HỘI NGHỊ SẢN PHỤ KHOA LẦN THỨ 21
VIỆT – PHÁP – CHÂU Á THÁI BÌNH DƯƠNG

PGS. Shilpa Nambiar

Chủ tịch Ủy ban đại diện quốc tế

Hội Sản Phụ khoa Hoàng gia Anh (RCOG)

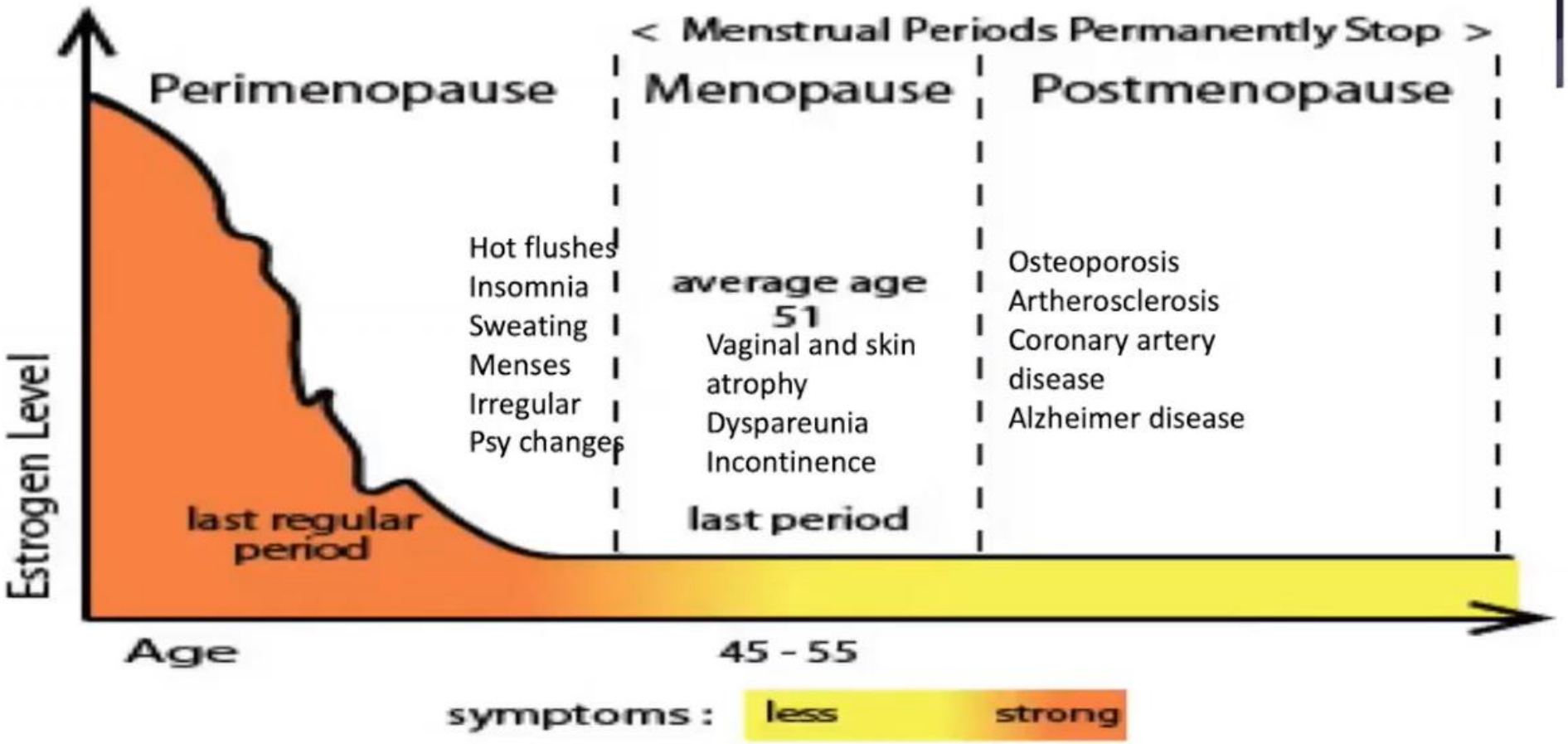
Thành viên Liên đoàn sản phụ khoa quốc tế (FIGO)

HỘI NGHỊ SẢN PHỤ KHOA LẦN THỨ 21
VIỆT – PHÁP – CHÂU Á THÁI BÌNH DƯƠNG

Liệu pháp nội tiết thay thế ở phụ nữ mãn kinh: Cải thiện & Cân bằng sức khỏe


THE WORLD'S 100
MOST POWERFUL
WOMEN 2020

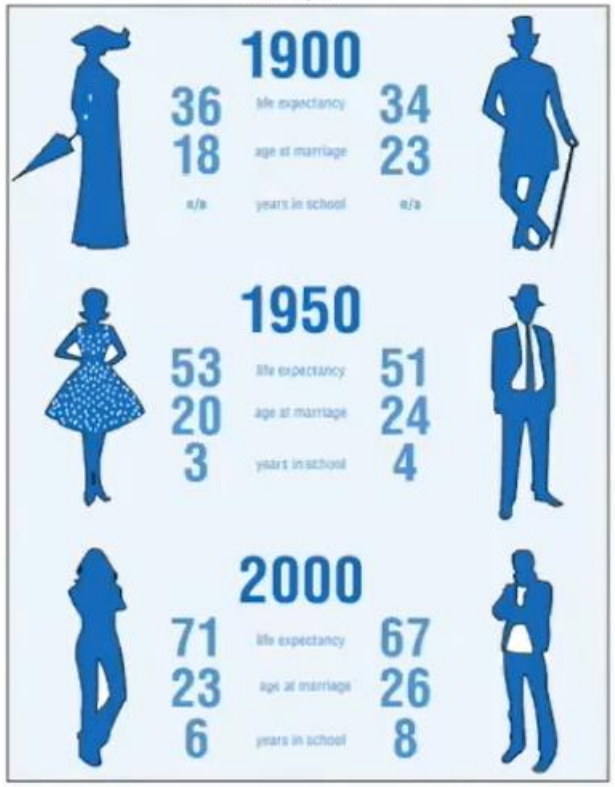
Phases of Menopause



WHY IS THIS SO IMPORTANT ?

