New Medicine Assessment

UTROGESTAN CAPSULES (ORAL)

Hormone Replacement Therapy (HRT)

Recommendation: GREEN for the following indications:

Progestogenic opposition of oestrogen HRT in women with an intact uterus.

Summary of supporting evidence:

- Progesterone is an established therapy with a well-known efficacy and safety profile.
- NICE recommends prescribing progesterone alongside oestrogen HRT in menopausal women with a uterus.
- The addition of progestogen to unopposed oestrogen therapy in women with intact uteri significantly reduces the risk of endometrial hyperplasia, when either sequential or continuous combined regimens are adopted.
- Utrogestan was licensed in 2003, so it is not new to the market and has been prescribed for many years.
- Systematic review evidence shows oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200mg/day for up to five years.
- Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens.
- Micronised progesterone is an oral equivalent to endogenous progesterone and is less androgenic than the testosterone derivatives.
- Micronised progesterone compared favourably with MPA with respect to bleeding patterns and lipid metabolism.
- Utrogestan is comparatively more costly than other progesterone only alternatives.
- Provides another alternative during periods of HRT supply problems.

Details of Review

Name of medicine (generic & brand name)**:**

Utrogestan (micronised progesterone)

Strength(s) and form(s):

100mg oral capsules

200mg vaginal capsules

Dose and administration:

Capsules (oral)[1]

The recommended dose is 200 mg daily at bedtime, for twelve days in the last half of each therapeutic cycle (beginning on Day 15 of the cycle and ending on Day 26). Withdrawal bleeding may occur in the following week.

Alternatively 100 mg can be given at bedtime from Day 1 to Day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule.

Capsules (vaginal)[2] (for Assisted Reproductive Technology)

The recommended dosage is 600 mg/day, in three divided doses, from the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy.

BNF therapeutic class / mode of action:

Sex hormones[3]

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability.

In women with a uterus a progestogen needs to be added to long-term oestrogen therapy for hormone replacement, to prevent cystic hyperplasia of the endometrium and possible transformation to cancer; it can be added on a cyclical or a continuous basis. Combined packs incorporating suitable progestogen tablets are available.

Licensed indication(s):

Utrogestan is indicated for adjunctive use with estrogen in post-menopausal women with an intact uterus, as hormone replacement therapy (HRT).1

Utrogestan Vaginal 200 mg Capsules is indicated in women for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.2

Proposed use (if different from, or in addition to, licensed indication above):

Progestogenic opposition of oestrogen HRT in women with an intact uterus.

Course and cost:

Progesterone micronised 100mg capsules (Utrogestan) x 30 = £5.13

Annual cost of treatment:

2 regimens licensed:

- Option 1 uses 24 caps for every 28 day cycle
- Option 2 uses 25 caps for every 28 day cycle

Assuming 13 cycles/year

- 13 x 24 = 312 capsules 312/30 = 10.4 packs
- 13 x 25 = 325 capsules 325/30 = 10.8 packs

Approx. 11 packs annually = 11 x £5.13 = £56.43

Price as per Drug Tariff Jan 2022

Current standard of care/comparator therapies:

There are two main groups of progestogen:

- Progesterone and its analogues
    - Dydrogesterone (available only in combination with oestrogens)
    - Medroxyprogesterone acetate (MPA)
    - Micronised progesterone (Utrogestan)
- Testosterone analogues
    - Norethisterone
    - Norgestrel
        - The newer progestogens (desogestrel, norgestimate, and gestodene) are all derivatives of norgestrel
        - levonorgestrel is the active isomer of norgestrel and has twice its potency.

Progesterone and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.3

Micronised progesterone is the only oral progestogen available that is equivalent to endogenous progesterone.

In practice there is reported off licence use of vaginal (Utrogestan, Cyclogest, Lutigest) and licensed intrauterine (Levonorgestrel) progesterone for endometrial protection.7

Relevant NICE guidance:

[NG23] Menopause: Diagnosis and Management[4]

- Vasomotor symptoms:
    - 1.4.2 Offer women HRT for vasomotor symptoms after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Offer oestrogen and progestogen to women with a uterus.
    - 1.4.5 Consider HRT to alleviate low mood that arises as a result of the menopause.

[QS143] Menopause[5]

- Quality statement 4: Reviewing treatments for menopausal symptoms
    - Women having treatment for menopausal symptoms have a review 3 months after starting each treatment and then at least annually.

NICE CKS[6]

Women vary in their tolerance to progestogens and changing the progestogen component of combined HRT may be needed if progestogenic adverse effects occur.

