The specialist authority for menopause & post reproductive health

British Menopause Society

Measurement of serum estradiol in the menopause transition

Introduction

Hormone replacement therapy aims to give sufficient estrogen to manage symptoms of the menopause and reduce the long-term health consequences of the menopause.

Uptake of HRT has increased significantly over recent years and whilst it is the most effective treatment for vasomotor symptoms, HRT may not be effective in managing every potential symptom of menopause[1]. Where there are ongoing distressing symptoms for women using HRT, clinicians may be tempted to measure a serum estradiol level to attempt to check absorption. However, there is uncertainty about the significance of a single serum estradiol level both in relation to symptom management and in managing long-term health consequences of the menopause, such as osteoporosis and cardiovascular disease. Furthermore, in the perimenopause it is not possible to distinguish between endogenous and exogenous estradiol through serum estradiol testing.

This BMS Tool for Clinicians will increase understanding of the significance of estradiol blood test results as well as highlight uncertainties around the value of a single serum estradiol level.

Key points

Before requesting a serum estradiol, clinicians should consider the following points.

- Whether symptoms are truly caused by low levels of estradiol, highlighting the significance and impact of sociodemographic factors and comorbidities on the impact of menopause symptoms.
- There is significant interindividual variability in serum estradiol associated with any given formulation and any given dose.
- There is variation of serum estradiol related to pharmacokinetic and pharmacodynamic processes.
- The variable rate of metabolism of estradiol in different individuals will impact serum estradiol concentration measured.
- In the perimenopause it is not possible to differentiate between endogenous and exogenous estradiol, making serum levels impossible to interpret unless very low, below an expected physiological nadir.
- Consider whether there is evidence that HRT can help manage ongoing symptoms experienced.
- The fluctuation as well as absolute concentrations of sex hormones may be responsible for symptoms – and this is not possible to capture by conventional means.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

- There is poor correlation between serum estradiol and symptom management with significant interindividual clinical response to the same dose of estradiol containing HRT.
- There is no value in checking serum estradiol if a patient is taking oral estradiol, as a significant percentage is metabolised to the weaker estrone.
- There is no value in measuring a serum estradiol in women taking combined hormonal contraception.
- There is no known threshold for serum estradiol and prevention of loss of bone density or prevention of osteoporotic related fractures.
- There is no evidence regarding the optimum HRT monitoring strategy for women with premature ovarian insufficiency (POI).
- If a patient has ongoing symptoms, listening to the patient, providing holistic care and changing HRT to alternative delivery routes may be more helpful strategies than measuring a serum estradiol level.

What is being measured?

Estrogens are sex steroid hormones responsible for the development and regulation of the female reproductive system and development of secondary sexual characteristics. Physiologically, they have numerous additional roles around the body including bone metabolism, maintenance of cardiovascular health and cognitive function[2]. Regarding "estrogen levels", estradiol is the estrogen measured. This is the most potent, naturally occurring estrogen.

Estrogens are synthesised in the ovaries and extra gonadal tissue.

Four estrogens are found in the female body. **Estrone (E1)** has weak activity and lower potency and is an important estrogen after the menopause. Estrone is converted from androstenedione by the enzyme aromatase or from estradiol by the enzyme 17beta hydroxysteroid dehydrogenase. Estrone can bind to both ERα and ERβ, but with weaker estrogenic activity and it is not a ligand of the G protein-coupled estrogen receptor. Estradiol and estrone exist in a dynamic relationship. The ratio of estradiol and estrone change after the menopause, so there is significantly more estrone.

17β-estradiol (E2) is the predominant circulating estrogen in humans. It is mainly secreted by the granulosa cells of the ovarian follicles and the corpora lutea. Estradiol is a small lipophilic molecule, and this characteristic has facilitated the development of transdermal estradiol delivery systems. Estradiol is used in both oral contraception and hormone replacement therapy.

