

Declaration of Financial Interests or Relationships

Speaker Name: DEIRDRE LUNDY

I have the following financial interest or relationship(s) to disclose with regard to the subject matter of this presentation:

Speaker for: Mylan, Bayer, Consilient, MSD, Amgen

Definitions and Terms

The "MENOPAUSE" is defined as the LAST day of the LAST menstrual period and so can only be identified retrospectively. It is the post reproductive phase of a woman's life aka "reproductive senescence"

But patients & HCP's all use the term "In the Menopause" or "In the Change" to identify the symptomatic phase of the transition from fertile to post fertile stage of life

More correctly WE should use the term **Peri menopause** or **Climacteric**

PERIMENOPAUSE or "CLIMACTERIC"

"MENOPAUSE TRANSITION"

Symptoms often precede Final Menstrual Bleed by Years but typically in 40's.

Don't out rule menopause just because patient still has periods so

Often juggling Contraception needs and Menopause symptoms

The Stigma of Menopause

Women are living longer and can often spend as much time in the post reproductive phase of their lives as they did in the first 50 years! Throughout history we see negative associations surrounding the menopause & later life

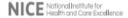




We as clinicians can have a positive impact on the approach of the second 50 years!



Menopause Consultations are becoming more common lately





Menopause: diagnosis and management

NICE guideline Published: 12 November 2015 nice.org.uk/guidance/ng23

- •NICE finally published the comprehensive guidelines for the Management of Menopause Disorder and Prescribing HRT 2015
- Nothing New in it actually
- •Same criticisms of the WHI and our response to it
- * Reassurances again about early intervention and long term use



What happens at the Peri Menopause?

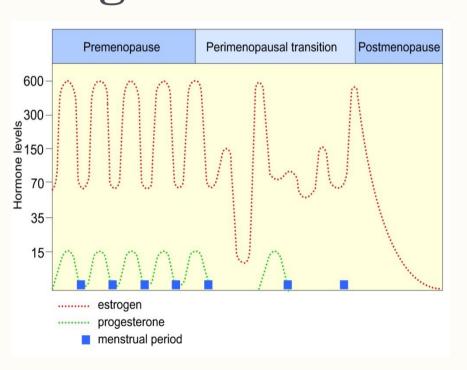
The menstrual cycle in the early/pre Menopause Transition

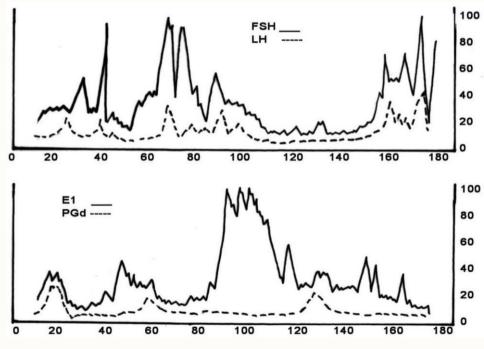
- The antral follicle count drops as menopause approaches
 (AMH levels become undetectable within 5 years of the FMP)
- The lower amount of granulosa cells means less Inhibin B is produced
- Less Inhibin B means less negative feedback on the pituitary and FSH levels rise in the early follicular phase which results in
- Multiple dominant follicle development (or overactive single dominant follicles) and this creates
- More E2 in the early follicular phase so the LH surge occurs earlier, ovulation occurs earlier so the Cycle is SHORTENED

Hormonal Changes During Menopause Transition

- Accelerated follicle development starts at 37-38 yrs and the antral follicle count drops
 (AMH levels become undetectable within 5 years of the Final Menstrual Period)
- The lower amount of granulosa cells means less Inhibin B which causes less negative feedback on the pituitary and FSH levels rise in the early follicular phase which results in
- FSH ↑ 20-40 X.... But this is unpredictable & may fluctuate
- LH ↑ 20 X
- Circulating levels of Oestradiol fall to 10-20 pg/ml
- Dominant circulatory estrogen becomes oestrone most of which is derived from peripheral conversion of androstenodione in fatty tissue
- Testosterone levels fall by 25%
- Androgen : Estrogen ratio increases