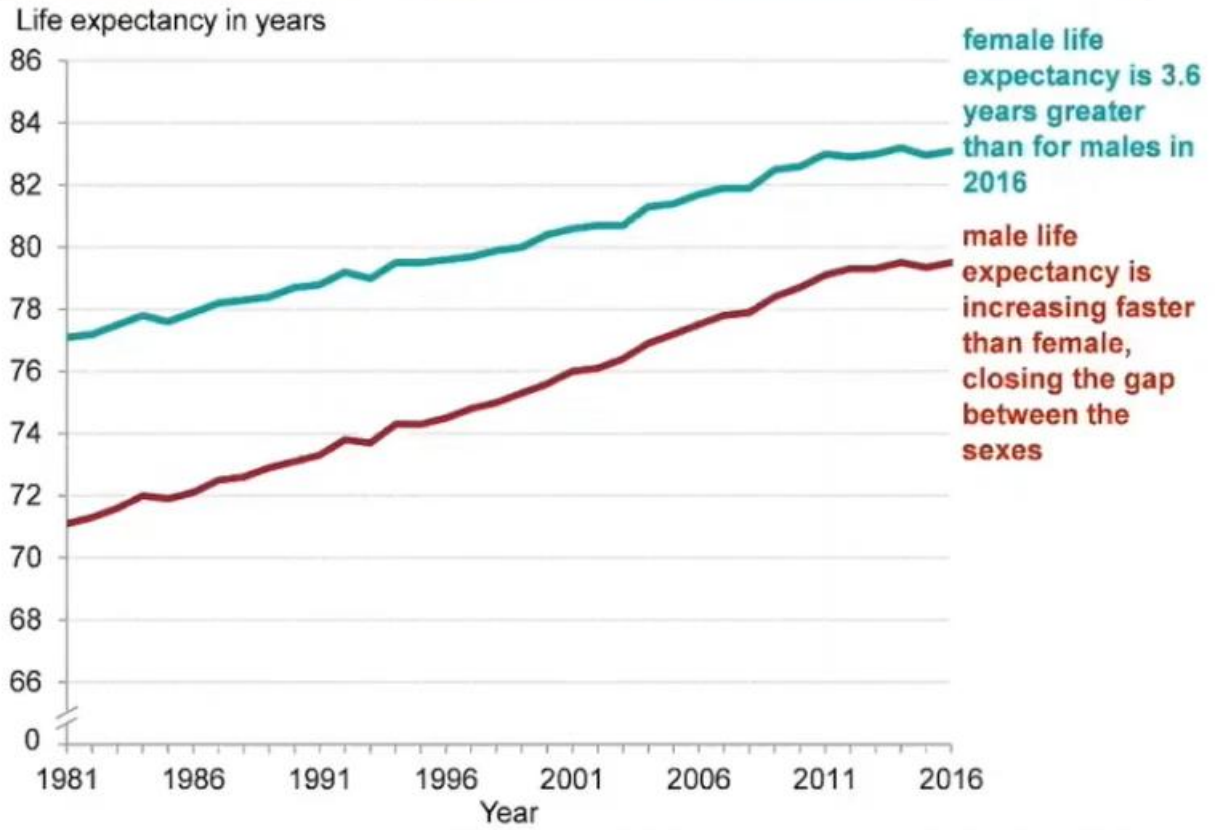
Figure 12.1. **Average life expectancy at birth, marriage age and average years of education for women and men in the 20th century**

Values in years



Note: Fc

Source: Clio-Infra, www.clio-infra.eu.