Estriol (E3) is the least potent estrogen and circulating levels are barely detectable. Estriol is not synthetised in the ovaries. It is formed from estrone and estradiol through 16α-hydroxylation, by cytochrome p450 enzymes in the liver. This estrogen plays a more prominent role during pregnancy, when it is produced in large quantities by placental aromatisation of fetal derived androgens. It prepares the vagina for delivery and causes breast tissue proliferation. It is prescribed in vaginal preparations for the management of genitourinary symptoms of the menopause (GSM).

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

Estetrol (E4) is produced by the fetal liver and is only detectable during pregnancy. Estetrol is the estrogen in the most recently developed combined contraceptive pill, where it is combined with drospirenone.

Other estrogens
Ethinyl estradiol is a synthetic estrogen found in many commonly prescribed combined hormonal contraceptive methods. It cannot be split to become 17β estradiol and is considered to have more pronounced hepatic effects than the estrogens described above.

Conjugated equine estrogens (CEE) are derived from the urine of pregnant mares. CEE is mostly listed with 10-16 estrogenic steroids plus progestogenic, androgenic and other corticosteroid components. All components have biological activity, as do many of the component's metabolites. The potency of CEE potency is significantly greater than estradiol with greater impact on hepatic protein production also[3].

Therefore, measuring a serum estradiol does not reflect all estrogenic activity. Other physiological estrogens and synthetic estrogens that are not measured have estrogenic activity. This is particularly true postmenopause, when there is relatively more estrone.

How is estradiol activity mediated?

For any hormone to be active, it relies on the presence of a receptor. There are 3 commonly occurring types of estrogen receptor:

- ERα
- ERβ
- Cell surface membrane receptors coupled with G proteins – G protein estrogen receptors

Estrogen receptors ERα and ERβ are intracellular receptors, belonging to the nuclear receptor family. Cell surface membrane receptors rapidly activate intracellular cascades.

There is variability in the expression and distribution of ERα and ERβ in various tissues and organs, which may explain the difference in response to different estrogens[2,4].

Estrogen and the estrogen receptor are not the only factors needed for estrogen activity and the presence of estrogen and its receptor is not enough to predict the effect of estrogen in any cell type[5]. Transcription factors and cofactors are also required as well as other activity for the estrogen and the receptor to be active. These factors may be determined by genetic and epigenetic factors[6].

In addition, there is evidence to suggest that estradiol may be implicated in the down regulation of its own receptors which may result in decreasing the clinical effect and tachyphylaxis[7].

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

Therefore, serum estradiol alone does not reflect estrogenic activity. Following the menopause, the ratio of estradiol and estrone changes. There are relatively greater concentrations of estrone and this is not measured. Many other genetic and epigenetic factors may influence activity of estrogen receptors.

How is estradiol measured?

Most labs measure estradiol using radioimmunoassay methodology. This has pitfalls including variable bias between assays and cross reactivity of conjugated and unconjugated metabolites[8]. Results between different labs should not be compared.

Liquid chromatography tandem mass spectrometry may be used if there is doubt as to the veracity of an estradiol measurement, but this method is not available in all pathology laboratories[9]. The result given includes albumin bound estradiol, free estradiol and sex hormone binding globulin (SHBG) bound estradiol. The free and albumin bound estradiol has activity, but the SHBG bound estradiol does not.

Neither assay differentiates between endogenous and exogenous estradiol, active and inactive SHBG bound estradiol. Assays cannot measure ethinyl estradiol or the entirety of estrogens found in conjugated equine estrogens. Estrone concentrations are not conventionally measured.

What are normal values for estradiol?

Does knowledge about normal values help work out what level of estradiol is ideal for women using HRT?

During the menstrual cycle, circulating estradiol varies considerably. The concentration slowly increases during the follicular phase and peaks just before ovulation. Levels then increase a second time during the luteal phase. There is considerable variation in normal estradiol levels and significant interindividual variability. Estradiol is lowest in the early follicular phase, greatest mid-cycle and then decreases in the luteal phase.