Progestogen-related adverse effects include:

Fluid retention, breast tenderness, headaches or migraine, mood swings, premenstrual syndrome-like symptoms, depression, acne vulgaris, lower abdominal pain, and back pain. They tend to occur in a cyclical pattern during the progestogen phase of cyclical HRT.

Micronized progesterone or dydrogesterone may be preferred in women with hypertriglyceridaemia due to their neutral effect on lipid profile.

Background and context

There are more than 11 million women over the age of 45 in the UK according to the Office of National Statistics 2011 census. This number has been steadily increasing and is forecast to continue to rise. The associated increase in the number of women going through the menopause is expected to result in more GP consultations and more new referrals to secondary care of women needing short-term symptom control and those who have associated long-term health issues.

Menopause is a biological stage in a woman's life when she is no longer fertile and is marked by the cessation of menstruation. A woman is defined as postmenopausal from 1 year after her last period. The changes associated with menopause and the perimenopause (the years leading up to the menopause) occur when ovarian function diminishes and ceases. This includes the cessation of both egg (oocyte) maturation and sex hormone (principally oestrogen and progesterone) secretion.4

A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle or a preparation which involves continuous administration of an oestrogen and a progestogen (or one which provides both oestrogenic and progestogenic activity in a single preparation). Continuous combined preparations or tibolone are not suitable for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT.3

Progestogen administration is required to oppose naturally produced or administered oestrogens to provide endometrial protection. Within HRT regimens, this should be delivered for at least the same duration as that produced during the luteal phase of the monthly cycle and in the recommended doses to protect against the risk of endometrial hyperplasia and endometrial cancer.7

Summary of evidence

Summary of efficacy data in proposed use:

British menopause Society (2021)[7]

Systematic review evidence showed oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200mg/day for up to five years.

The dose of the progestogen should be proportionate to the dose of oestrogen. Women who require high dose oestrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection.

Based on current evidence if progesterone were considered for vaginal administration (out of license use) in women who experience side effects with oral intake, this should be given in similar doses and durations to those applied to oral progesterone intake with HRT. There is limited evidence assessing the efficacy and the optimal regimen of vaginal progesterone administration in the context of HRT.

Cochrane (2012)[8]

Unopposed oestrogen is associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years.

For women with a uterus the risk of endometrial hyperplasia with hormone therapy comprising low-dose oestrogen continuously combined with a minimum of 1 mg norethisterone acetate

(NETA) or 1.5 mg medroxyprogesterone acetate (MPA) is not significantly different from placebo at two years (1 mg NETA: OR 0.04; 95% confidence interval (CI) 0 to 2.8; 1.5 mg MPA: no hyperplasia events).

The addition of progestogen to unopposed oestrogen therapy in women with intact uteri significantly reduced the risk of endometrial hyperplasia, when either sequential or continuous combined regimens were adopted.

Note: Micronised progesterone did not appear to have been used in the studies included in this review.

This review is restricted to trials of oral hormone therapy (HT). However it should be noted that intrauterine progestogen-releasing systems are available, and can be used in combination with oral oestrogen in HT. Intrauterine progestogen-releasing systems induce profound endometrial suppression and may overcome many of the problems of sensitivity to systemic progestogens while also offering benefits such as control of heavy menstrual bleeding and contraception in perimenopausal women.

Scottish Medicines Consortium (2009)[9]

Following a full submission micronised progesterone (Utrogestan) is not recommended for use within NHS Scotland for adjunctive use with oestrogen in post-menopausal women with an intact uterus (HRT).

The pivotal trial demonstrated that micronised progesterone at a dose of 200mg daily for 12 days of the cycle was as effective as the two MPA regimens in protecting the endometrium from the hyperplastic changes associated with oestrogen therapy.

No evidence on the use of the 100mg dose of micronised progesterone was submitted.

The submitting company has suggested that micronised progesterone is likely to be reserved for patient's intolerant of synthetic progestogens or for those with diabetes or a family history of breast cancer, however there is no evidence of efficacy in these specific patient populations.