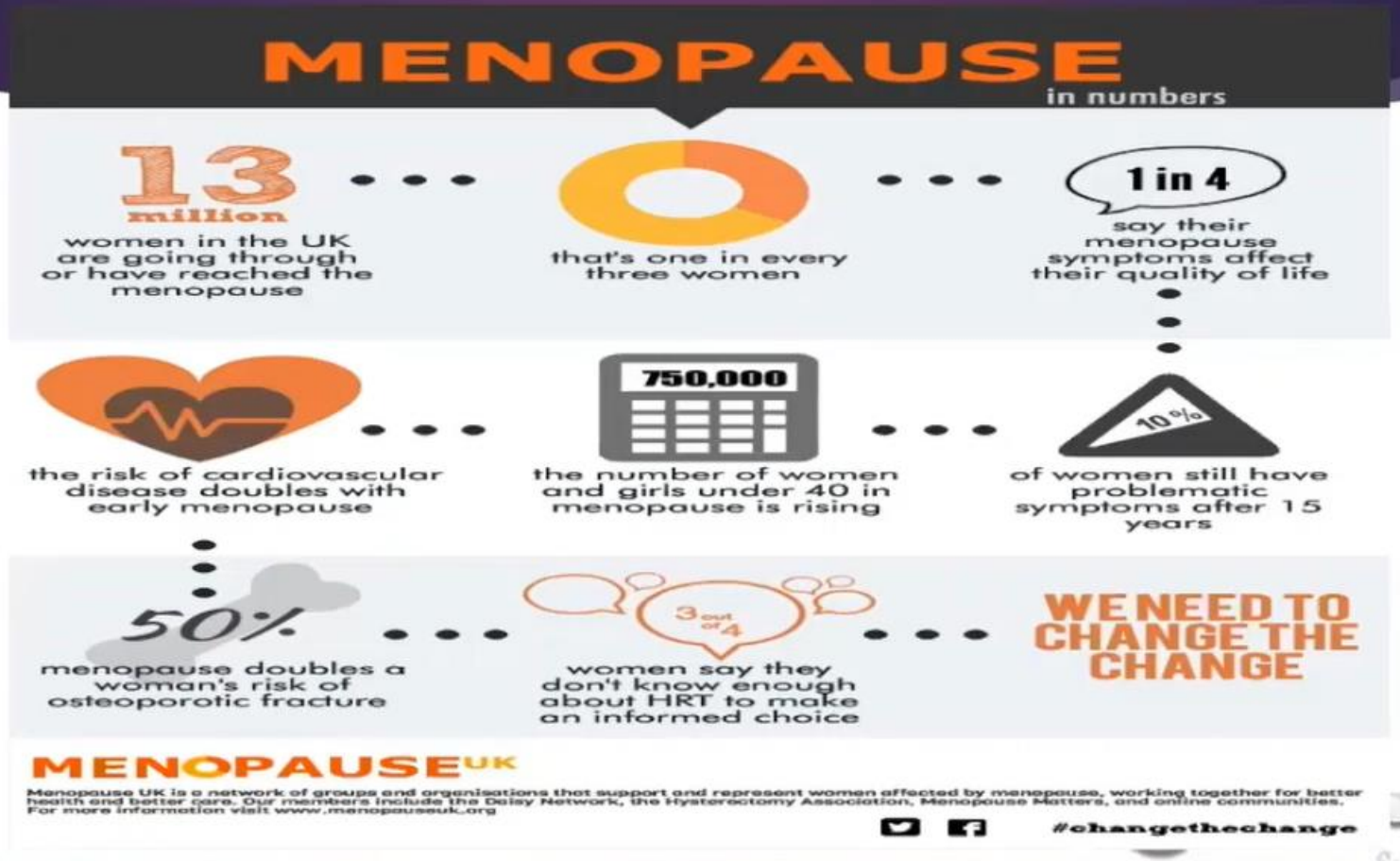


female life expectancy is 3.6 years greater than for males in 2016

male life expectancy is increasing faster than female, closing the gap between the sexes

StatLink http://dx.doi.org/10.1787/888933096255

AND the MENOPAUSE MATTERS!!




So... Now what?
I don't think he expected you to live that long...
NO TRESPASSING
©2014 BY ALEX MARTIN

2002 - WHI Study Publication

THE Sun

HRT DANGER FOR WOMEN

'Huge increase' in killer disease risk

MILLIONS of women on hormone replacement therapy are in danger of getting heart disease or breast cancer, a study showed yesterday.

HOW THE DEBATE HAS RAGED

2002: US Women's Health Initiative study claims long term use of HRT is linked to higher risk of heart disease, strokes and cancer

2003: Cancer Research UK Million Women Study claims HRT users are at double the risk of breast cancer

2004: Second MWS report says the breast cancer risk for women in their 50s using HRT for five years is 50 per cent higher. Doctors are advised by the government's Medicines and Healthcare Products Regulatory Agency (MHRA) to prescribe the 'lowest effective dose for shortest possible time'

2007: WHI researchers publish analysis showing women on HRT are not more at risk of heart problems – and could be less at risk than non-users. MHRA says HRT should only be used to prevent osteoporosis in women who cannot take other medicines

2011: MWS report says the increased risk of breast cancer from HRT reverts to level of non-users two years after stopping it

2012: Danish study finds HRT can protect against heart disease

2013: The British Menopause Society says potential benefits of HRT outweigh harm

A wasted decade: How one HRT scare has 'caused thousands of women 10 years of needless suffering'

By JENNY HOPE

PUBLISHED: 00:00, 22 May 2012 | **UPDATED:** 08:21, 22 May 2012

Comments (116) | Share | +1 1 | Tweet 0 | Like 126

Thousands of women have had a 'wasted decade' of suffering since the HRT scare, according to an international panel of experts.

A major reassessment of the research into hormone replacement therapy has concluded that menopausal women were the victims of 'mass fear' generated by findings from ten years ago.

Many of the conclusions reached by the 2002 study, including the raised risk of breast cancer, have now been overturned.

British doctors are calling for the rules on prescribing HRT to be rewritten, allowing a new generation to benefit from bone protection and improved quality of life.

At present, women in their 50s are told to use hormone replacement therapy drugs for the shortest period of time that is possible and not for longer than five years.

Some younger doctors have never prescribed HRT because they wrongly believe the risks of the treatment outweigh the benefits, it is claimed.

The new analysis of the evidence by leading

Thousands of women are to be offered HRT

'Milestone' for menopause patients

Health watchdog: Women should be given HRT to fight menopause

PANEL'S MEDICAL EXPERTS WITH LINKS TO DRUG FIRMS

Give women HRT despite cancer fears, doctors told

Chris Smyth Health Editor

Hundreds of thousands more women should be offered hormone replacement therapy by their GPs, according to guidelines from the NHS treatments adviser.

Many women are "suffering in silence" because cancer fears have scared doctors away from prescribing HRT, the National Institute for Health and Care Excellence said in its first policy on the menopause.

Nice accepts that HRT raises a woman's chances of cancer, but says that the risk is small and doctors need to be more confident about offering the treatment.

About 20 per cent of the two million women going through the menopause experience debilitating symptoms, including hot flushes, sweats, low moods and tiredness.

HRT, which replaces hormones lost as periods stop, is the most effective treatment for such symptoms. However, since studies a decade ago found that it increased the risk of cancer, use of the therapy has more than halved. At present roughly one in ten menopausal women takes HRT.

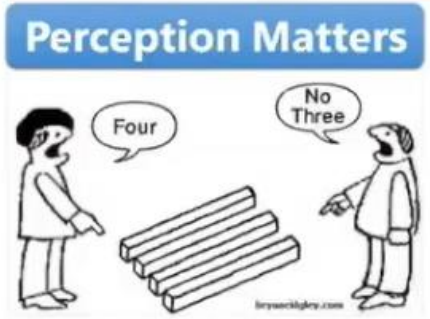
Nice urged women with troublesome symptoms to talk to a GP, while telling doctors to consider HRT and explain the real risks. Imogen Shaw, a GP who helped to develop the "milestone" guidance, said: "Women have lost confidence and think HRT is scary so they don't bother to come and ask [a doctor] and they suffer in silence."

She added: "Just because menopause is a normal process, that doesn't mean women should have to grit their teeth and get on with it. Childbirth is also a normal process but we don't treat women in labour like that — we give them a range of pain-relief options."