Why Peri menopausal Sex Hormone Levels aren't an acceptable diagnostic tool







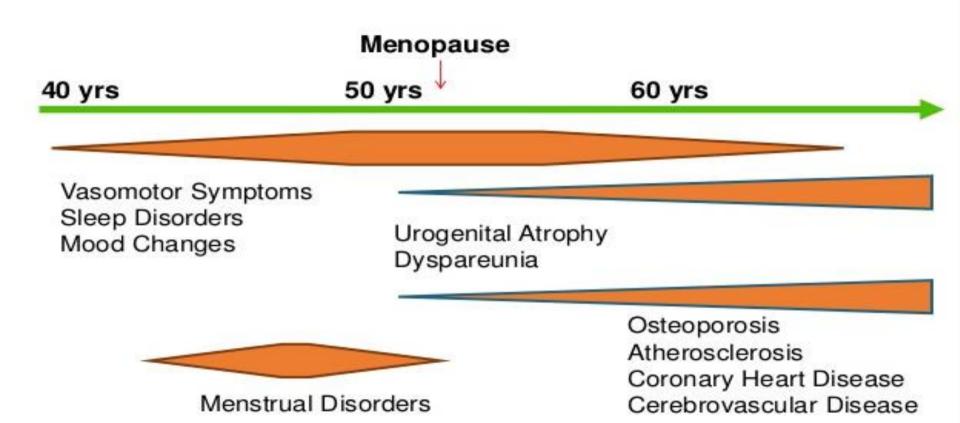
PERI-MENOPAUSAL SYMPTOMS

PHYSICAL

- NIGHT SWEATS &
- HOT FLUSHES
- MENSTRUAL CHANGES: Menorrhagia, Irregularity
- LOSS OF VAGINAL ELASTICITY & LUBRICATION
- DECREASE IN METABOLISM
- Increase in incidence of METABOLIC SYNDROME
- HAIR & SKIN CHANGES
- JOINT COMPLAINTS
- BLADDER COMPLAINTS

EMOTIONAL

- DEPRESSION,
- MOOD SWINGS
- ANXIETY
- TIREDNESS
- MEMORY LOSS
- CONCENTRATION LOSS
- LOSS OF LIBIDO
- PMS-TYPE SYMPTOMS



MANAGEMENT OF THE PERI MENOPAUSE

- Take a thorough history and ALWAYS ENQUIRE DIRECTLY ABOUT
 Incontinence
 Sexual Dysfunction
- EXCELLENT OPPORTUNITY FOR A GENERAL MEDICAL EXAMINATION but not necessary prior to Rx HRT

Blood pressure, BMI Optional Breast/ Pelvic examination +/- SMEAR TEST and MAMMOGRAPHY if required

COUNSEL AND ADVISE wrt
 Diet & Exercise, Contraception, Health Screening

Offer the OPTION OF HORMONE REPLACEMENT THERAPY

HORMONE REPLACEMENT THERAPY 'HRT'

Replacing the FALLING levels of endogenous Oestrogen with small doses of exogenous Oestrogen+/-additional Progestagen

HRT & MISINFORMATION

> 50 % of women say their symptoms are SEVERE

But

Patients either don't attend at all or refuse to even discuss HRT because of the general consensus that HRT causes Breast Cancer (among other things)

This fear is NOT supported by reliable data.

So let's look at that data:

HRT: BENEFITS vs UNCERTAINTIES

Worries about HRT are based on three main studies:

1. Heart Estrogen/Progestin Replacement Study (1998: USA)

2. Women's Health Initiative (2002: USA)

&

3. Million Women Study (2003: UK)

WOMENS HEALTH INITIATIVE (WHI) USA JAMA 2002

- Largest randomised clinical trial

(> 68,000 women) conducted to determine if older, post menopausal women might obtain Cardiovascular, Malignant & Osteoporosis Disease Protection from HRT

- Should have been higher quality study than the other two (Level I Evidence)

WHI

BUT....

Enrolees were aged from 50-79 (average 63yo with only 3.5 % of participants were in 50-54 group)

Women with severe symptoms were excluded.

Women with previous serious CVD were included.

Only used CEE .625mg (E only) for the hysterectomised ladies (WHI- ERT arm) or CEE .625mg + MPA 2.5mg (E+P) for the non- hysterectomised (WHI- PERT arm)

WHI BREAST CANCER DATA

WHI initially concluded that Breast Cancer Rates in relation to HRT were:

- Never used	16 cases/ 1000 women/ 5 yrs treatment
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- E only	16 cases/1000 women/5 yrs treatment
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- EE+ MPA...... 20 cases/1000 women/5 yrs treatment

.. risk returns to normal within 5 years of discontinuing

RATES OF PRE INVASIVE BREAST CA & BREAST CA MORTALITY WERE THE SAME FOR PLACEBO & HRT GROUPS

When they published this breast cancer data they wrote that:

'a small increased RR in Breast CA (1.26) was observed which did not reach statistical significance'

(Similar to what we saw in the MWS & what we were already telling the patients)

 BUT the following year a JAMA editorial reported the WHI study demonstrated that

Breast CA rates were "markedly increased" in the HRT group!

