NEW GUIDELINES ON PRESCRIBING PROGESTOGENS IN HRT

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DISCLOSURES

Member of the BMS Medical Advisory Council

Paid facilitator on Menopause Special Skills Course (FSRH)

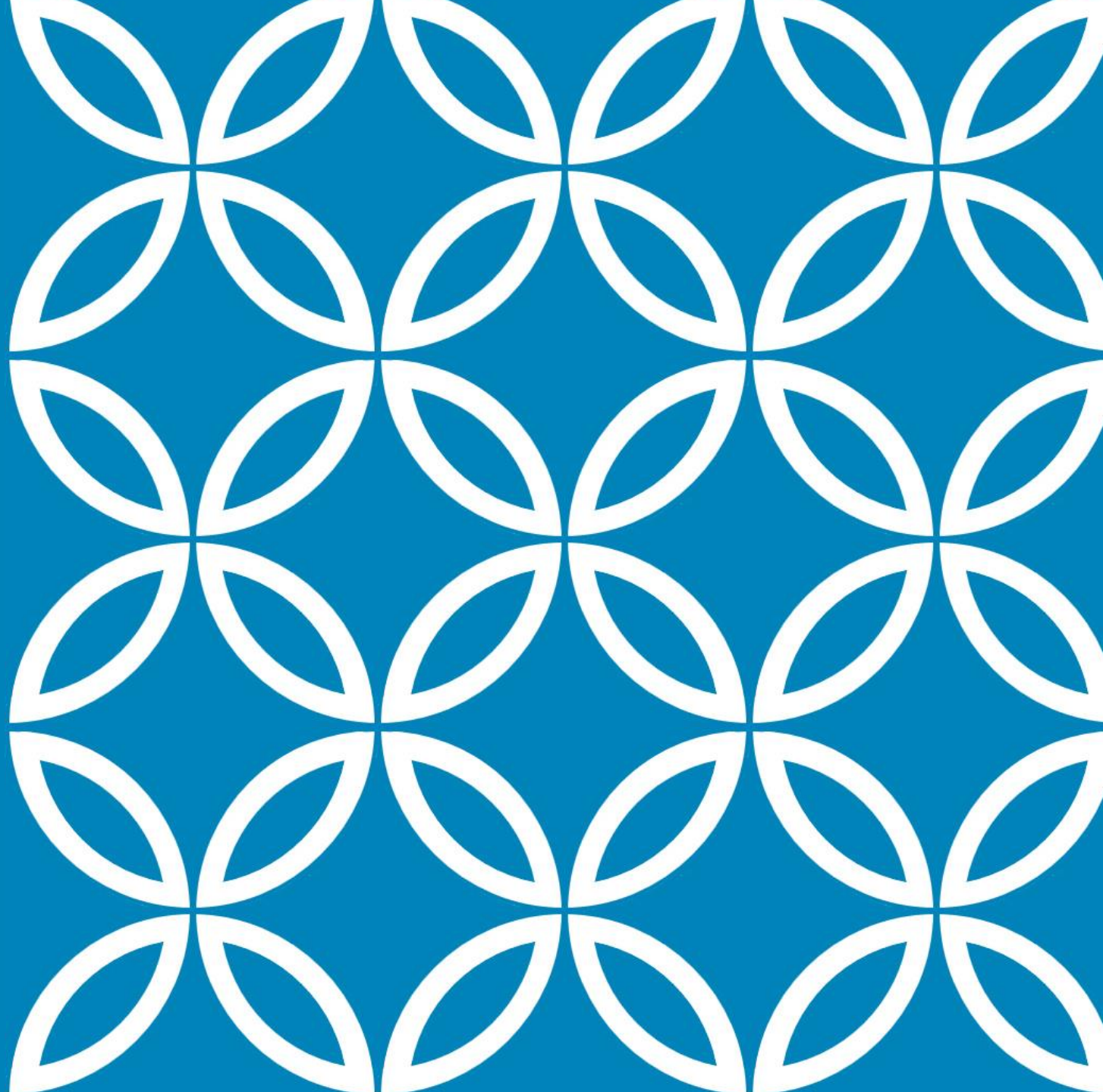
Director of a private menopause clinic, not taking on new patients

Non-promotional educational sessions sponsored by Theramex and Sylk

Part of the Menopause Mandate campaign group

AIMS

- Why have guidelines changed?
- Progestogen doses
- Unscheduled bleeding guidelines
- Prescribing very high dose estrogen
- Estradiol blood tests
- Action points



WHY ARE NEW CONSENSUS GUIDELINES NEEDED?