In a study set up to establish the normal range for androgens, estradiol was also measured at set points during the menstrual cycle. The overall median estradiol was 372.6 pmol/L with a range of 5.51 to 3582.9 pmol/L (Skiba, et al., 2019) (Deecher & Dorries, 2007). The fluctuation of estradiol levels in a normal menstrual cycle cannot be replicated by giving HRT.

During the menopause transition there is an overall decline in estradiol, but in the perimenopause estradiol can fluctuate erratically and dramatically[7,10,11]. Fluctuations themselves are responsible for some symptoms of the menopause in some women, for example migraine and psychological symptoms[8,9,10,12].

Estradiol levels can be supraphysiological at times during the perimenopause. It is thought that this is related to an increase in FSH, resulting in a second increase in E_2 during the mid- and late luteal phases, which continues to a peak during the subsequent menstrual phase. This second rise and fall in E_2 is typical of a normal follicular phase, except that it is superimposed on an existing ovulatory cycle[7,10].

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

In the postmenopause, serum estradiol continues to fall after the last menstrual period although this may not be measured through conventional lab monitoring[13].

Therefore, the wide range of 'normal' estradiol values is significant. It is normal to have varying estradiol fluctuations premenopausally and in the perimenopause. HRT cannot replicate the fluctuation of the premenopause. It is therefore difficult to use normal premenopausal values to work out a serum estradiol level to aim for in the peri or post menopause, for women going through a natural menopause in the average age range. In the perimenopause there can be even greater fluctuation of estradiol than premenopausally.

Can we use predicted serum concentration of estradiol for different routes of delivery and at different doses?

To comprehend the challenges in understanding this, we need to have an appreciation of the pharmacokinetics of estradiol absorption, the time course of the serum concentrations of sex steroid hormones after administration, and the pharmacodynamics, i.e. the metabolic and biological changes caused by the treatment. For a more detailed review of the differing delivery systems of estradiol in HRT see[1,14].

Oral delivery

When estradiol is swallowed, is it absorbed through the gastrointestinal tract and passes first through the portal circulation. The 'first pass' through the liver results in most of the estradiol being metabolised to estrone and its metabolites[3]. There is a significant (around seven-fold) peak to trough ratio after ingestion with considerable interindividual variation due to genetic or acquired differences in the intestinal and hepatic metabolism[3]. Other factors that affect absorption include diet, alcohol or drug consumption, smoking, physical activity, stress, etc, which may cause rapid and transitory changes in peripheral or splanchnic blood flow, absorption or metabolism[15].

Implant delivery

Crystalline estradiol pellets are inserted using a trochar into the subcutaneous fat of the lower abdomen, or buttock. The implant represents a depot delivery system, which releases estradiol at an even, slow rate. In contrast to other transdermal treatment options, the administration of estradiol pellets is associated with relatively small fluctuations in serum estradiol during the 6 months plus after implantation, and there is less interindividual variation[16].

Transdermal estradiol delivery

Transdermal estradiol is transported through the layers of the skin – the stratum corneum of the epidermis and then the dermis – by passive diffusion into local capillaries to enter the main circulation. The concentration gradient across the stratum corneum is potentially a rate limiting factor in absorption.

Many other factors impact absorption including age, ethnicity, hydration, anatomical site, skin temperature and the presence of inflammation[17]. Levels of estradiol in the systemic circulation will also be influenced by effective drug clearance to the tissues.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

Gel delivery
Oestrogel Pump Pack™ and Sandrena™ gel are applied to the skin daily. Serum estradiol depends on time from application to measurement. As the dose increases, serum estradiol increases, but there is considerable interindividual variation of serum estradiol for a single dose[18,19].

Patch delivery
The adhesive layer of the matrix patch consists of a layer in which estradiol molecules are distributed. The diffusion rate remains relatively constant, but there is still significant fluctuation even after long term use, and interindividual variation of serum estradiol[20,21,22]. In addition to the pharmacodynamics, variation and inconsistencies can arise as patches may fall off[23].

Spray delivery
The liquid spray Lenzetto™ contains estradiol with octisalate which enhances skin penetration and facilitates slow diffusion into the dermis into the subcutaneous fat where a reservoir is formed from which estradiol is slowly released into the systemic circulation. Available data still indicates serum estradiol variation with continual use[24].