How did that happen!?

Relative Risk of Breast Cancer as seen in Meta analyses

Relative risk data can seem more important than they are.

Which of the following gives women the least relative risk of developing breast cancer?

- -Eating one serving of French fries every week.
- -Eating more than a quarter of a grapefruit every day.
- -Working night shifts.
- -Taking antibiotics.
- -Using an electric blanket if you are an African American.
- -Taking estrogen- only HRT to alleviate the effects of menopause; WHI data

Of course.... HRT is the "safest"

FACTOR/ Study	
HRT (Conj EE) WHI 2002	
FRIES International Journal of Cancer 2006	1.27
GRAPEFRUIT British Journal of cancer 2007	
NIGHT SHIFT WORK European Journal of Cancer 2005	
ANTIBIOTIC USE JAMA 2004	
ELECTRIC BLANKET USE American Journal of Epidemiology 2003	

Understanding the risks of breast cancer



A comparison of lifestyle risk factors versus Hormone Replacement Therapy (HRT) treatment.

Difference in breast cancer incidence per 1,000 women aged 50-59.

Approximate number of women developing breast cancer over the next five years.

Control Management

23 cases of breast cancer diagnosed in the UK general population

An additional four cases in women on combined hormone replacement therapy (HRT)

Four fewer cases in women on destrogen only Hormone Replacement Therapy (HRT)

++++++++++++++++++++++++++

An additional four cases in women on combined hormonal contraceptives (the pill)

An additional five cases in women who drink 2 or more units of alcohol per day

Three additional cases in women who are current smokers

An additional 24 cases in women who are overweight or obese (BMI equal or greater than 30)

Seven fewer cases in women who take at least21's hours moderate exercise per week



Women's Health Concern is the patient arm of the BMS.
We provide an independent service to advise, reassure and educate women
of all ages about their health, wellbeing and lifestyle concerns.

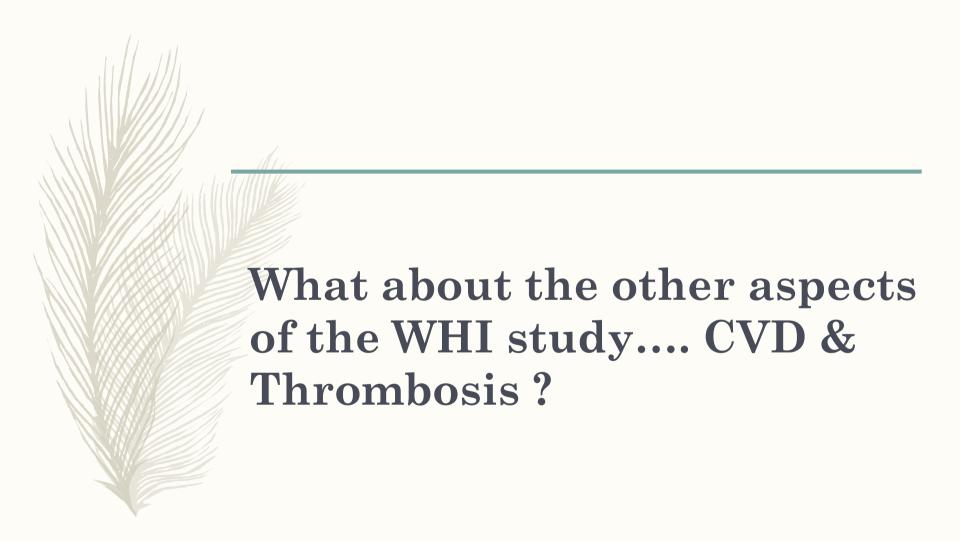




So what do we tell the patients?