35% increase in HRT prescribing from 2021to 2022

Unscheduled bleeding (USB) affects 40% of women taking HRT

Massive increase in prescribing of micronised progesterone (MP)

MICRONISED PROGESTERONE (MP) IS A POPULAR OPTION BECAUSE:

Little or no increase in breast cancer risk for first 5 years of use, gradual increase with prolonged use
Neutral effect on coagulation, unlike synthetic oral progestogens
Less androgenic
No adverse effect on LDL cholesterol
Calming and a natural hypnotic for some women

BUT . . .

. . .with increasing use, it is becoming apparent that it is not always effective at keeping the endometrium thin, leading to unscheduled bleeding+++

PLUS…

More women are being given higher doses of estrogen

Recent shortages of Utrogestan and other progestogens

Some women forget their progestogen part of HRT

Some women miss out or reduce the progestogen on purpose due to side-effects

Some are wrongly advised by clinicians to reduce the dose e.g.

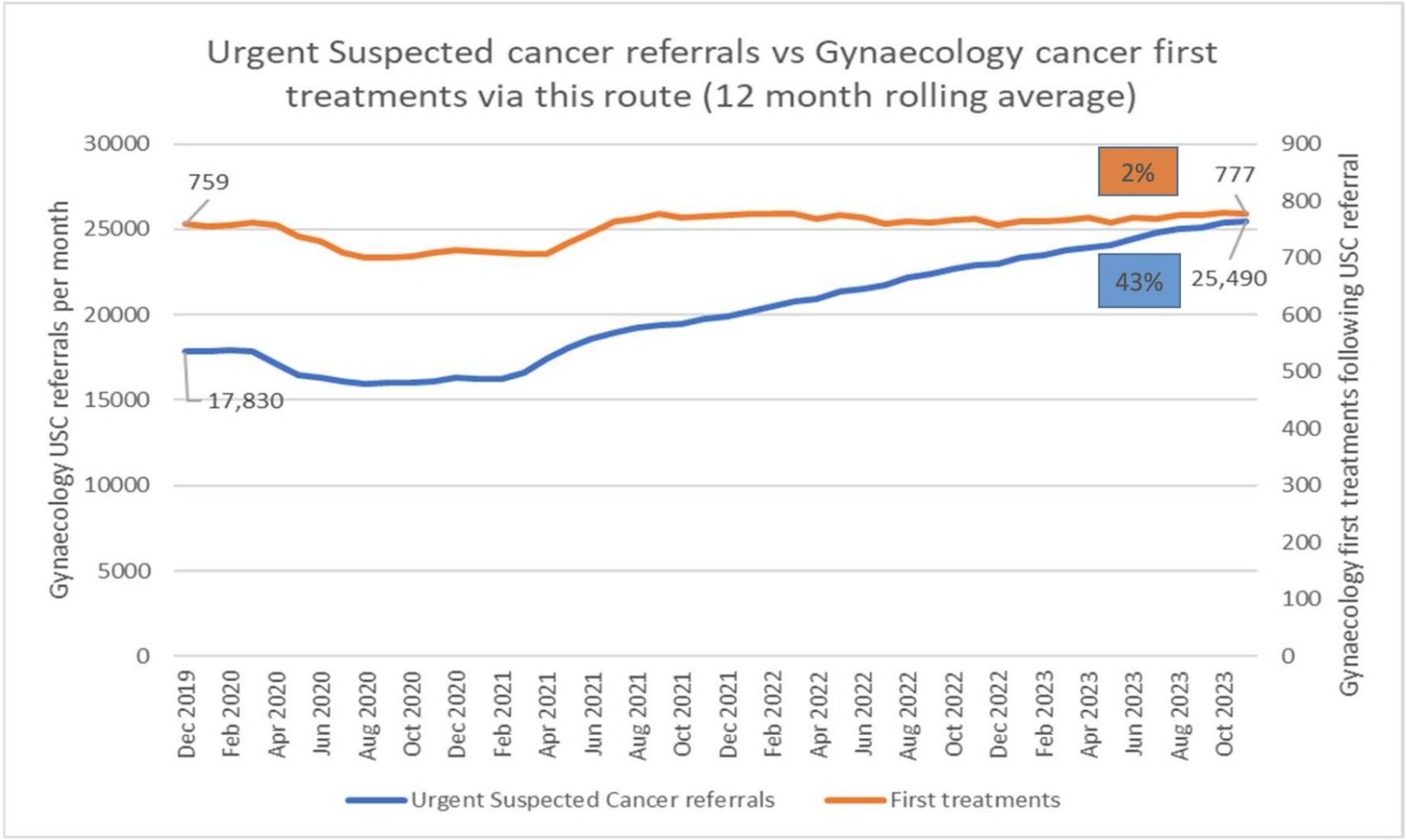
- when using micronised progesterone vaginally
- using 3 monthly regimes (2/52 progestogen per 3/12 of estrogen – not safe)

