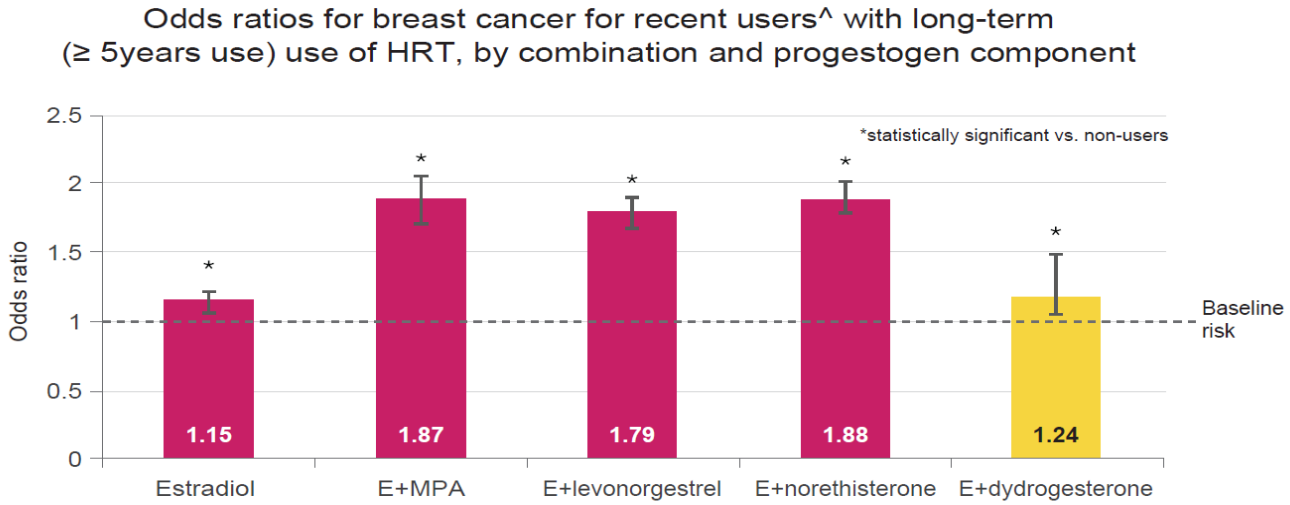


Different types of HRT showed varying patterns of increased breast cancer risks with time.

Amongst the combined HRT preparations, **estradiol-dydrogesterone** formulations showed the slowest rate of increase.

Vinogradova Yana,CouplandCarol,Hippisley-CoxJulia.Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databasesBMJ2020;371:m3873

Breast cancer risk – different progestogens



^Recent users is defined as those with prescriptions more than one year and less than five years before the index date.
E: Estrogen; MPA: Medroxyprogesterone acetate.

Vinogradova Yana, Coupland Carol, Hippisley-Cox Julia. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2020; 371 :m3873

Wendy, aged 53

- Struggling with symptoms, last period just over a year ago
- CVD risk - BP 132/84
- VTE risk – Smoker, BMI 35
- PMH – gestational diabetes but HbA1C normal, meds – sertraline.
- Keen to start HRT
- Only wants a tablet (fits her lifestyle)

What are the options?

What do we know?

- Is she at increased risk of VTE?
- Contraception?
- Severity of symptoms?
- Any bleeding

- Family History
- Previous VTE
- Hereditary thrombophilia
- Obesity (BMI>30)
- Major Surgery
- Multiple physical trauma
- Immobilisation
- Increasing age
- Cardiac or respiratory failure
- Malignancy