The guidance says there is some evidence that herbal treatments such as St John's Wort can help with hot flushes and cognitive behavioural therapy with mood problems, but Dr Shaw said: "HRT is the most effective

Continued on page 4, col 3

WOMENS PERCEPTION OF RISK



	PERCEIVED
CORONARY ARTERY DISEASE	4%
BREAST CANCER	46%
ALL CANCERS	16%
UTERINE /OVARIAN CANCER	3%
AIDS	4%

Pilote and Hlatky, *Am Heart J* 1995

Difference in breast cancer incidence per 1,000 women aged 50-59.
Approximate number of women developing breast cancer over the next five years.

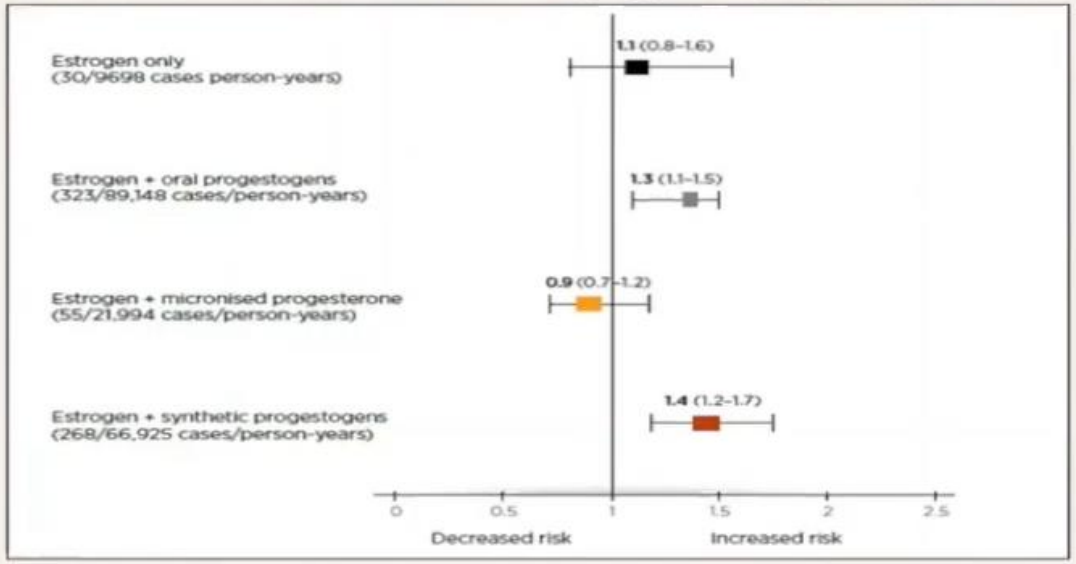
NICE Guideline, Menopause: Diagnosis and management November 2015

Does type of progestogen matter?

SYNTHETIC PROGESTINS vs BODY-IDENTICAL MICRONISED PROGESTERONE:

RISK OF BREAST CANCER

Relative risk of breast cancer by type of progestogen used vs non-exposed women



Compared to non-exposed women, the risk increased significantly for users of estrogens combined with progestogens...but this increase was limited to synthetic progestins...there was no evidence of increased risk associated with the use of estrogens combined with micronized progesterone

Adapted from Fournier A *et al.* 2005. Study assessed the risk of breast cancer associated with MHT use in 54,548 post-menopausal women who had never taken any MHT 1 year before entering the E3N-EPIC cohort study (mean age at inclusion: 52.8 years); 948 primary invasive breast cancers were diagnosed during follow-up (mean duration: 5.8 years [standard deviation 2.4; range: 0.1–10.6 years]).

Fournier A *et al. Int J Cancer* 2005;114:448–454.

BESINS HEALTHCARE

MHT and breast cancer in perspective

- No increased risk with
  - Estrogen alone
  - Estrogen + micronized progesterone

- Lifestyle factors play a MUCH LARGER role

Cardiovascular disease

- Cardiovascular disease leading cause of death in women but uncommon in premenopausal women.

Effect of estrogen preparations on the main intermediate risk markers of CHD in comparative randomised trials

	Oral CEE/ estradiol	Transdermal estradiol
Triglycerides	↑	↓
LDL particle size	↓	↑
Fragment 1 + 2 prothrombin	↑	=
Von Willebrand Factor	↑	=
C-Reactive Protein	↑	= or ↓

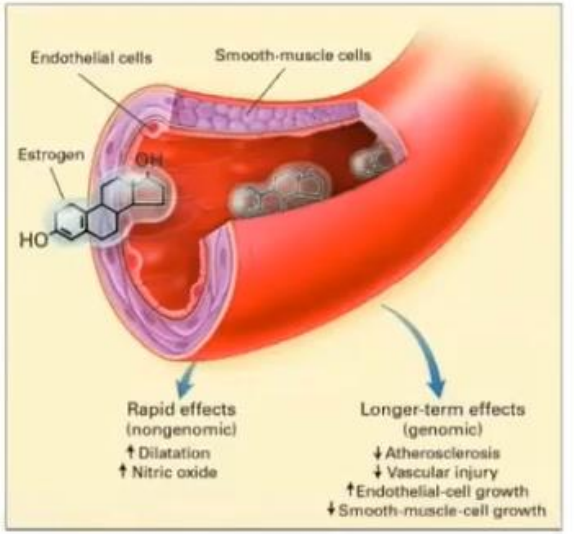
Adapted from Modena *et al.*, 2005.