MISINFORMATION ON SOCIA MEDIA+++

Data from Cancer Alliance Insights Team

- 43% increase in 2WW referrals

- but only 2% increase in cancer



THIS IS IMPACTING ON:

On primary care

On secondary care and 2WW referrals

On our patients (worry and unnecessary investigations)

Worry re endometrial and other cancers although the majority on HRT will have a benign cause for their symptoms.

https://thebms.org.uk/publications/bms-joint-guidelines/management-of-unscheduled-bleeding-on-hormone-replacement-therapy-hrt/

BMS | GUIDELINE

The specialist authority for menopause & post reproductive health

BMS British Menopause Society

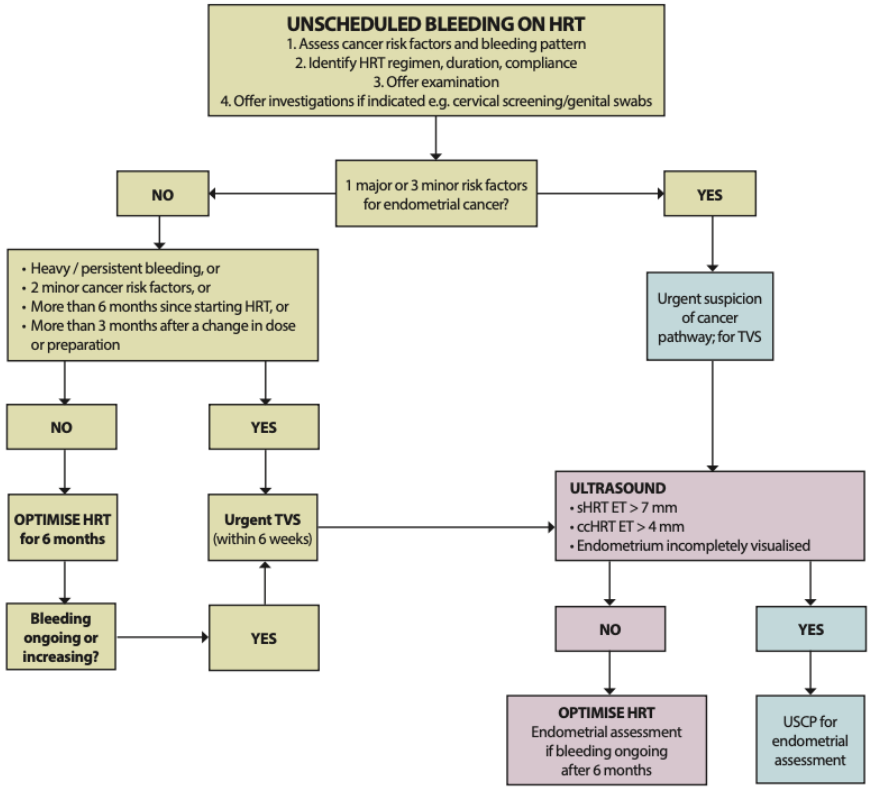
Management of unscheduled bleeding on hormone replacement therapy (HRT)

The British Menopause Society (BMS) is the specialist authority for menopause and post reproductive health in the UK. The BMS educates, informs and guides healthcare professionals, working in both primary and secondary care, on menopause and all aspects of post reproductive health.

BMS guidelines, prepared by the BMS medical advisory council in partnership with other specialist organisations and Royal Colleges, address key disorders and controversial topics relating to menopause and post reproductive health. They reflect new studies together with recent medical and scientific information from articles in professional journals, plus informal consensus.

The guidelines are evidence-based, comprehensively referenced and peer reviewed and they are regularly updated.

Management of unscheduled bleeding on hormone replacement therapy (HRT)



MAJOR risk factors for endometrial cancer

- BMI ≥ 40
- Genetic predisposition (Lynch / Cowden syndrome)
- Estrogen-only HRT for > 6 months in women with a uterus
- Tricycling HRT (quarterly progestogen) for > 12 months
- Prolonged sHRT regimen: use for more than 5 years when started in women aged ≥ 45
- 12 months or more of using norethisterone or medroxyprogesterone acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen

MINOR risk factors for endometrial cancer

- BMI 30-39
- Unopposed estrogen > 3 months but < 6 months
- Tricycling HRT (quarterly progestogen) for > 6 but < 12 months
- > 6 months but < 12 months of using norethisterone or medroxyprogesteorne acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen
- Where the progestogen dose is not in proportion to the estrogen dose for > 12 months (including expired 52 mg LNG-IUD)
- Anovulatory cycles, such as in Polycystic ovarian syndrome
- Diabetes

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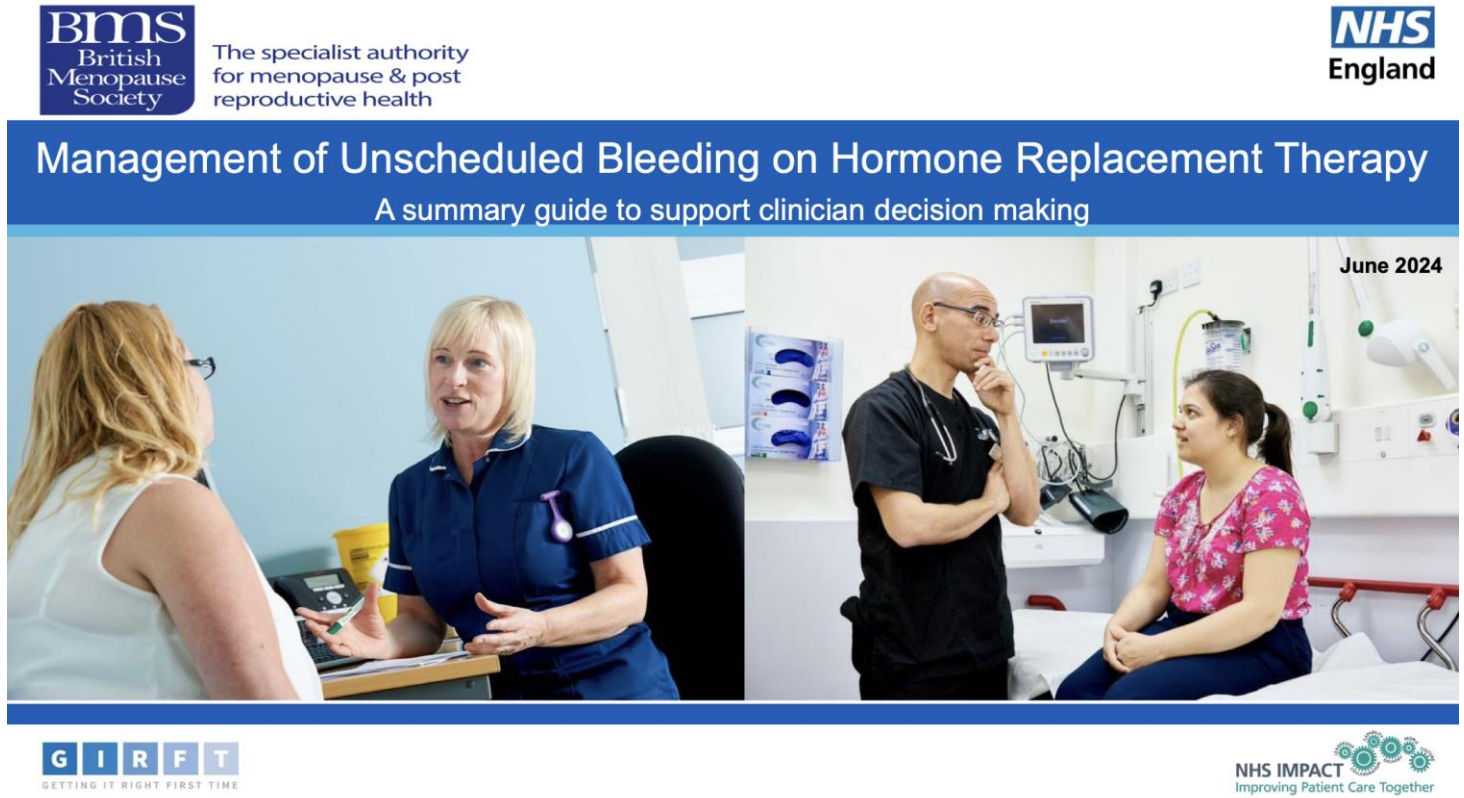
https://gettingitrightfirsttime.co.uk/wp-content/uploads/2024/06/Summary-Guide-Management-of-Unscheduled-Bleeding-on-HRT-June-2024.pdf



FOR PATIENTS

https://www.womens-health-concern.org/wp-content/uploads/2024/08/33-WHC-FACTSHEET-Management-of-unscheduled-bleeding-on-HRT-AUG2024-D.pdf

WOMEN'S HEALTH CONCERN FACT SHEET

Information for women

Management of unscheduled bleeding on HRT

Women's Health Concern

A confidential independent service for women and their partners

The British Menopause Society (BMS) has published a joint guideline on the management of unscheduled bleeding on hormone replacement therapy (HRT).