- HRT USE BEFORE THE AGE OF 50 YO CARRIES NO ADDITIONAL RISK OF BREAST CA
 DETECTION (don't discourage access to HRT to the younger patients particularly those who go through PREMATURE MENOPAUSE)
- HRT USE BETWEEN 50-54 YOA IS LINKED TO A SMALL ADDITIONAL RISK OF BREAST CA
- HRT USE OVER 54 YOA IS LINKED TO AN INCREASED BREAST CA RISK-going from 30 cases/10,000 women who
 never used it to 38 cases/10,000women
 - (Keep the dose low –minimum effective for symptoms. Mind the type(s) you prescribe:?tibolone, 17 beta, Dydro, Neta, Drospir vs MPA??, and the routes of administration, transdermal??)
- EXAMINE REGULARLY
- REMEMBER ...MORE WOMEN DIE FROM OSTEOPOROTIC FRACTURE-RELATED DISEASE THAN FROM CANCERS OF THE BREAST, UTERUS & CERVIX COMBINED...BUT OFTEN NOT LISTED ON DEATHS CERTS

Mortality after admission to hospital with fractured neck of femur: database study



WHI + Cardiovascular SUMMARY

Rossouw JAMA 2007

EFFECTS PER 10,000 WYRS of E only Use:

10 Fewer DEATHS

10 Fewer CHD Events

2 Fewer STROKES

EFFECTS PER 10,000 WYRS of E+P Use:

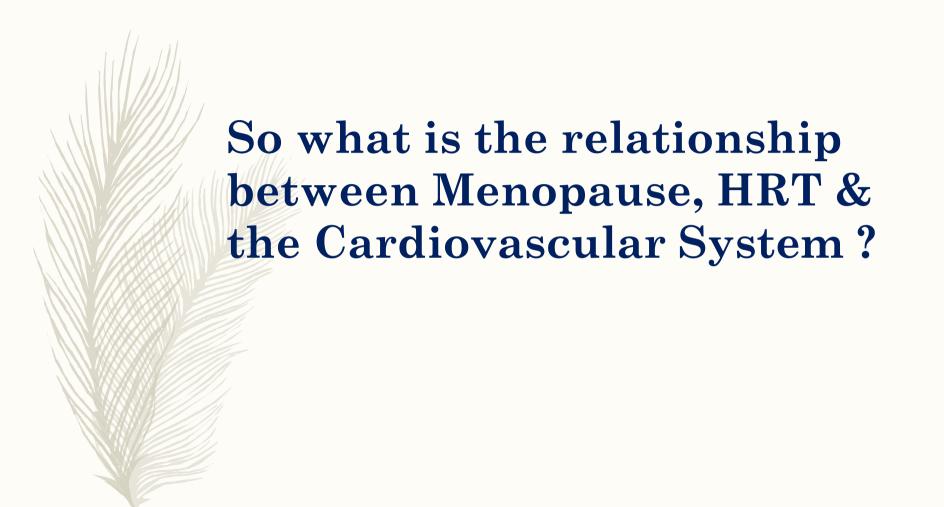
9 Fewer DEATHS

5 More CHD Events in >60's in the 1st year*

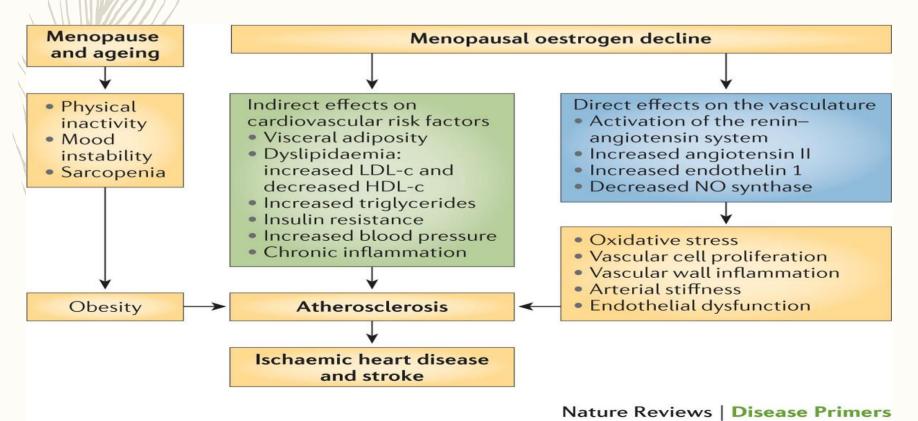
5 More STROKES in >60's in the 1st year*