BJOG An International Journal of Obstetrics and Gynaecology
Royal College of Obstetricians & Gynaecologists
Systematic Review | Full Access

Duration of estrogen exposure during reproductive years, age at menarche and age at menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: a systematic review and meta-analysis

SR Mishra, H-F Chung, M Waller, GD Mishra

First published: 23 September 2020 | https://doi.org/10.1111/1471-0528.16524 | Citations: 1



Cardioprotection

- Clinically epidemiological studies show reduced cardiovascular disease by 40-50% in healthy women when on MHT
- In established CVD,
  - 50-80% reduction in incidence of events
  - Increased survival over 10 years
- The greatest benefit in survival in women with the most severe coronary atheromas


BJOG An International Journal of Obstetrics and Gynaecology

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Systematic Review Full Access

Duration of estrogen exposure during reproductive years, age a menarche and age at menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: a systematic review and meta-analysis

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Cochrane - Risk by Years since Menopause

- <10 ysm
  - Mortality — RR 0.70 (0.52 to 0.95)
  - Coronary heart disease — RR 0.52 (0.29 to 0.96)
  - Thromboembolism — RR 1.74 (1.11 to 2.73)
  - Stroke — RR 1.37 (0.80 to 2.34)
- >10 ysm
  - Mortality — RR 1.06 (0.95 to 1.18)
  - Coronary heart disease — RR 1.07 (0.96 to 1.20)
  - Thromboembolism — RR 1.96 (1.37 to 2.80)
  - Stroke — RR 1.21 (1.06 to 1.38)

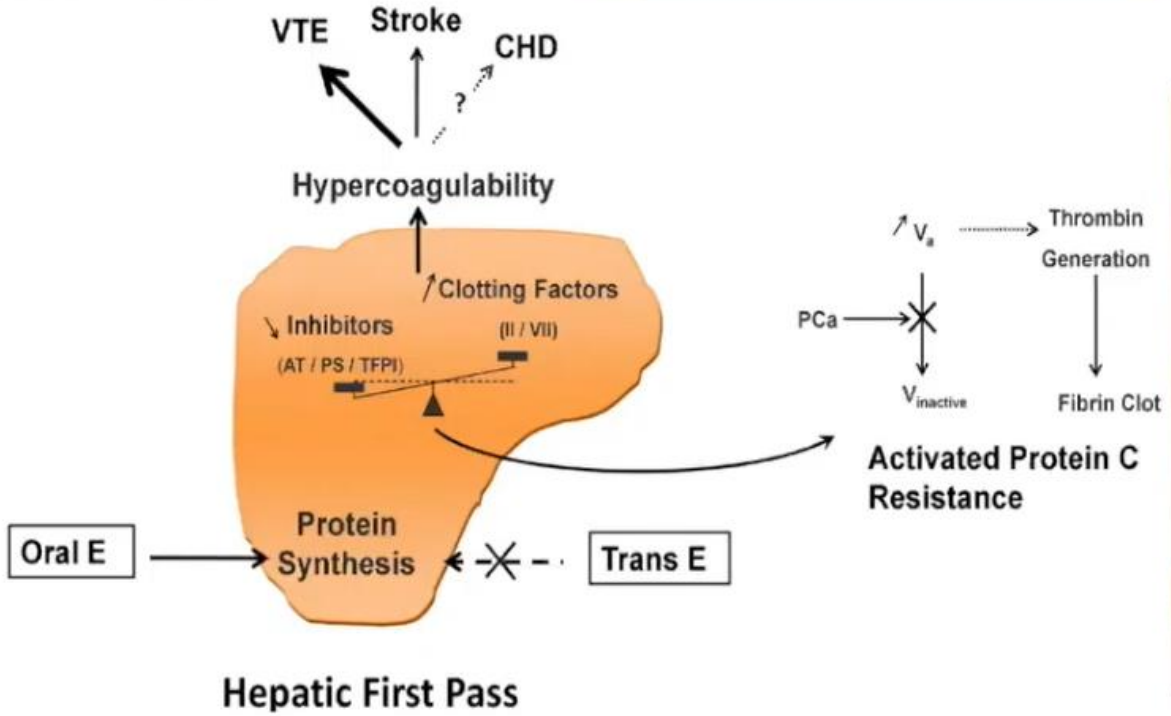
Boardman HMP Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database of Systematic Reviews 2015, Issue 3.

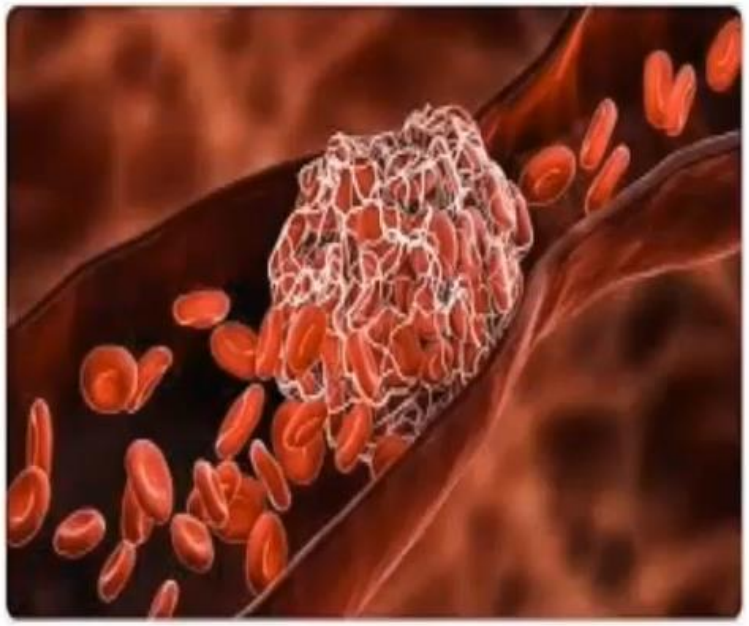
Cochrane Conclusion

- For every 1000 women, when given at the right time, HRT could save 6 lives and prevent 8 women from suffering heart disease at the cost of 5 extra women experiencing blood clots.