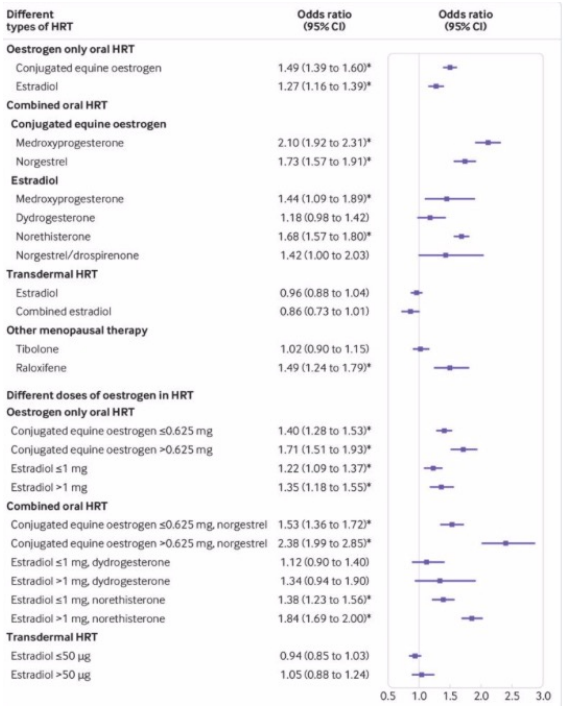
HRT and VTE

thebmj Research Education News & Views Campaigns Archive

Research

Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases

BMJ 2019 ; 364 doi: https://doi.org/10.1136/bmj.k4810 (Published 09 January 2019)
Cite this as: *BMJ* 2019;364:k4810



Different types of HRT	Odds ratio (95% CI)
Oestrogen only oral HRT	
Conjugated equine oestrogen	1.49 (1.39 to 1.60)*
Estradiol	1.27 (1.16 to 1.39)*
Combined oral HRT	
Conjugated equine oestrogen	
Medroxyprogesterone	2.10 (1.92 to 2.31)*
Norgestrel	1.73 (1.57 to 1.91)*
Estradiol	
Medroxyprogesterone	1.44 (1.09 to 1.89)*
Dydrogesterone	1.18 (0.98 to 1.42)
Norethisterone	1.68 (1.57 to 1.80)*
Norgestrel/drospirenone	1.42 (1.00 to 2.03)
Transdermal HRT	
Estradiol	0.96 (0.88 to 1.04)
Combined estradiol	0.86 (0.73 to 1.01)
Other menopausal therapy	
Tibolone	1.02 (0.90 to 1.15)
Raloxifene	1.49 (1.24 to 1.79)*
Different doses of oestrogen in HRT	
Oestrogen only oral HRT	
Conjugated equine oestrogen ≤0.625 mg	1.40 (1.28 to 1.53)*
Conjugated equine oestrogen >0.625 mg	1.71 (1.51 to 1.93)*
Estradiol ≤1 mg	1.22 (1.09 to 1.37)*
Estradiol >1 mg	1.35 (1.18 to 1.55)*
Combined oral HRT	
Conjugated equine oestrogen ≤0.625 mg, norgestrel	1.53 (1.36 to 1.72)*
Conjugated equine oestrogen >0.625 mg, norgestrel	2.38 (1.99 to 2.85)*
Estradiol ≤1 mg, dydrogesterone	1.12 (0.90 to 1.40)
Estradiol >1 mg, dydrogesterone	1.34 (0.94 to 1.90)
Estradiol ≤1 mg, norethisterone	1.38 (1.23 to 1.56)*
Estradiol >1 mg, norethisterone	1.84 (1.69 to 2.00)*
Transdermal HRT	
Estradiol ≤50 µg	0.94 (0.85 to 1.03)
Estradiol >50 µg	1.05 (0.88 to 1.24)

- Review GP records – women with primary diagnosis VTE.
- Significant risk of VTE in women exposed to oral HRT within 90 days.
- No increase VTE risk in women using trans-dermal HRT

Conclusion:

- Transdermal HRT safest option

MHRA Risk Guide

Medicines & Healthcare products Regulatory Agency

MHRA

Table 1: Summary of HRT risks and benefits* during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT

	Risks over 5 years use (with no use or 5 years current HRT use)		Total risks up to age 69 (after no use or after 5 years HRT use†)		Risks over 10 years (with no use or 10 years current HRT use)		Total risks up to age 69 (after no use or after 10 years HRT use†)	
	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT
Risks associated with **combined estrogen-progestogen HRT**								
Breast cancer	13	+8	63	+17	27	+20	63	+34
Sequential HRT	13	+7	63	+14	27	+17	63	+29
Continuous combined HRT	13	+10	63	+20	27	+25	63	+40
Endometrial cancer							10	-
[illegible] cancer	2	+ <1	10	+ <1	4	+1	10	+1
Venous thromboembolism (VTE)‡	5	+7	26	+7	8	+13	26	+13
Stroke	4	+1	26	+1	8	+2	[illegible]	[illegible]
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	1.5	-	12	-	1	-	12	-
Risks associated with **estrogen-only HRT**								
Breast cancer	13	+3	63	+5	27	+7	63	+11
Endometrial cancer	[illegible]				[illegible]	[illegible]	10	+32
[illegible] cancer	2	+ <1	10	+ <1	4	+1	10	[illegible]
Venous thromboembolism (VTE)‡	5	+2	26	+2	10	+3	26	+3
Stroke	4	+1	26	+1	8	+2	[illegible]	[illegible]
Coronary heart disease (CHD)	14	-	88	-	28	-	88	-
Fracture of femur	0.5	-	12	-	1	-	12	-

*Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT.

†Best estimates based on relative risks of HRT use from age 50 (see table 2 for relative risks). For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use.

‡Latest evidence suggests that transdermal HRT products have a lower risk of VTE than oral preparations.

Resources: www.pcwhf.co.uk/resources

Available from: MHRA https://assets.publishing.service.gov.uk/media/5d680409e5274a1711fbe65a/Table1.pdfHRT Accessed October 22 hormone replacement therapy

'I can't sleep Doc'

- *Gemma is a 38 year old fitness instructor . She is attending your clinic for her asthma review*
- *She complains about not being able to sleep.*
- *She started with this problem 3 months ago and now she is really fed up.*
- *On further questioning she admits that she is waking up several times each night sweating and she has to change her nightie regularly because it is wet through.*
- *She feels 'old and tired'.*

Premature Ovarian insufficiency (POI)

Classified as menopause before age 40

1% women under 40

0.1% under 30

Important to diagnose, investigate appropriately and pro-actively manage.

Gemma should be treated with 'oestrogen replacement'

Making a diagnosis of POI

- Diagnostic criteria:
  - Oligo/amenorrhoea for at least 4 months and
  - An elevated FSH > 30IU/l on two occasions at least 4 weeks apart
- Symptoms are more important than FSH levels
- Routine anti-Mullerian hormone testing is not recommended

Treatment

- Issues:
  - May need referral to exclude other causes
  - May need higher dose of oestrogen to control her symptoms
  - May have more problems with reduced libido
  - Don't forget contraception requirements
  - May need psychological support

  - If using seq combined HRT need to change to continuous combined after approx. 2 years

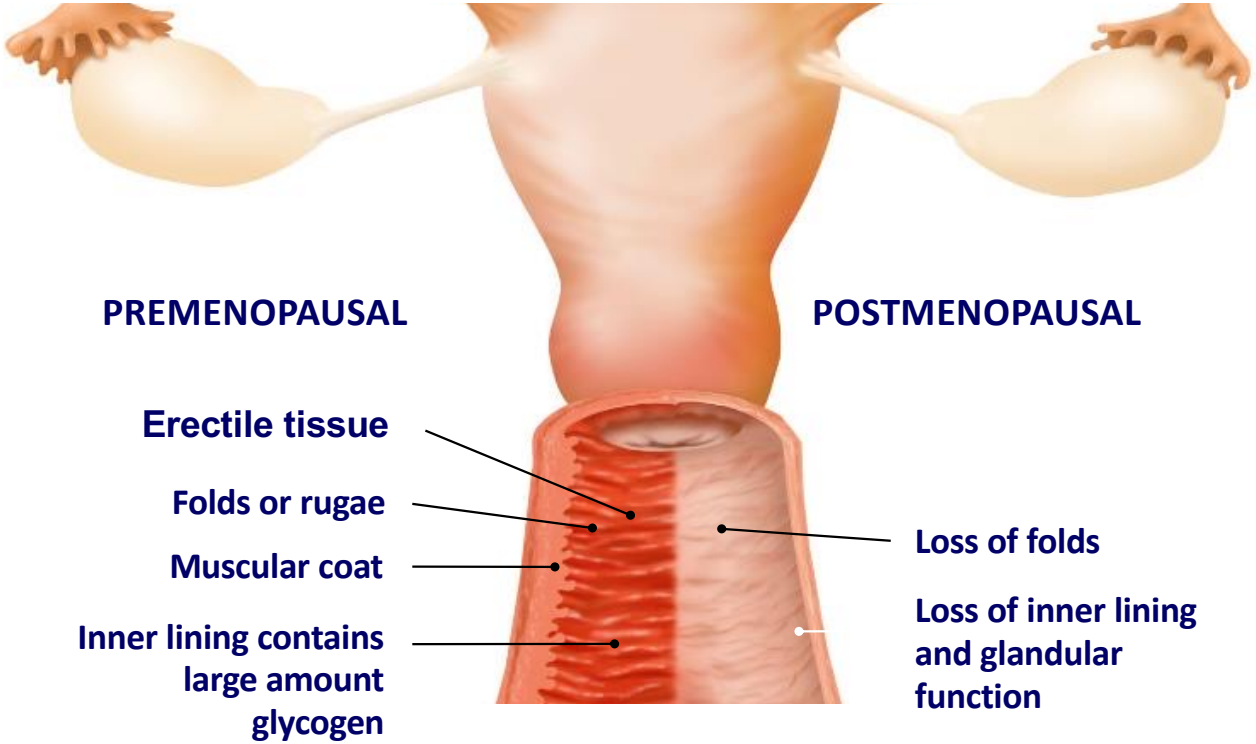
'It hurts Doc'