Therefore, there is variation of measured serum estradiol for any dose of HRT in any given individual[3,25]. Measuring a serum estradiol level is particularly unhelpful in patients taking oral estradiol as the main circulatory metabolite is estrone.

We may have an idea of the order of magnitude of serum estradiol as a result of HRT use – but there is vast variation of serum estradiol over time, and significant interindividual variation.

Is there clinical correlation between serum estradiol and symptom management?

The aim of any hormonal treatment for women in the menopause transition is not to restore the physiological serum levels occurring in ovulatory cycles of fertile women, but to prevent or reduce symptoms caused by low levels of estrogen[3].

Evidence suggests that hot flush frequency differs widely in women with similar estradiol levels associated with transdermal estradiol delivery, indicating that an absolute estradiol concentration cannot predict the response to vasomotor symptoms in any given patient[26].

Data from oophorectomized women using estradiol implants (where the serum estradiol is generally more stable) has demonstrated good symptom control at a serum estradiol of around 200 pmol/L, with no further symptom improvement at higher concentrations[27]. A small group of women in the referenced studies had more resistant symptoms and required a higher dose of estradiol to achieve a higher estradiol level, which was linked to symptom control. This suggests that there is interindividual variation in the symptom response threshold, but it is impossible to know where that threshold sits for each individual, and managing symptoms rather than an estradiol level is key[28,29]. Some women, may experience an adverse effect of estrogen on mood, particularly as the dose of estrogen increases, but this is a less common problem[30].

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

Other clinical studies have shown an HRT dose related response, but no overall threshold for symptom control has been demonstrated[31,32,33].

In general, clinical studies reviewed were frequently small, using different forms of HRT, including Premarin, with lack of detail of sample timing.

Blood samples are generally taken to aid diagnosis and to offer validation and reassurance to patients[34]. Serum estradiol is often measured (anecdotally) when HRT is perceived to be ineffective for the management of menopause symptoms. HRT is the most effective method of managing symptoms of the menopause but, in managing expectation, it is important to consider whether there is evidence for HRT helping manage every possible symptom. For example, HRT may not fully treat cognitive symptoms particularly in the early post menopause[35]. The impact of other psychosocial and demographic factors plus any comorbidities should also be considered, as they may impact on the severity and experience of menopause symptoms[36].

When assessing side effects and clinical response, the progestogen used may be an important factor, independent of estradiol[37].

There is a correlation between serum estradiol and clinical effect within a threshold level for estradiol, which varies between individuals. The serum level in an individual woman does not predict therapeutic effect.

Is there a serum estradiol threshold needed for prevention of long-term health consequences of the menopause?

There is a Cochrane review suggesting that starting HRT before the age of 60 or within 10 years of the menopause may reduce the risk of cardiovascular disease, though evidence used in the updated NICE guidance does not support this view[38,39]. Regarding estradiol levels and cardiovascular effect, a review of data by Gulamhusein and colleagues, where information was available on serum estradiol levels and cardiovascular events, the conclusion was that the association between serum estradiol levels and cardiovascular events in postmenopausal women remains unclear[40].

A dose dependent effect of estradiol on bone mineral density has been demonstrated with the serum estradiol being proportional to bone density[41,42].

Menopausal hormone therapy was shown to reduce hip and all fractures in the Women's Health Initiative with little difference between the estrogen-alone and the estrogen plus progestogen trials[43]. Bone density at the lumbar spine has been shown to be preserved with lower estradiol levels, such as those achieved with a 25 mcg estradiol patch, and even ultra-low doses preserve or increase bone mineral density[2,44,45]. Prevention of osteoporotic related fractures has been found to be related to estradiol concentration, with fracture prevention at very low levels – for example, total estradiol levels <5 pg/ml were associated with a 2.5-fold increase in hip and vertebral fractures in older women, an association that was independent

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

of age and body weight[46]. Studies looking at serum estradiol levels needed for preservation of bone density give variable results, also dependent upon delivery method with differing estradiol values preserving bone density in women using patches versus gel, although sampling times should be factored in also[45]. It is therefore not possible to give a threshold from current evidence. Factors other than absolute estradiol levels include the possibility of an impact of specific gene polymorphisms of estrogen receptors[47].