NO OVERALL ↑ IN CVD OVERALL*

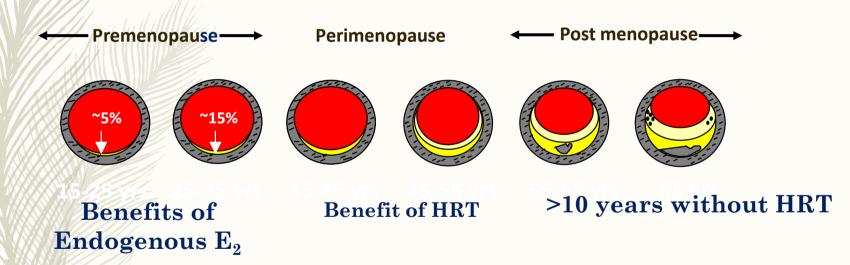
*HRT: Putting Benefits & Risks into Perspective M.Warren MD; Columbia Univ Med School



Consequences of Menopause on the Cardiovascular system

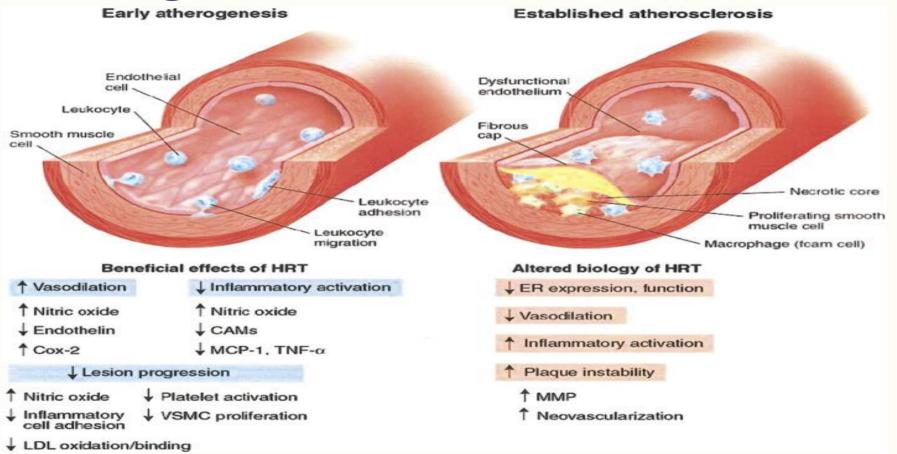


Effect of Hormone Therapy on Atherosclerosis Varies With Stage of Reproductive Life



Mikkola TS, et al. Ann Med. 2004;36:402-13.

Timing is Critical



So what do we tell the patients?

- Women with known CVD (Angina, MI, etc) should avoid HRT as should women > 10 years past the menopause
- Women with a very strong Family Hx of CVD (e.g.. First degree pre menopausal female relative) should consider some CV screening in the peri- Menopausal years (BP monitoring, ECG, fasting Lipids, Glucose, etc)

 Women < 10 years from the menopause or under 60 yo are in fact derive some cardio-protection from HRT use but further studies need to be done.

ALL THIS SUPPORTED & REPEATED BY NICE 2015

HRT & Thrombosis

- WHI did show ↑ risk in VTE within the first 2 years (although the absolute risk remained low) particularly for the E+ P group
- PE rates were NOT increased

- Observational data also suggest that Transdermal HRT may be less thrombogenic than Oral NICE
- Is MPA thrombogenic??
- Should we be favouring micronised progesterone??? NICE

So what do we tell the patients?

 In the first year or two from starting oral HRT the risk of getting a DVT is slightly elevated

- HRT should be avoided in women with a current or recent past Hx of DVT & caution with women who had VTE around pregnancy or while on the COCP
- Women with a strong FHx of or multiple risk factors for DVT might benefit from Haematological review before Rx and then may be safer on Transdermal products

CONTRAINDICATIONS/ PRECAUTIONS:

ABSOLUTE

- Suspected Breast or Endometrial cancer
- Ischemic Heart disease
- Undiagnosed abnormal genital bleeding
- Active TE disorder
- Active liver or gall bladder disease
- Pregnancy or Breast feeding

RELATIVE

- Migraine headache
- History of liver or gall bladder disease
- History of Endometrial cancer
- History of TE events

FAMILY HISTORY OF BREAST CA IS NOT AN ABSOLUTE CONTRAINDICATION to HRT USE !!!

CONTROLLED HYPERTENSION IS also OK

General information for women near the Menopause

- Consider screening for hypothyroidism, anaemia, primary depression – all common around the menopause & can present as perimenopause-like symptoms
- Contraception !!!