Boardman HMP Lancet Blog

Thrombotic risk

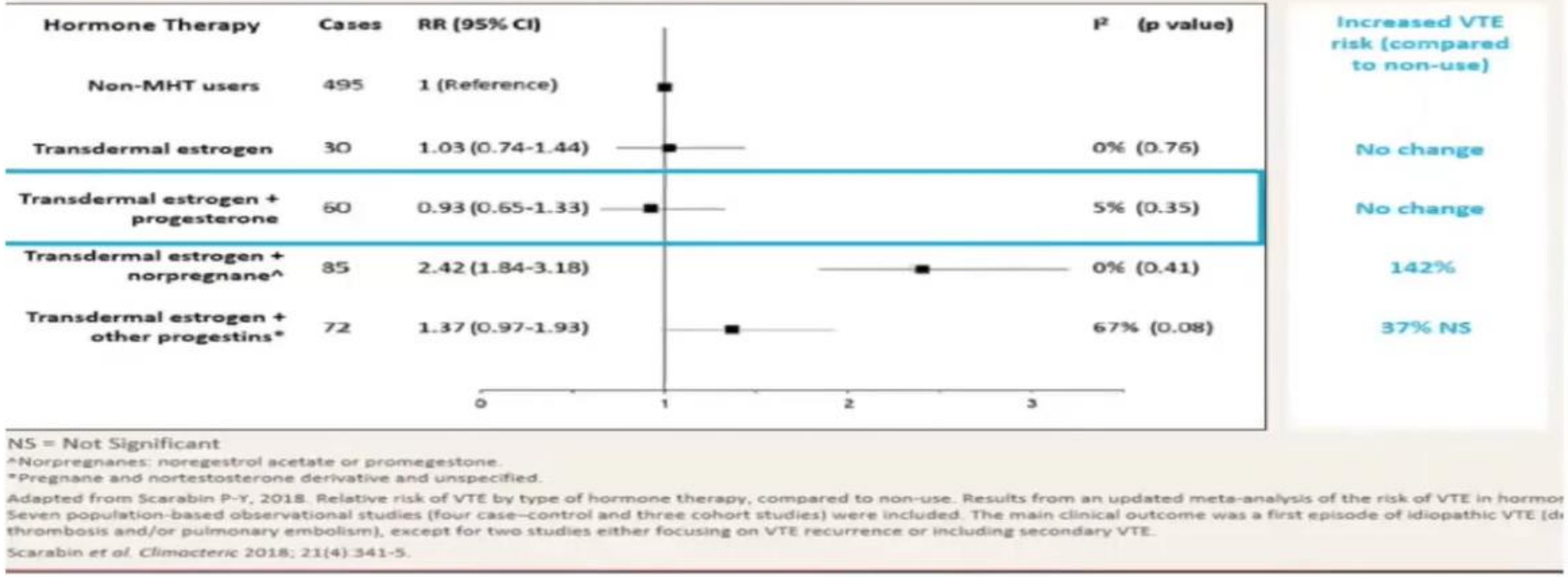




Does type of progestogen matter?

RISK OF VENOUS THROMBOEMBOLISM (VTE)

Relative risk of VTE by the type of progestogen



NS = Not Significant

^Norpregnanes: noregestrol acetate or promegestone.

*Pregnane and nortestosterone derivative and unspecified.

Adapted from Scarabin P-Y, 2018. Relative risk of VTE by type of hormone therapy, compared to non-use. Results from an updated meta-analysis of the risk of VTE in hormo
Seven population-based observational studies (four case–control and three cohort studies) were included. The main clinical outcome was a first episode of idiopathic VTE (d
thrombosis and/or pulmonary embolism), except for two studies either focusing on VTE recurrence or including secondary VTE.

Scarabin *et al. Climacteric* 2018; 21(4):341-5.

MHT and cardiovascular /thrombotic risk

- Oral oestrogen and synthetic progestogens increase the risk most
- Transdermal estrogen – NO increased risk and may even reduce risk
- Micronised progesterone does not increase the risk
- Intravaginal or intrauterine delivery of progesterone can reduce systemic effects and target delivery for endometrial protection

Osteoprotection

Springer OSTEOPOROSIS INTERNATIONAL

Osteoporos Int. 2020; 31(12): 2271–2286. PMCID: PMC7661391
Published online 2020 Jul 8. doi: 10.1007/s00198-020-05497-8 EMSID: EMS86780
PMID: 32643851

Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis?

S. Rozenberg,[1] N. Al-Daghri,[2] M. Aubertin-Leheudre,[3] M.-L. Bianchi,[4,5] A. Cano,[6] P. Collins,[7,8] C. Cooper,[9,10,11] A. R. Genazzani,[12] T. Hillard,[13] J. A. Kanis,[14,15] J.-M. Kaufman,[16] I. Lambrinoudaki,[17] A. Lasley,[18] E. McCloskey,[19] S. Palacios,[20] D. Prieto-Alhambra,[21] J.-Y. Reginster,[22,23] R. Rizzoli,[24] G. Rosano,[25] F. Trémollieres,[26] and N.C. Harvey[9,10]

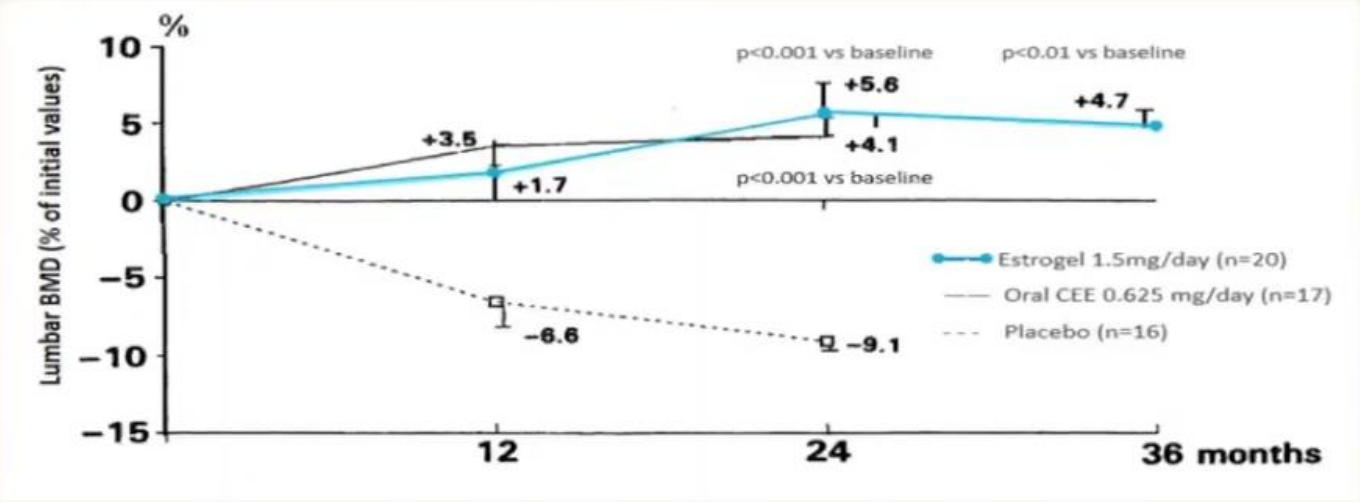
- Last 30 years osteoporosis change in view from inevitable consequence to being understood as a major non communicable disease (NCD)
- One thing all the studies including WHI agree on
- Principal effect – direct effect osteoclastic and osteoblastic activity