Due to the lack of formal economic analysis to justify the additional cost of the treatment and the inappropriate comparator the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

- An analysis of the 596 women with intact uterus revealed endometrial hyperplasia rates after three years of 2.5%, 62%, 1%, 5% and 5% for the placebo, oestrogen monotherapy, oestrogen plus continuous MPA, oestrogen plus cyclic MPA, and oestrogen plus micronised progesterone groups, respectively.
- Analysis of episodes of excess bleeding in women with a uterus who took at least 80% of their assigned medication demonstrated that the 3-year cumulative quantities, days, and episodes of bleeding were significantly lower for oestrogen plus cyclic micronised progesterone than for oestrogen plus cyclic MPA.
- Intention-to-treat analyses found mean changes from baseline in high-density lipoprotein cholesterol (HDL-C) of: placebo (decrease of 0.03mmol/L); MPA regimens (increases of 0.03 to 0.04mmol/L); oestrogen plus micronised progesterone (increase of 0.11mmol/L) and oestrogen monotherapy (increase of 0.14mmol/L).
- For all hormone regimens, HDL-C levels increased during the first 6 to 12 months and gradually decreased thereafter, although not to baseline level. Women treated with oestrogen plus micronised progesterone had significantly higher HDL-C levels than women treated with oestrogen plus MPA.
- All active treatments produced decreases in mean low-density lipoprotein cholesterol (of 0.37 to 0.46mmol/L), and increases in mean triglyceride (of 0.13 to 0.15mmol/L) that differed significantly from placebo.
- The manufacturer submitted a simple drug budget impact analysis comparing micronised progesterone with MPA in post-menopausal women with an intact uterus. The

manufacturer estimated that the introduction of micronised progesterone would result in an increased cost of £15.48 per patient per year.

The main weaknesses of the analysis were:

- No formal economic evaluation was carried out
- The comparator used was inappropriate given the positioning of micronised progesterone as a second-line therapy for patients unable to tolerate synthetic progestogens.
- No clinical evidence or drug cost comparison was presented comparing micronised progesterone with levonorgestrel IUS or with existing oestrogen/anti-androgenic progestogen combinations.

Summary of safety data:

British menopause society consensus statement (updated 2021)[10]

Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens.

British menopause society and Women's health concern (2020)[11]

Current evidence suggests that oestrogen alone HRT is associated with little or no change in the risk of breast cancer while combined HRT can be associated with an increased risk which appears duration dependent and may vary with the type of progestogen used. However, this risk is low in both medical and statistical terms, particularly compared to other modifiable risk factors such as obesity and alcohol intake, and this should be taken in the context of the overall benefits obtained from using HRT. Vaginal oestrogen is not associated with an increased risk in breast cancer. Large observational trial data suggest that micronised progesterone and dydrogesterone are likely to be associated with a lower risk of invasive breast cancer compared to that noted with other progestogens.

Micronised progesterone has a more selective effect on progesterone receptors and results in less interaction with androgenic and mineralocorticoid receptors compared with other progestogens. Micronised progesterone can minimise the metabolic impact and side-effects associated with other progestogens.

Women with perimenopausal depression are often intolerant to progestogens, with many women reporting mood changes during the progestogenic component of combined sequential HRT. Micronised progesterone is associated with fewer side-effects than the more androgenic progestogens which are best avoided in such women.

The type of progestogen significantly affects VTE risk with micronised progesterone and dydrogesterone conferring a lower risk compared to that with other synthetic progestogens. Consideration should also be given to using micronised progesterone or dydrogesterone in women at risk of VTE as these are unlikely to increase the risk of venous thrombosis compared with other progestogen preparations.

A systematic review by Stute et al. (2016) assessed the impact of micronised progesterone on the endometrium. Forty studies were included in the systematic review and it concluded that oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200 mg/day for up to five years. In addition, vaginal micronised progesterone may provide endometrial protection if applied sequentially for 10 days/month in a dose of 45 mg/day at 4% for up to 3–5 years. The systematic review concluded that transdermal micronised progesterone does not provide sufficient endometrial protection.

Collaborative Group on Hormonal Factors in Breast Cancer, Lancet (2019)[12]

Principal analyses used individual participant data from all eligible prospective studies that had

sought information on the type and timing of Menopausal Hormone Therapy (MHT) use. Studies were identified from Jan 1, 1992, to Jan 1, 2018. During prospective follow-up, 108 647 postmenopausal women developed breast cancer at mean age 65 years (SD 7); 55 575 (51%) had used MHT. Every MHT type, except vaginal oestrogens, was associated with excess breast cancer risks, which increased steadily with duration of use and were greater for oestrogen-progestagen than oestrogen only preparations.

During years 5–14 of use of an oestrogen-progestagen combination, the risk ratio (RR) was greater for oestrogen plus daily progestagen than for oestrogen plus intermittent progestagen (which usually involved 10–14 days of progestagen per month); RR 2·30 (2·21–2·40) and RR 1·93 (1·84–2·01), respectively, heterogeneity p<0·0001.