- *Molly is a 58 year old who had attended to her routine smear. She is nervous because last time she found the speculum very painful.*
- *On further questioning she bursts into tears and tells you she is struggling with sex because it feels like a 'hot poker'. She does her best to avoid any time in bed with her husband, Arthur. She has started going to bed early and gets up early to avoid any contact.*
- *Arthur doesn't understand what the problem is and they have had some arguments about this.*

Genito-urinary syndrome of the menopause (GSM)

- Very common
  - Approx 80% of post-menopausal women
  - Huge taboo
- At least a third of women do not seek medical advice
- Around 50% of women have symptoms for more than 3 years before asking for help

Vaginal epithelium



Samsioe G. *A profile of the Menopause,* 1995:49 (Figure 6.4)

Genito-urinary syndrome of the menopause (GSM)

- **Vaginal atrophy symptoms**
  - Dryness
  - Dyspareunia
  - Vaginal itching
  - Vaginal discharge
  - Vaginal pain
  - Burning

- **Urinary tract symptoms**
  - Dysuria
  - Nocturia
  - Increased urgency
  - Urinary incontinence
  - Recurrent UTIs

Vaginal preparations

BRAND NAME	INGREDIENT	STRENGTH	DOSAGE	COST[1]
VAGIFEM® VAGIRUX®	Estradiol pessary	10mcg	1 every night 2 weeks the twice weekly	£16.72 (24) £11.34 (24)
ESTRING®	Estradiol ring	7.5mcg per 24 hours for 90 days	Change after 90 days (2yrs)	£31.42
OVESTIN®	Estriol cream	1mg in 1g (0.1%)	1 Applicatorful (500mcg) for max 4 weeks then 2x weekly	£4.45 (15g)
BLISSEL®	Estriol gel	5mcg/g (0.005%)	Applicatorful (50mcg) 3wks then 2x weekly	£18.90 (30g)
IMVAGGIS®	Estriol pessary	30mcg	Pessary every night for 3 weeks then 2x weekly	£13.38 (24)

1. All drug prices listed on this page can be found at https://bnf.nice.org.uk/drug/ . Prices were correct as of March 2022

Local estrogen treatments

- Low dose vaginal estrogens are safe to use AS LONG AS NEEDED
- Note 'class effect' warnings on insert
- Safe on repeat prescription
- Can give with HRT
- Many women need lubricants/moisturisers too
- Do not need to give progestogens

Learning points

- Menopause can affect women in different ways and some have severe symptoms which interfere with their physical, social, psychological and sexual abilities to function.
- Individualise menopause management and address lifestyle risks
- Do not check FSH routinely
- HRT is safe for most women – recent breast cancer data needs further understanding.
- Women with POI need oestrogen replacement till age 51
- Topical oestrogens have little systemic absorption & need to be used long term
- Don't forget contraception (and HRT is not a contraceptive!)

PRIMARY CARE
WOMEN'S HEALTH FORUM

Thank you

Questions?