This WHC factsheet provides a summary version of the clinical guideline for those who use HRT and who may have unscheduled bleeding. The full joint guideline is available on the BMS website and it should be used by healthcare professionals for any clinical decision making.

NO NEED TO WORRY IF USB:

- Occurs within 6 months of starting HRT
- Occurs in first 3 months after a change in HRT

Unless

- Bleeding is prolonged or heavy
- 2+ minor risk factors for endometrial cancer
- A major risk factor for endometrial cancer

ADJUSTING MP IF ONGOING USB

Reduce the estrogen dose

Adjust the MP dose

- increase to 300mg at night for 12 to 14 per cycle for sequential and 200mg every night for continuous

- if sequential can extend the regime to 21 days on/7 days off

- if continuous can try 25 days on/3 days off

- try vaginally – same capsule, dose and regime as oral (must explain is off-licence)

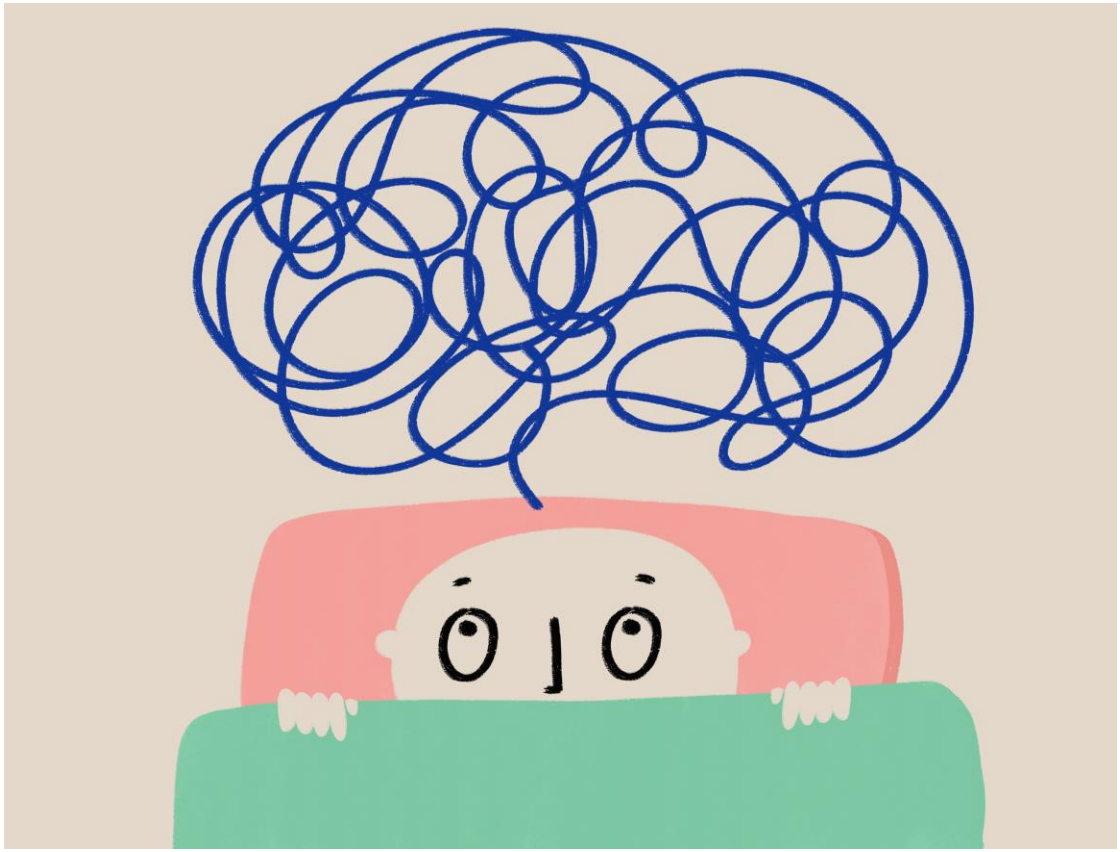
Change back from continuous combined to sequential

Add in desogestrel if perimenopausal

Swap to alternative progestogen (be aware of thrombosis risk)

MIRENA

ALSO NEW GUIDANCE FOR THOSE ON HIGH DOSE ESTROGEN (EVEN IF NOT BLEEDING)



Key: Prescribed estrogen dose for ultra-low, low, standard, moderate and high dose regimens