In general, the RR did not differ substantially by the progestagenic constituent of the combinations, including rarely used hormones, such as micronised [natural] progesterone (RR 2·05, 1·38–3·56), although the RR appeared to be somewhat lower for oestrogen plus dydrogesterone. The RR was significantly increased during years 5–14 of progestagen-only MHT (1·39, 1·11–1·75; p=0·0055) and of tibolone (1·57, 1·43–1·72; p<0·0001).

British Menopause Society (2019)[13]

BMS response to Lancet paper on the link between different forms of HRT and breast cancer incidence:

The report showed an increase in the risk of breast cancer with HRT intake. The meta-analysis sought information on breast cancer incidence but did not collect information on breast cancer mortality.
The review only included a small number of women on micronised progesterone and as a result it would be difficult to draw meaningful conclusions from this report on the risk of breast cancer with micronised progesterone.

Cochrane (2017)[14]

In relatively healthy postmenopausal women (i.e. generally fit, without overt disease), combined continuous HT increased the risk of a coronary event (after 1 year's use: from 2 per 1000 to between 3 and 7 per 1000), venous thromboembolism (after 1 year's use: from 2 per 1000 to between 4 and 11 per 1000), stroke (after 3 years' use: from 6 per 1000 to between 6 and 12 per 1000), breast cancer (after 5.6 years' use: from 19 per 1000 to between 20 and 30 per 1000), gallbladder disease (after 5.6 years' use: from 27 per 1000 to between 38 and 60 per 1000) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: from 5 per 1000 to between 6 and 13 per 1000).

Women over 65 years of age who were relatively healthy and taking continuous combined HT showed an increase in the incidence of dementia (after 4 years' use: from 9 per 1000 to 11 to 30 per 1000). Among women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism (at 1 year's use: from 3 per 1000 to between 3 and 29 per 1000). Women taking HT had a significantly decreased incidence of fracture with long-term use.

Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented.

Scottish Medicines Consortium (2009)[9]

In the pivotal trial, there was no difference in adverse effects between the micronised progesterone and medroxyprogesterone treatment arms.

Micronised progesterone compared favourably with MPA with respect to bleeding patterns and lipid metabolism.

Limited safety evidence suggests a lower risk of breast cancer with micronised progesterone compared with synthetic progestogens.

There is no trial evidence comparing micronised progesterone with its closest analogue, dydrogesterone. Neither is there evidence comparing micronised progesterone with synthetic progestogens administered by non-oral routes, eg. levonorgestrel intrauterine system which SMC experts have indicated is an option for patient's intolerant of oral synthetic progestogens.

A prospective French cohort trial assessed the association between different HRT regimens and breast cancer risk. During follow-up, (mean duration 8.1 postmenopausal years), 2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women. The association of oestrogen–progestogen combinations with breast cancer risk varied significantly according to the type of progestogen: compared with never-users, the relative risk was 1.00 (95% CI: 0.83 to 1.22) for oestrogen plus a natural micronised progesterone, 1.16 (95% CI: 0.94 to 1.43) for oestrogen plus dydrogesterone and 1.69 (95% CI: 1.50 to 1.91) for oestrogen combined with other progestogens.

SPC[1]

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Utrogestan 100 mg Capsules are not suitable:

- in confirmed pregnancy
- in the treatment of premature labour, or
- as a contraceptive

The table below lists adverse experiences who received cyclic micronized Progesterone capsules, 200 mg daily (12 days per calendar month cycle) with daily 0.625 mg conjugated estrogen, in a multicenter, randomised, double-blind, placebo-controlled clinical trial (Postmenopausal Estrogen and Progestin Interventions (PEPI) Trial):

Adverse experiences (>10%) reported in an 875 patient placebo-controlled trial in postmenopausal women over a 3-year period				
System Organ Class	**Preferred Term**	**Micronized progesterone capsules 200 mg with conjugated estrogens 0.625 mg (N=178)**	**Conjugated estrogens 0.625 mg (only) (N=175)**	**Placebo (N=174)**
Gastrointestinal disorders	Abdominal bloating	12	10	5
	Abdominal pain	10	13	10
Nervous system disorders	Headache	31	30	27

	Dizziness	15	5	9
Psychiatric disorders	Depression	19	18	12
Reproductive system and breast disorders	Breast tenderness	27	16	6
	Hot flushes	11	14	35
	Vaginal discharge	10	10	3
Miscellaneous	Joint pain	20	22	29
	Urinary problems	11	10	9

Post-Marketing experience

The information given below is based on extensive post marketing experience, primarily from oral administration of progesterone.