HRT is beneficial in the prevention of loss of bone mineral density. There is a dose related impact, but there is no clear lower threshold. Benefit has been demonstrated at low estradiol doses and low systemic estradiol levels.

Is there an upper estradiol level or a level considered the upper limit of normal?

Is there a point to monitoring serum estradiol levels to make sure that clinicians don't prescribe doses that will result in serum levels breaching a 'normal threshold'? High levels of serum estradiol can result in tachyphylaxis, where women with a high estradiol level continue to experience menopausal symptoms, leading potentially to ever increasing doses of estrogen being recommended[48]. When monitoring serum estradiol with implant use, the acceptable upper limit varies amongst clinics and is not based on robust evidence. Many clinics, anecdotally, use 600 pmol/L as a level consistent with that of the luteal phase of the menstrual cycle, whilst other services are comfortable with higher levels. High doses of estradiol can result in persistent symptoms, a phenomenon known as tachyphylaxis, but there is no known consistent threshold at which this has been identified as being likely to occur[29].

Breast cancer risk has been shown to be duration rather than dose dependent, in women using standard doses of estradiol, and there is lack of data to indicate risk at doses beyond this[49]. Women with higher endogenous estradiol levels may be at an increased risk of breast cancer, but the data is not clear, and more studies are needed[50].

Risk of endometrial hyperplasia increases with increased doses of estradiol, without adequate progestogen cover, but there is no data to recommend a serum estradiol threshold at which this risk becomes clinically significant. A Cochrane review demonstrated that unopposed estrogen is associated with a significant increase in the risk of endometrial hyperplasia, that is both dose and duration dependent, with exposure between one and three years[51].

The risk of venous thromboembolic (VTE) disease is dose related for oral estradiol, but not transdermal preparations at standard licensed doses[52]. Serum estradiol in women using transdermal estradiol is therefore not helpful in assessing risk of VTE.

The upper limit of estradiol may vary between individuals in terms of tachyphylaxis and there is a lack of data to inform any threshold in terms of risk.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

Should serum estradiol be monitored in the treatment of female hypogonadism?

Women with premature ovarian insufficiency (POI) and other causes of female hypogonadism need estrogen replacement to reduce the risk of associated long-term health consequences. Affected women may not always experience symptoms associated with low levels of estrogen.

There is currently no evidence regarding the optimum HRT monitoring strategy for women with POI[53]. Accepting limitations of estradiol assays, the most recent ESHRE guidance on POI advises that measurement of estradiol may be helpful in clinical practice where there is inadequate symptom relief, failure to achieve adequate bone protection or where there are adverse effects[54].

The Society for Endocrinology advise that, in the absence of more robust evidence, doses of estradiol are monitored using a combination of clinical assessment of symptom control (acknowledging this may not be reliable) and general wellbeing, DEXA bone densometry and serum estradiol concentrations to ensure a 'reasonable' level is achieved. Serum estradiol target ranges for transgender women are empirically set at the mid follicular phase level of a cis-gendered woman 300-600 pmol/L[38]. Guidance from the International Turner Syndrome Society advise 350-500 pmol/L. However, there is currently insufficient evidence to recommend whether serum estradiol testing or non-testing is better for efficacy and safety outcomes for women with female hypogonadism[55].

Monitoring serum estradiol may be useful in monitoring women with female hypogonadism including POI, but a holistic approach is necessary to ensure adequate treatment.