– Address MODIFIABLE factors:

Health Promotion: Diet

- Encourage oily fish, low GI fruits & veg, whole grains, soya, legumes
- Discourage excess red meat & simple sugars

- Vitamin D intake of at least 400mIU (10 microg) /day consider supplements
- Calcium 700-1200mg/day ideally via diet

Health Promotion: Exercise

Regular Exercise:

- Decreases premature death, CVD, DM, HTN, CA colon & Obesity.
- Has a beneficial effect on Bone, Muscle & can reduce the risk of falling by improving strength, flexibility & balance.
- Improves psychological symptoms
- Decreases LDLs, & Increases HDLs

The WHO recommends:

- 75 min vigorous or 150 min moderate aerobic exercise / week

Health Promotion: Weight Management

Menopause can bring weight gain

- Metabolic slow down
- Shift from Gluteo- femoral to Central adipose deposition
- Tiredness & Low Mood promote increased calorie intake

Health Promotion: Reducing Alcohol

- Moderate alcohol intake (< 2 units/day) is linked to lower mortality than abstinence although the link is unclear
- Breast Cancer risk however is higher in women who consume even low levels of alcohol (compared to abstinent women)
- Heavy alcohol consumption is linked to increased rates of breast cancer, low bone density, falls & fractures and more

Health Promotion: Smoking Cessation

12 mos after smoking cessation, the risk of CVD death is reduced by 50% (INTERHEART Study)

Smoking cessation is shown to be more likely when:

- the GP intervenes &/or
- Nicotine replacement is used



CHOICES IN HRT in the Irish MIMS

PRESCRIBING INFO OFTEN INACCURATE!!

20 products: 17 are HRT + vagifem + some progestins

ESTROGEN

- Oral
- Transdermal Patch
- Transdermal Gel
- IntraVaginal Gel
- IntraVaginal Pessary
- IntraVaginal Ring
- IntraNasal Spray
- IntraAbdominal Implant

PROGESTAGEN

- Oral
- Transdermal Patch
- IUS (Mirena)

 Plus.....TIBOLONE; a synthetic steroid whose metabolites have Oestrogenic, Progestagenic & Androgenic properties

CURRENT BLEED-PRODUCING HRT in MIMS

FEMOSTON 2/10 -Sequential Oral 2mgOestradiol+/-10mg.Dydrogesterone

Femoston 1/10- Sequential Oral 1mgOestradiol+/-10mg.Dydrogesterone

NOVOFEM -Sequential Oral 1mg.Estradiol+/- 1mg.Norethisterone

ESTALIS SEQUI-Sequential Transdermal
Estradiol 50 microg.+/- 250microg. Norethisterone

ESTRACOMBI-Sequential Transdermal 50microg.Oestradiol+/-250microg.Norethisterone

PREMPAK-C- Sequential Oral Conj Oestrogen 0.625 & 1.25mg.+/-Norgestrel 0.15mg.

TRISEQUENS- Sequential Oral Estradiol 2 & 1mg+/- 1mg.Norethisterone

NUVELLE-Sequential Oral

2mg.Oestradiol+/-75microg.Levonorgestrel

PREMIQUE CYCLE 10 - Sequential Oral Conj. Equine Oestrogen.625mg.+/-10mg.MPA

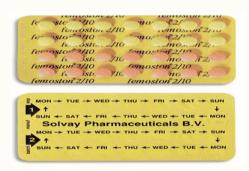
PLUS...

UTEROGESTAN- Oral Micronised Progesterone 100mg. NOT in MIMS & DUPHSTON Oral Dydrogesterone 10mg

















CURRENT NON-BLEED -PRODUCING HRT

ACTIVELLE – Continuous Combined Oral 1mg. Estradiol + .5mg Norethisterone

ANGELIQ- Continuous Combined Oral 1mg.Estradiol + 2mg.Drospirenone

EVOREL CONTI -ContComb.Transdermal 50microg.Oestradiol + 170microg.Norethisterone

FEMOSTON-CONTI 1/5 -Cont.Comb. Oral 1mg Estradiol + 5mg.Dydrogesterone

FEMOSTON-CONTI 0.5/2.5-Cont.Comb. Oral .5mg Estradiol + 2.5mg.Dydrogesterone

INDIVINA - Cont.Comb. Oral1 mg. Oestradiol+Medroxyprogesterone acetate(MPA);2.5 or 5mg

KLIOGEST- Cont.Comb. Oral 2mg.Oestradiol/ 1mg.Norethisterone

PREMIQUE - Cont.Comb. Oral Conj Oestrogen .625mg + 5mg. MPA

& LIVIAL-2.5mg. Tibolone.. Synthetic steroid, Gonadomimetic



















CURRENT OESTROGEN-ONLY

Hysterectomised Women or Mirena IUS < 5 yrs. old

CLIMARA-Transdermal Estradiol patch 50microg/day-(weekly)

DIVIGEL-Transdermal .1% Estradiol gel

ESTROFEM - Oral 2mg.Estradiol

EVOREL -Transdermal 50microg. Estradiol

FEMATAB -Oral 2 mg. Estradiol

FEMATAB -Oral 1mg. Estradiol

ESTRADOT-Transdermal Estradiol 37.5, 50. 75 & 100 microg.