	Ultra-low dose	Low Dose	Standard dose	Moderate dose	High dose
Oestrogel	½ pump	1 pump	2 pumps	3 pumps	4 pumps
Sandrena	0.25 mg	0.5 mg	1 mg	1.5-2 mg	3 mg*
Lenzetto spray	1 spray	2 sprays	3 sprays	4-5 sprays*	6 sprays*
Patch	12.5 µg	25 µg	50 µg	75 µg	100 µg
Oral estradiol	0.5 mg	1 mg	2 mg	3 mg^	4 mg^

* Off-license use
mg = milligrams
^ Off-license use – rarely required to achieve symptom control
µg = micrograms

Progestogen dose per licensed estrogen dose in the baseline population

Estrogen dose	Micronised Progesterone		Medroxy progesterone		Norethisterone		LNG-IUD (52mg)
	continuous	sequential	continuous	sequential	continuous	sequential	
Ultra/Low	100 mg	200 mg	2.5 mg	10 mg	5 mg*	5 mg*	One – for up to 5 years of use
Standard	100 mg	200 mg	2.5-5 mg	10 mg	5 mg*	5 mg*	
Moderate	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	
High	200 mg+	300 mg+	10 mg^	20 mg^	5 mg	5 mg	

*1 mg provides endometrial protection for ultra-low to standard dose estrogen but the lowest stand-alone dose currently available in the UK is 5 mg (off-license use of three noriday POP i.e 1.05 mg, could be considered if 5 mg is not tolerated).
^There is limited evidence in relation to optimal MPA dose with high dose estrogen; the advised dose is based on studies reporting 10 mg providing protection with up to moderate dose estrogen.
+There are limited evidence in relation to optimal micronised progesterone dose for moderate or high dose estrogen; until evidence is available to guide practice, the advised dose is based on studies reporting 100 mg/day providing protection with up to standard dose estrogen.
If unscheduled bleeding occurs with ultra-low to moderate dose estrogen, and other progestogens are not acceptable, offer micronised progesterone at the dosage recommended for high dose estrogen.

INCREASING MP DOSE ON HIGH DOSE ESTROGEN

If sequential – take 300mg MP at bedtime for 12 to 14 days per cycle

If on continuous combined – increase to 200mg MP daily at bedtime

BUT

Some women may get unacceptable side-effects

No data on safety of these regimes

We need to share uncertainty with patients

COULD CONSIDER

- reducing estrogen dose instead
- changing to a 52mg LNG-IUD or a different progestogen

MIRENA

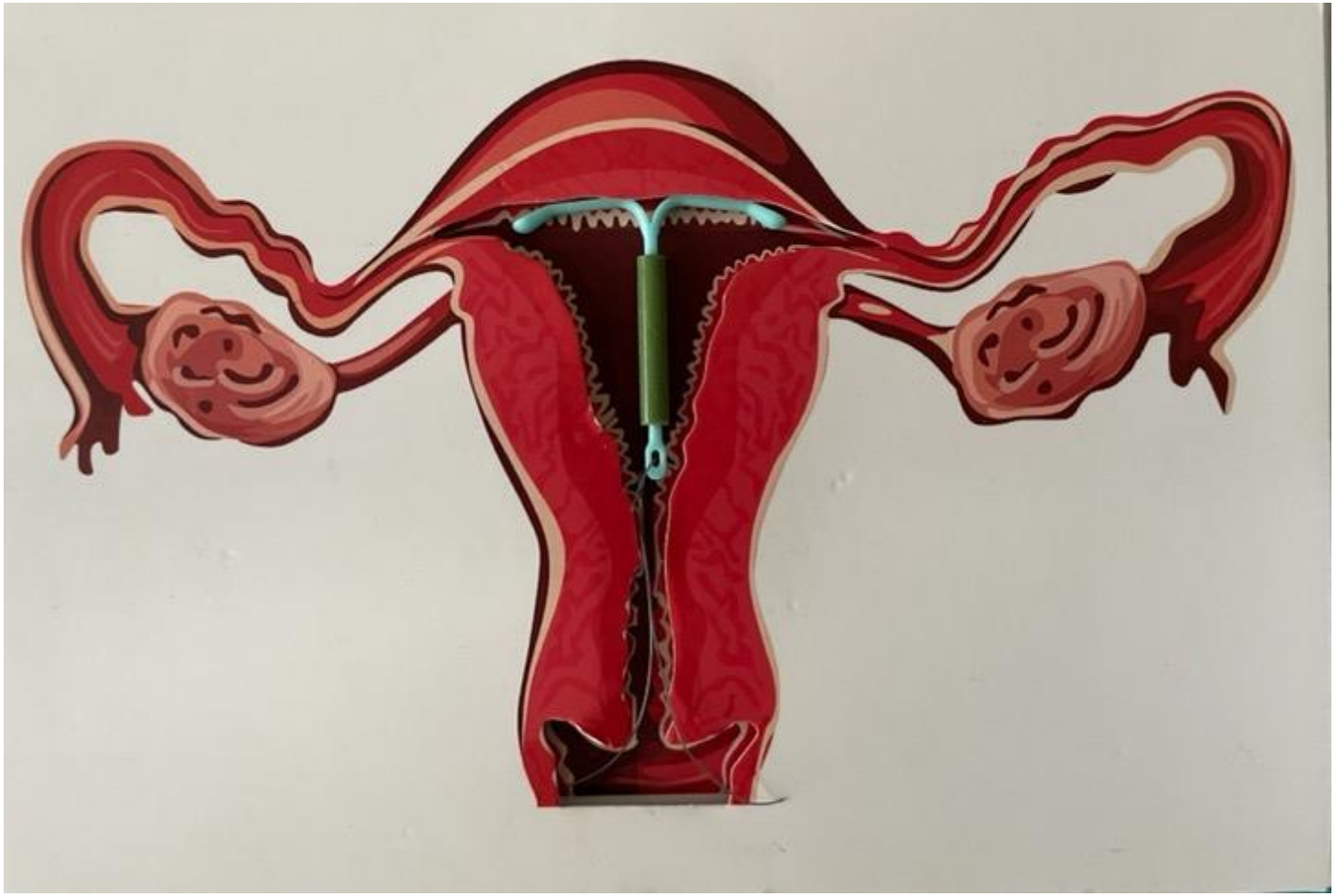
Licensed for 4 years for endometrial protection