Summary

In summary, it is easy to reach for a blood test when HRT is not perceived to be adequately managing symptoms of the menopause transition. Before an investigation is requested, clinicians should assess whether symptoms are truly caused by low levels of estradiol, highlighting the importance of also considering sociodemographic factors. Lack of data confirming a treatment threshold for serum estradiol should be considered, along with the variation of serum estradiol related to pharmacokinetic and pharmacodynamic processes. In the perimenopause it is not possible to differentiate between endogenous and exogenous estradiol, making serum levels impossible to interpret unless very low. Furthermore, the fluctuation of sex hormones may be responsible for symptoms – and this is not possible to capture by conventional means. Advice differs for younger women, where long-term health risks associated with low levels of estrogen are more significant.

If a patient has ongoing symptoms, listening to the patient, providing holistic care and changing HRT to alternative delivery routes may be more helpful strategies than measuring a serum estradiol level.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

References

1. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Hamoda, H, et al. 4, 2020, Post Reproductive Health, Vol. 26, pp. 181-209.
2. Estrogen and bones after menopause: a reappraisal of data and future perspectives. Anagnostis, P, et al. June 2021, Springer Nature Link, Vol. 20, pp. 13-21.
3. Pharmacology of estrogens and progestogens: influence of different routes of administration. Kuhl, H. Suppl 1, August 2005, Climateric, Vol. 8 , pp. 3-63.
4. The life and times of the estrogen receptors: an interim report. Albertazzi, P and Purdi, D W. 3, September 2001 , Climacteric., Vol. 4, pp. 194-202.
5. Hormone Replacement Therapy in Cancer Survivors - Review of the Literature. Deli , T, Orosz, M and Jakab , A. 1, 2020, Pathology and Oncology Research, Vol. 26, pp. 63-78.
6. The epigenetics of estrogen:epigenetic regulation of hormone-induced memory enhancement. Frick , K M, Zhao, Z and Fan, L. 6, Epigenetics, Vol. 6, pp. 675-680.
7. Estradiol-induced down-regulation of estrogen receptor. Effect of various modulators of protein synthesis and expression. J Steroid Biochem Mol Biol. 1994 Mar;48(4):325-3. Borrás , M, et al. 4, March 1994, The Journal of Steroid Biochemistry and Molecular Biology, Vol. 48, pp. 1376-1387.
8. Challenges to the measurement of estradiol: an Endocrine society position statement. Rosner, W, et al. 4, April 2013, Journal of Clinical Endocrinology and Metabolism, Vol. 98, pp. 1376-1387.
9. During the Reproductive Years: What Is Normal for Women? Skiba, Marina A, et al. 11, November 2019, The Journal of Clinical Endocrinology and Metabolism, Vol. 104, pp. 5382-5392.
10. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. Deecher, D C and Dorries, K. 6, 2007, Archives of Women's Mental Health, Vol. 10, pp. 247-257.
11. The complex relationship between estrogen and migraines: a scoping review. Syst Rev. 2021 Mar 10;10(1):72. Reddy , N, et al. 1, March 2021, Systematic Reviews, Vol. 10, p. 72.
12. Estradiol Fluctuation, Sensitivity to Stress, and Depressive Symptoms in the Menopause Transition: A Pilot Study. Gordon, Jennifer L, et al. June 2019, Frontiers in Pyschology, Vol. 10, p. 1319.
13. Trajectory clustering of estradiol and follicle-stimulating hormone during the menopausal transition among women in the Study of Women's Health across the Nation (SWAN). Tepper, P G, et al. 8, August 2012, Journal of Clinical Endocrinology and Metabolism, Vol. 97, pp. 2872-2880.
14. Estrogen-based therapies for menopausal symptoms. Laing, A and Hillard, T. 1, January 2024, Best Practice and Research Clinical Endocrinology and Metabolism, Vol. 38.
15. Pharmacokinetic and pharmacologic variation between different estrogen products. O'Connell, M B. 9S, September 1995, Journal of Clinical Pharmacology, Vol. 35, pp. 18S-24S.
16. A randomized comparison of nonoral estradiol delivery in postmenopausal women. Stanczyk, F Z, et al. 6, December 1988, American Journal of Obstetrics and Gynecology, Vol. 159, pp. 1540-1546.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