PREMARIN - Oral Conj. Equine Oestrogen .625 & 1.25 mg.

AERODIOL-Intranasal Estradiol spray

OESTROGEL - Transdermal 17beta-Oestradiol 1.5mg.

ESTRADERM TTS - Transdermal Estradiol 25, 50 & 100microg.

VAGIFEM - Intra Vaginal Estradiol .010mg Minimal systemic absorption. Ideal for women with local symptoms- unlikely to have direct influence on Breast, CVD, etc.















Please..... offer VAGIFEM/ OVESTIN/ BLISSEL to all women (& disregard the SmPC!)

Intra Vaginal Estradiol .010mg allows Minimal systemic absorption so is Ideal for women with local symptoms-unlikely to have direct influence on Breast, CVD, etc..

SHOULD BE OFFERED TO ALL WOMEN AT WHATEVER DOSE (max 5 a day) /INTERVAL THEY REQUIRE WITH NO RESTRICTION TO DURATION OF USE

Twice weekly applications will, in one year (104 pessaries), result in less systemic exposure than a single PO HRT tablet

Other Menopause Preparations

Progestogens ('Duphaston' is oral dydrogesterone, Mirena IUS,
 'Uterogestan' is oral micronised progesterone) & previously an Androgen ('Intrinsa' testosterone patch)

and

Testosterone ("Testim" or "Testogel")

- "S.E.R.M."s

S.E.R.M.s SELECTIVE ESTROGEN RECEPTOR MODULATORS

- E 2 -LIKE EFFECTS

TAMOXIFEN-LIKE EFFECTS

Increases BONE DENSITY

Decreases BREAST CA RISK

Decreases LDLs

Decreases ENDOMETRIAL CA RISK

Increases TE risk

Increases VASOMOTOR SYMPTOMS

TSECs

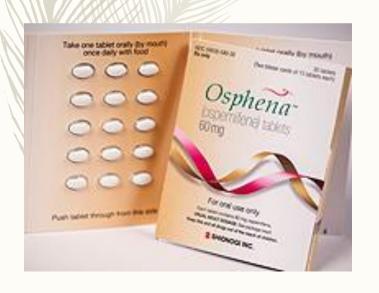
- Combination of SERM and Oestrogen
- Currently offereing "Aprela" & "Duavive" in the USA & UK, resp
- "Duavive" in the UK (0.45 mg of CEE and bazedoxifene acetate equivalent to 20 mg bazedoxifene)
- Useful for women with unassuageable HRT fears maybe??
- No NICE guidance for these as yet in the UK

"DUAVIVE"

- Premarin .045 mg +
- Bazedoxifene 20 mg ("Conbriza")
 SERM
- Licensed in UK
- Still caution after breast cancer treatment but might be safer than E+P



"Osphena" a Tissue Selective Estrogen Complex



- Ospemifene 60mg is a new TSEC
- It has an E2 like impact on the vaginal epithelium; building vaginal wall thickness which in turn reduces the pain associated with dyspareunia
- Like other SERMs it reduces BREAST Cancer risk & can be Rx after Chemo/Radio Tx done
- Approved by the US FDA in February 2013
- Not yet licensed in Ireland but has a European License

What about replacing Testosterone?