System organ class	**Frequency Not known (cannot be estimated from the available data)**
Gastrointestinal disorders	Abdominal pain Nausea
General disorders and administration site conditions	Fatigue
Nervous system disorders	Headache Somnolence Dizziness
Reproductive system and breast disorders	Vaginal haemorrhage
Skin and subcutaneous tissue disorders	Pruritus

Strengths and limitations of the evidence:

Strengths

- Progesterone is an established therapy with a well-known efficacy and safety profile.
- NICE recommends prescribing progesterone alongside oestrogen HRT in menopausal women with a uterus.
- The addition of progestogen to unopposed oestrogen therapy in women with intact uteri significantly reduces the risk of endometrial hyperplasia, when either sequential or continuous combined regimens are adopted.
- Micronised progesterone is an oral equivalent to endogenous progesterone and is less androgenic than the testosterone derivatives.
- Utrogestan was licensed in 2003, so it is not new to the market and has been prescribed for many years.
- Systematic review evidence shows oral micronised progesterone provides endometrial protection if applied sequentially for 12–14 days/month in a dose of 200mg/day for up to five years.
- The pivotal trial demonstrated that micronised progesterone at a dose of 200mg daily for 12 days of the cycle was as effective as the two MPA regimens in protecting the endometrium from the hyperplastic changes associated with oestrogen therapy.
- Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens.
- Micronised progesterone compared favourably with MPA with respect to bleeding patterns

and lipid metabolism.
- Micronised progesterone or dydrogesterone may be preferred in women with hypertriglyceridaemia due to their neutral effect on lipid profile.

Limitations

- Following a full submission micronised progesterone (Utrogestan) is not recommended for use within NHS Scotland for adjunctive use with oestrogen in post-menopausal women with an intact uterus due to the lack of formal economic analysis to justify the additional cost of the treatment and an inappropriate comparator.
- There is no trial evidence comparing micronised progesterone with its closest analogue, dydrogesterone. Neither is there evidence comparing micronised progesterone with synthetic progestogens administered by non-oral routes, eg. levonorgestrel intrauterine system
- Comparatively more costly than other progesterone only alternatives.
- The pivotal trial does not include data for the 100mg dosing regimen.

Summary of evidence on cost effectiveness:

Prescribing and risk management issues:

MHRA Drug Safety Update (2019): Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping.[15]

MHRA Drug Safety Update (2014): Hormone-replacement therapy: updated advice.[16]

Utrogestan capsules should not be used by patients with known hypersensitivity to soy or peanut.[1]

Commissioning considerations:

Innovation, need and equity implications of the intervention:

None identified

Financial implications of the intervention:

Approx annual cost per patient of **Utrogestan** 100mg oral capsules in regimens defined above = £56

In the 12 months up to and including November 2021 Utrogestan 100mg capsules were prescribed to 2285 patients across Lancashire at a total cost of £65,245.

Annual cost of relevant comparators per patient

MPA - 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle[3] = approx. £45

Levonorgestrel – 20mcg/24 hours, intra-uterine administration; effective for 4 years[3] = £22

Dydrogesterone - Available only in combination with oestrogens

Price as per Drug Tariff Jan 2022

Service Impact Issues Identified:
None identified
Equality and Inclusion Issues Identified:
None identified
Cross Border Issues Identified:
The **Pan Mersey APC** has progesterone (micronised) 100mg capsules listed with a Green RAG rating in their formulary (Chapter 6, endocrine system). The **Greater Manchester Medicines Management Group** (GMMMG) rejected an application to add Utrogestan capsules to the formulary in February 2019. The group considered the application and felt comments that micronised progesterone may carry a lower risk of breast cancers versus synthetic progestogens were not backed by robust evidence. It was also noted that adjuvant use with an oestrogen preparation carried cost implications versus combined preparations, depending on the oestrogen preparation chosen. This decision was reviewed again 12 months later. GM primary care prescribing data for Utrogestan demonstrated that prescribing had almost tripled in the past 12 months but remained relatively low. The group felt this growth was likely to have been driven by supply problems with other HRT preparations, particularly since the product has been available for more than 10 years without having seen a significant uptake in prescribing before this time. It was agreed that no further action was needed at the time.
Legal Issues Identified:
None identified
Media/ Public Interest:
None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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[12] Collaborative Group on Hormonal Factors in Breast Cancer, "Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence", *Lancet*, vol. 394, pp 1159–68, 2019

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