17. Performance of transdermal therapeutic systems: Effects of biological factors. Singh, I and Morris, A P. 1, January 2011, International Journal of Pharmacological Investigation, Vol. 1, pp. 4-9.
18. www.medicines.org.uk/emc/product/353/smpc#gref. [Online]
19. https://www.medicines.org.uk/emc/product/1048/smpc%20accessed%20Dec%202024. [Online]
20. Plasma profiles of transdermal 17 beta-estradiol delivered by two different matrix patches. A four-way cross-over study in postmenopausal women. Rohr, U D, Ehrly, A M and Kuhl, H. 6, June 1997, Arzneimittelforschung, Vol. 47, pp. 761-767.
21. Variability of serum estrogens among postmenopausal women treated with the same transdermal estrogen therapy and the effect on androgens and sex hormone binding globulin. Kraemer, G R, et al. 3, March 2003, Fertility and Sterility, Vol. 79, pp. 534-542.
22. Comparative absorption and variability in absorption of estradiol from a transdermal gel and a novel matrix-type transdermal patch. Jarvinen, A, et al. 2, April 2001, Mauritas, Vol. 38, pp. 189-196.
23. Transdermal menopausal hormone therapy: delivery through skin changes the rules. Buster, J E. 9, June 2010, Expert Opinion on Pharmacotherapy, Vol. 11, pp. 1489-1499.
24. Steady-state pharmacokinetics following application of a novel transdermal estradiol spray in healthy postmenopausal women. Morton, T L, et al. 9, September 2009, Journal of Clinical Pharmacology, Vol. 49, pp. 1037-1046.
25. The range and variation in serum estradiol concentration in perimenopausal and postmenopausal women treated with transdermal estradiol in a real-world setting: a cross-sectional study. Glynne S, Reisel D, Kamal A, Neville A, McColl L, Lewis R, Newson L. 2, 2025, Menopause, Vol. 32, pp. 103-111.
26. Treatment of hot flashes with transdermal estradiol administration. Steingold, K A, et al. 4, October 1985, Journal of Clinical Endocrinology and Metabolism, Vol. 61, pp. 627-632.
27. A comparison of 25 mg and 50 mg oestradiol implants in the control of climacteric symptoms following hysterectomy and bilateral salpingo-oophorectomy. Panay, N, Versi, E and Savvas, M. 8, August 2000, British Journal of Obstetrics and Gynaecology, Vol. 107, pp. 1012-1016.
28. Biological effects of hormone replacement therapy in relation to serum estradiol levels. Yasui, T, et al. 1-2, April 2001, Hormone Research, Vol. 56, pp. 38-44.
29. Hormone implants and tachyphylaxis. Garnett, T, et al. 10, October 1990, British Journal of Obstetrics and Gynaecology, Vol. 97, pp. 917-921.
30. A randomised comparison over 8 months of 100 micrograms and 200 micrograms twice weekly doses of transdermal oestradiol in the treatment of severe premenstrual syndrome. Smith, R N, et al. 6, June 1995, British Journal of Obstetrics and Gynaecology, Vol. 102, pp. 475-484.
31. Comparative endocrinological and clinical effects of percutaneous estradiol and oral conjugated estrogens as replacement therapy in menopausal women. Dupont, A, et al. 4, October 1991, Maturitas, Vol. 13, pp. 297-311.
32. Pharmacokinetics of percutaneous estradiol: a crossover study using a gel and a transdermal system in comparison with oral micronized estradiol. Scott, R T, et al. 5, May 1991, Obstetrician and Gynecologist, Vol. 77, pp. 758-764.
33. Hormone replacement therapy: clinical benefits and side-effects. De Lignieres, Bruno. Supplement, May 1996, Maturitas, Vol. 23, pp. S31-S36.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