  - Evidence for fracture reduction with HRT was robust
  - 23 fewer fragility fractures per 1000 women aged 50-59 over 7.5 years
  - Protection persisted after HRT discontinuation
  - Age and duration of treatment did not influence conclusions

EFFICACY – BONE HEALTH:

IMPROVEMENT IN BONE MINERAL DENSITY[1]

Change in bone mineral density over time



Adapted from Palacios S *et al.* 1995. A randomised study to compare the effects on bone density of Estrogel, oral conjugated estrogens or no treatment in women with hysterectomy. BMD was measured by dual gammagraphic densitometry in the lumbar spine (L2-L4).

- Estrogen therapy (oral CEE and Estrogel) significantly improved BMD vs baseline
- BMD reduced over time in untreated women

1. Palacios S *et al.* *Maturitas* 1995; 20(2-3):209-13.

Urogenital atrophy/GSM

- Offer vaginal estrogen long term
  - Even if taking HRT already systemically
  - Even if HRT c/i (Specialist advice)
- Increased dose if required (Specialist advice)
- Report unscheduled vaginal bleeding
- Moisturisers and lubricants can be used as well
- No routine endometrial monitoring

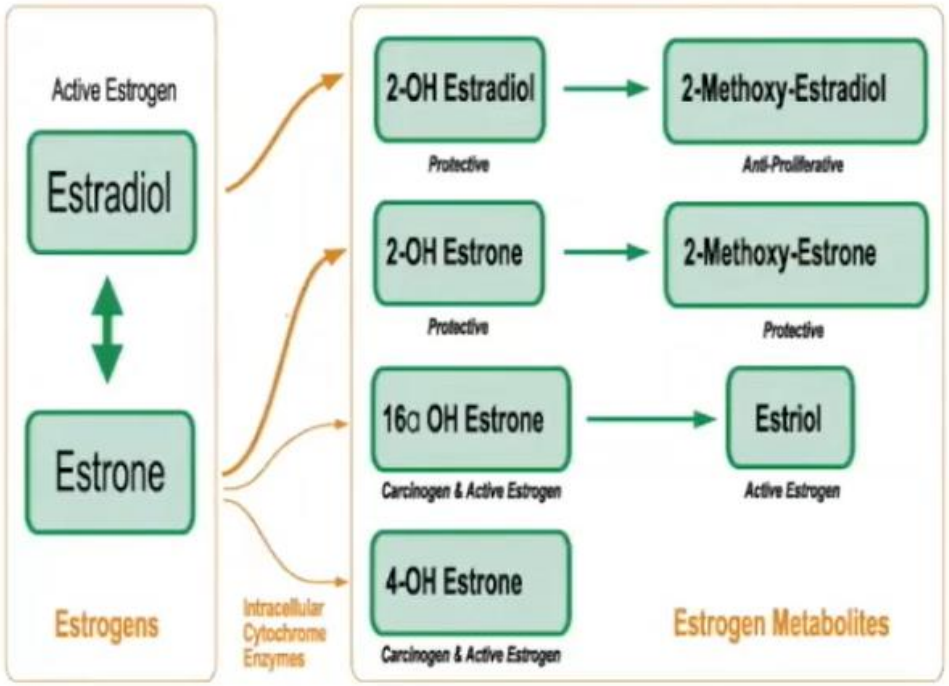
MHT Benefits

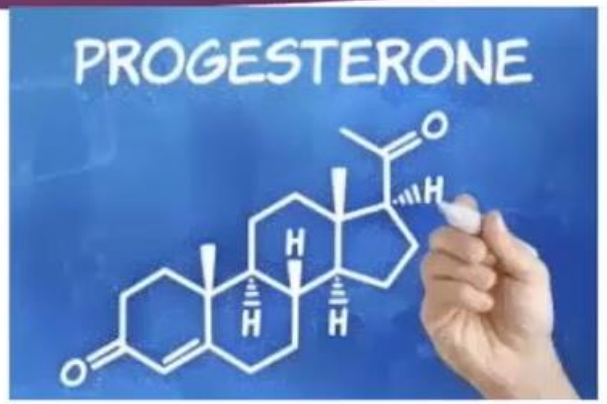
- Vasomotor Symptoms
- Concentration
- Mood
- Sleep
- Energy Levels
- Night sweats
- Joint aches and pains
- Brain 'Fog'
- Vaginal dryness
- Femininity
- Cardiovascular disease
- Osteoporosis
- Reduced Death

We have learned some tricks

- What we give
  - Estrogen alone
  - Estrogen + Progesterones
  - Body identical, bio identical or synthetic
- How we give it
  - Oral
  - Transdermal / Implants
  - Vaginal
  - Intrauterine

What needs replacing ?