BUT

Is authorised for 5 years by FSRH

Levosert/Benilexa (the other 52mg LNG IUD) can now also be used but the lower dose options can not

Safest option for obese patients



COMBINED PATCHES

Containing norethisterone

- Evorel Sequi
- Evorel Conti

Containing levonorgestrel

- FemSeven Conti

ORAL COMBINED HRT – MOST CONTAIN SYNTHETIC PROGESTOGENS, SUGGESTED OPTIONS:

FEMOSTON PRODUCTS

Contain dydrogesterone

Similar safety profile to MP

BIJUVE

New tablet, fixed dose

Estradiol 1mg plus Utrogestan100mg

IF STILL SYMPTOMATIC ON STANDARD HIGH DOSE ESTROGEN

Check how/where using product

- correct site?
- do patches irritate or fall off?
- is the gel being rubbed in? (not recommended)
- are other lotions being applied before or too soon afterwards?
- is the gel being washed off as showering/swimming too soon?

Consider changing product or delivery method rather than increasing dose above recommended doses

Rarely need to go higher than maximum recommended doses

Symptoms of too much estrogen can be the same as not enough estrogen

ADDRESS ANY LIFESTYLE ISSUES

IS THERE ANOTHER CAUSE FOR THEIR SYMPTOMS?

PRESCRIBING ESTROGEN DOSES ABOVE 100MCG PATCH OR EQUIVALENT

This has recently become a big issue, mainly initiated in some private menopause clinics who may be:

- Starting patients at 100mcg patch and/or increasing dose too quickly (ideally should wait 3/12 before changing estrogen dose)
- Sometimes adding extra measures of gel or spray to maximum dose estrogen patch or extra estrogen to a combined patch
- Relying on estradiol blood tests to show patients are poor absorbers

N.B. Women can feel awful if/when try to reduce the dose

HOW RELIABLE ARE ESTRADIOL LEVELS?

- Not very!
- Can't do on oral estrogen, debatable on Lenzetto spray
- Test can't distinguish between endogenous and exogenous estradiol
- Many factors affect absorption of gel or patch so levels variable in same person at different times
- Many other factors affect the result e.g. conversion to other estrogens

The estradiol blood test does not accurately reflect estrogen levels in cells

WHEN ARE ESTRADIOL BLOOD LEVELS NEEDED?

- Rarely – we are moving away from doing these
- Guided by symptom control instead
- Can occasionally consider (accepting the limitations) to check absorption if still symptomatic on maximum licensed dose of estrogen patch or gel (trough level for gel)
- If very low (e.g. less than 75 - 100 pmol/l), can indicate non-absorption, then change product rather than increase dose

APRIL 2023

BMS Members
News Alert

The following news has just been published on the BMS website:

Joint BMS FSRH RCGP RCOG SfE and RCN Women's Health Forum safety alert

Joint safety alert from the British Menopause Society, Faculty of Sexual & Reproductive Healthcare, Royal College of General Practitioners, Royal College of Obstetricians & Gynaecologists, Society for Endocrinology and the Royal College of Nursing Women's Health Forum.