34. Blood tests in primary care: A qualitative study of communication and decision-making between doctors and patients. Watson, J, et al. 5, July 2022, Health Expectations, Vol. 25, pp. 2453-2461.
35. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. Maki, P M, et al. 13, September 2007, Neurology, Vol. 69, pp. 1322-1330.
36. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). El Khoudary, S R, et al. 10, October 2019, Menopause, Vol. 26, pp. 1213-1227.
37. Relationships of serum estradiol levels, menopausal duration, and mood during hormonal replacement therapy. Klaiber, E L, et al. 7, October 1997, Psychoneuroendocrinology., Vol. 22, pp. 549-558.
38. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Boardman, H M, et al. CD002229, March 2015, Cochrane Database Systemic Review, Vol. 3.
39. https://www.nice.org.uk/guidance/ng23. [Online]
40. Measurements of Postmenopausal Serum Estradiol Levels and Cardiovascular Events: A Systematic Review. Gulamhusein, N, et al. 6 (2Part B), November 2023, CJC Open, Vol. 17, pp. 347-354.
41. Dose effects of oral estradiol on bone mineral density in Japanese women with osteoporosis. Mizunuma, H, et al. 1, February 2010, Climacteric, Vol. 13, pp. 72-83.
42. The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants. Studd, J, et al. 5 Pt 1, November 1990, American Journal of Obsterics and Gynecology, Vol. 163, pp. 1474-1479.
43. The WHI: the effect of hormone replacement therapy on fracture prevention. de Villiers, T J and Stevenson, J C. 3, June 2012, Climacteric : the journal of the International Menopause Society, Vol. 15, pp. 263-266.
44. Low and conventional dose transdermal estradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. Evans, S F and Davie, M W. 1, Oxford : s.n., January 1996, Clinical Endocrinology, Vol. 44, pp. 79-84.
45. Hormone replacement therapy (oestradiol-only preparations): can the laboratory recommend a concentration of plasma oestradiol to protect against osteoporosis? Armston, A and Wood, P. Pt 3, May 2002, Annals of Clinical Biochemistry, Vol. 39, pp. 184-193.
46. Estrogen and bone health in men and women. Cauley, J A. (Pt A), July 2015, Steroids, Vol. 99, pp. 11-15.
47. Associations between ERα/β gene polymorphisms and osteoporosis susceptibility and bone mineral density in postmenopausal women: a systematic review and meta-analysis. Zhu, H, et al. 1, February 2018, BMS Endocrine Disorders, Vol. 18, p. 11.
48. https://thebms.org.uk/2023/09/tachyphylaxis-with-hrt/. [Online]
49. Risk of breast cancer with HRT depends on therapy type and duration. Saul, H, et al. o485, March 2022, BMJ (Clinical research ed.), Vol. 376.
50. Postmenopausal serum androgens, estrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Kaaks, R, et al. 4, December 2005, Endocrine-related Cancer, Vol. 12, pp. 1071-1082.
51. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Furness, S, et al. 8, August 2012, Cochrane Database of Systematic Reviews, p. CD000402.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

52. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. Vinogradova, Y, Coupland, C and Hippisley-Cox, J. January 2019, BMJ, Vol. 364, p. k4810.
53. Guideline: management of women with premature ovarian insufficiency. ESHRE Guideline Group on POI, et al. 5, May 2016, Human Reproduction, Vol. 31, pp. 926-937.
54. Evidence-based guideline: premature ovarian insufficiency. ESHRE, ASRM, CREWHIRL and IMS Guideline Group on P, et al. 6, December 2024, Climacteric: the journal of the International Menopause Society, Vol. 27, pp. 510-520.
55. Society for Endocrinology guideline for understanding, diagnosing and treating female hypogonadism. Jayasena, C N, et al. 5, Oxford : s.n., November 2024, Clinical Endocrinology, Vol. 101, pp. 409-442.

Authors: Dr Clare Spencer and Dr Heather Currie, in collaboration with the medical advisory council of the British Menopause Society.

PUBLISHED: JULY 2025

This BMS Tool for Clinicians will be updated when guidance changes and/or new data becomes available.

Copyright © 2025 British Menopause Society. All rights reserved.
Permission granted to reproduce for personal and educational use only. Commercial copying and distribution is prohibited.

Reg Charity No: 1015144 Company Reg No: 02759439