WHAT IS OUT THERE

Estrogen	
Estradiol	> 0.5mg (combined only)/ 1mg / 2mg oral > 25mcg / 37.5mcg / 40mcg / 50mcg / 75mcg / 80mcg/ 100 mcg patches > 0.06% Oestrogel 0.75mg > 500mcg / 1mg Sandrena gel > 10mcg vaginal tablets > 7.5mcg vaginal ring
Estriol	> 0.1% / 0.01% vaginal creams, vaginal pessary, 50mcg/g vaginal gel
Conjugated estrogens	> 0.3mg / 0.625mg / 1.25mg

Non-Estrogens	
Gonadomimetic	> 2.5mg oral tablet (systemic treatment)
DHEA Prasterone	> 6.5mg pessary (vaginal treatment)
SERM	> 60mg oral tablet (vaginal treatment)

Progesterones _ ONLY for endometrial protection

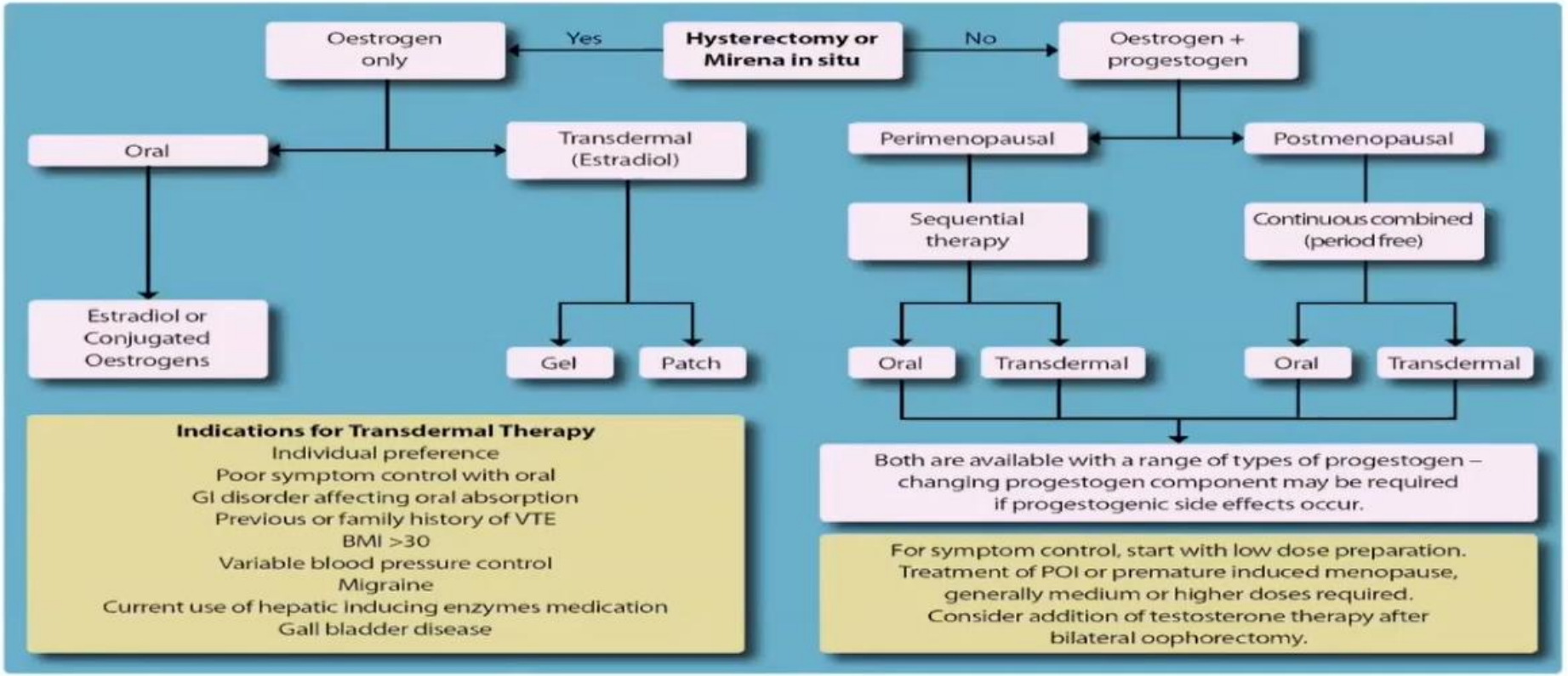
Progestogens	
Norethisterone	
Dydrogesterone	> Combined only
Levonorgestrel	> Combined and IUS
Norgestrel	> Combined only
Micronised progesterone	
Medroxyprogesterone acetate	

Micronised progesterone dosing for endometrial protection

- Oral Route
  - Cyclical 200 mg for 12-14 days per month
  - Continuous 100 mg daily

- Vaginal route
  - Alternate day 100 mg
  - Sequential 45-100 mg at least 10 days a month

Systemic HRT Treatment



Authors: Dr Julie Ayres and Dr Heather Currie in collaboration with the medical advisory council of the British Menopause Society.

PUBLICATION DATE: JULY 2020
REVIEW DATE: JULY 2022

Contraindications of MHT

Box 1. Contraindications of MHT.

- Breast carcinoma – current, in personal anamnesis, suspected
  - invasive breast carcinoma, premalignant changes of breast (atypical ductal hyperplasia, lobular neoplasia) and a ductal carcinoma *in situ* (intraductal carcinoma)
- Estrogen-dependent malignant carcinoma – known or suspected
  - e.g. unfounded bleeding from genitals as a sign of endometrial carcinoma
- Untreated estrogen-dependent carcinomas
  - endometrial carcinoma, breast carcinoma, endometrial stromal sarcoma
- Active hepatopathy
- Anamnestic or current idiopathic thromboembolic disease
  - pulmonary embolism, phlebothrombosis
- Active or recent arterial thromboembolism
  - e.g. coronary thrombosis, angina pectoris
- Known intolerance to a certain constituent of the preparation.

MHT, menopause hormone therapy.

Take Home Message

- Menopausal Hormone Therapy is important and should be prescribed for its benefits unless there are contraindications
- It remains the most effective treatment for vasomotor and hormone related symptoms of the climacteric
- There is a definite role for cardio and osteoprotection
- There is a 10 year window for which therapy can be safely administered for maximum benefit
- Estrogen alone is safer that estrogen + progesterone
- Type of progesterone matters with micronized progesterone , intravaginal and intrauterine delivery ameliorating risk

BOTTOM LINE .....

Is **Hormone Replacement Therapy** (HRT) Safe?