This safety alert has been produced in response to questions raised in relation to appropriate doses of oestrogen and progestogen provided to women experiencing symptoms of menopause.

It is important that women requiring treatment are managed safely within established guidelines set out by the National Institute for Health and Care Excellence (NICE), MHRA and national and international guidance. The guidance is to aim for the lowest effective dose to control symptoms.

BMS STATEMENT ON TACHYPHYLAXIS

News

Tachyphylaxis with HRT

12 September 2023

We are aware of an increase in the number of women being prescribed high dose estradiol, outside of product licence. In some circumstances, this may be acceptable, as some women do not absorb medication well through their skin. This would be supported by low systemic estradiol levels. However, some women prescribed high dose estradiol will have levels in excess of what is needed to control menopausal symptoms, irrespective of where the women is in the menopause transition. This can lead to a syndrome, known as tachyphylaxis, in which women with high estradiol levels continue to experience menopausal symptoms, leading them to believe that they need more estrogen. However, higher levels of estrogen can also cause adverse mood related symptoms.

Menopause and mood

Some women experience depression and anxiety during the menopause transition and post-menopausal period. This can occur for several reasons, including fluctuating estrogen levels and the impact that this has in the central nervous system (CNS). There is no Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) definition or classification for depression associated with the menopause transition, reflecting the lack of understanding of this problem[1]. NICE guideline NG23 recommends that clinicians "Consider HRT to alleviate low mood that arises as a result of the menopause" and also recommends cognitive behavioural therapy (CBT)[2]. The use of antidepressant medication first line for depression linked specifically with menopause is associated with modest or poor outcomes[1] and estrogen (with a progestogen if required), delivered within the physiological range, is increasingly being used for its potential beneficial effect on mood in peri and post-menopausal women.

Tachyphylaxis

Tachyphylaxis is a medical term describing a decrease in response to a previously effective drug treatment. In the case of estrogen, this means that women feel as though they need increasingly higher doses to achieve symptom control. However, increasing the dose of estrogen, outside of licence, can lead to high or supraphysiological estradiol levels which can be associated with low mood or anxiety, in contrast to any beneficial effect seen with standard licensed doses in many women and reported in the Kronos Early Estrogen Prevention Study (KEEPS)[3]. Women with pre-existing mental health problems appear to be particularly sensitive to adverse effects in relation to mood, in association with excessively high levels of estradiol.

Tachyphylaxis with estradiol implants is a well-recognised phenomenon[4], and a similar adverse response to high systemic levels of estrogen was suggested more recently in association with use of estradiol, delivered transdermally[5].

In conclusion, there is a lack of understanding between hormone levels associated with the menopause and the impact that these have on depression in mid-life women. Care is needed, particularly in women with pre-existing psychiatric problems, to ensure that supraphysiological estradiol levels are avoided. When physiological levels of estradiol are not found to improve mood symptoms in menopausal women, it is important to consider other potential underlying causes including mental illness, psychological and social factors. This is likely to require close collaboration with the patient's psychiatric team or general practitioner to ensure that the most appropriate treatment is provided.

[1] Herson, M., Kulkarni, J. (2022) 'Hormonal Agents for the Treatment of Depression Associated with the Menopause'. Drugs and Aging, 39(8), pp607-618.

[2]NICE Guideline NG23 Menopause: Diagnosis and Management

[3] Miller, V.M. et al. (2019) 'The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned?', Menopause (New York, N.Y.), 26(9), pp. 1071–1084.

[4] Garnett, T. et al. (1990) 'Hormone implants and tachyphylaxis', BJOG: an international journal of obstetrics and gynaecology, 97(10), pp. 917–921.

[5] Kersey, N., Briggs, P. (2019) 'Possible tachyphylaxis with transdermal therapy'. Post Reproductive Health 25 (2), 111-112.

ACTION POINTS

Adequate endometrial protection

- Can sort out progestogen dose at annual HRT check or via practice pharmacist
- Always ask patient re progestogen use at review
- FAQ document coming soon
- App planned to help with USB decision-making

Safe estrogen doses

- No safety data or guidance for those over the maximum recommended dose
- Patients need to be informed when prescribed off-license doses
- Consider each case individually, reduce slowly or change product where possible but some younger women, e.g. with POI, may need slightly higher doses

THANK YOU