- Menopausal ovarian failure results in less circulationg androgen in women
- This may cause low mood, energy, libido but clinical trials are
 LIMITED
- No longer able to Rx female strength testosterone ("Intrinsa" twice weekly patches)
- Consider "Testim" or "Testagel " but use 1/7 to 1/10 the usual daily dose for men, debate as to whether they should be offered before post Menopause
- Testosterone can impact SHBG so Monitor Free Androgen Index if no response

Hormone therapy in women at high risk of breast cancer

- ► Family history has no additive impact on breast cancer risk with HRT use^{1,2} although women with gene mutations are at vastly increased lifetime risk of breast cancer
- ► HRT use and family history had **independent and non interacting risk factors** for breast cancer in WHI³
- ▶ Long term observational studies have reported no extra risk for those using HRT with a family history of breast cancer
- ► HRT following risk reduction surgery appears not to increase risk^{4,5}
- ▶ HRT in such women should use minimal progestogen and ideally MICRONISED progesterone or dydrogesterone
 - 1. Rippy L Marsden J Climacteric 2006;9:404-15 2. Sellars T et al Ann Intern Med 1997;127:973-80
 - 3. Gramling R et al Epidemiology 2009;20:752-6
 - 4. Rebeck T et al J Clin Oncol 2005;23:7804-10 5. Eisen J et al J Nat Cancer Inst. 2008;100:1361-67

Alternatives to HRT in Menopause Symptom Care

Alternative Therapies: Flushes & Sweats: Alpha Agonists

CLONIDINE HCl 50-75 microg BD

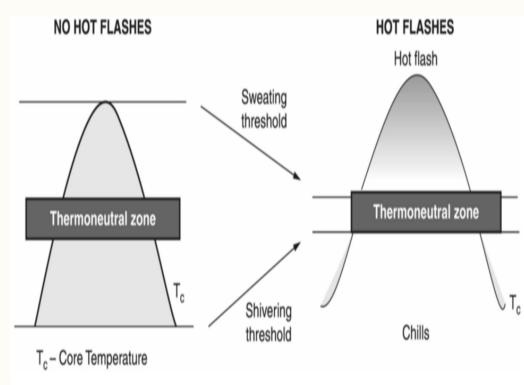
Alpha adrenergic agonist

Licensed for Migraine & VSM symptoms of the Menopause

(can be used for HTN but at much higher doses)

It widens the "thermo-regulatory zone "

Can cause insomnia, dry mouth, drowsiness



Alternative Therapies: Flushes & Sweats: The Pill

- COC; Combined Oral/TD/TV Contraception
- Much larger quantities of more potent Estrogen & Progestins
- Should provide full VMS relief & is CONTRACEPTIVE
- Consider Cat 3 & 4 risks though
- May prefer Zoely/Qlaira





Alternative Therapies: Flushes & Sweats: Seroxat SSRI

- Selective Serotonin Reuptake Inhibitors
- 10mg Seroxat (paroxetine) was found to reduce VMS in women on Tamoxifen¹
- Obviously may help with low mood in higher doses
- Good for women with personal history of breast CA

¹ Nelson HD, Vesco KK, Haney E, et.al. Nonhormonal therapies for menopausal hot flashes: systematic review & meta- analysis. JAMA 2006; 295:2057-71

Alternative Therapies: Flushes & Sweats: Gabapentin

- NICE says 900mg daily of GabaP has been shown to reduce VMS by approx 50%

- may be of use in women with breast cancer

Alternative Therapies: Flushes & Sweats: CBT & Mindfulness

- -Cognitive Behavioural Therapy has been found beneficial over placebo in several aspects of Peri menopausal management including VMS relief*
- -Mindful Meditation Practice is recommended by NICE for help with low mood & anxiety

Complimentary & Herbal Therapies

- Phyto Estrogens: so far not proven superior to placebo in RCT

Isoflavones are found in Soya, Red Clover & Chick Peas

Lignans are found in Bran, Flax, Legumes

- <u>Herbal Remedies</u> (all are probably safe but not yet proven effective)

e.g. Black Cohosh, Ginseng, EP oil, Dong Quai, Gingko biloba, Sage, Wild Yam, St John's Wort (beware LEI activity)

- <u>Vaginal interventions</u>: moisturisers, lubricants, vaginal LASER rejuvenation
- <u>"Bio Identical Hormones"</u> + saliva testing, compounding pharmacies unregulated and not recommended by NICE



"GP BUDDY"



https://www.gpbuddy.ie/go/education

PATIENT SUPPORT & REASSURANCE

- The British Menopause Society has good publications; membership is required (£100 at www.bms.org.uk) well worth it!
- Menopause Matters website, run by Dr Heather Currie, has some useful recommendations, registration is free
 - see: www.menopausematters.co.uk
- Primary Care Women's Health Forum Is a UK charity that works with the NHS on all aspects of health promotion offering free publications & factsheets on Menopause & HRT see www.pcwf.co.uk

I'M STILL HOT, IT JUST COMES IN FLASHES NOW

