Tailoring transdermal estradiol dose to maximize benefits and minimize risks

Sarah J. Glynne, BSc, MBBS, MSc, MRCP, MRCGP[1] and James A. Simon, MD, CCD, MSCP, IF[2]

Abstract

Transdermal estradiol is licensed to treat estradiol deficiency symptoms and prevent osteoporosis in postmenopausal women. There is no one-size-fits-all estradiol dose or serum concentration that will achieve symptom relief and bone protection in all women. Dose is usually titrated to symptom response, but measurement of serum estradiol concentration can be used to support or inform dose decisions in certain clinical scenarios. The optimal level for an individual varies according to tissue sensitivity (pharmacodynamic effects), the method used for estradiol quantitation (immunoassay vs. mass spectrometry), the clinical endpoint (symptoms vs. bone protection), and treatment goals, including patient preferences. An understanding of transdermal estradiol pharmacokinetics and pharmacodynamics, and the limitations of the methods used to measure serum estradiol, is essential to ensure that all women who choose to use menopausal hormone therapy (MHT) can reap the benefits and avoid the harms of over-treatment and under-treatment. Achieving and maintaining optimal estradiol levels for all MHT users is consistent with menopause guidelines that promote high-quality, patient-centred, personalized menopause care.

Key Words: Immunoassay, Mass spectrometry, Menopausal hormone therapy, Menopause, Personalized medicine, Transdermal estradiol.

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From the [1]Portland Hospital, London, UK; and [2]George Washington University School of Medicine, IntimMedicine Specialists, Washington, DC.

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Address correspondence to: Sarah J. Glynne, BSc, MBBS, MSc, MRCP, MRCGP, The Portland Hospital, 212 Great Portland Street, London W1W 5QN, UK. E-mail: sarahglynne@clairemellon.co.uk.

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Menopausal hormone therapy (MHT) is licensed to treat postmenopausal vasomotor and genitourinary symptoms. In many countries, for example, the United Kingdom, the United States, and Australia, MHT is also licensed to prevent osteoporosis based on high-quality evidence of benefit.[1] MHT can additionally be used off-label to treat other menopausal symptoms (eg, sleep disruption, negative mood symptoms), and to treat menopausal symptoms in perimenopausal women. In randomized clinical trials (RCTs), MHT has been shown to decrease new-onset diabetes by 30%,[2] and coronary heart disease by 30%-48% when initiated in women below 60 years and/or within 10 years of menopause,[3,4] but it is not currently licensed for either of these indications.

Transdermal estradiol formulations are usually preferred because, unlike oral estrogens, the transdermal route bypasses first-pass hepatic metabolism and is not associated with an increased risk of venous thrombosis, pulmonary embolism, or stroke.[5-8] However, there is substantial variation in transdermal estradiol absorption and metabolism with up to 10-fold differences in serum estradiol concentration among women using the same dose/formulation.[9,10] In addition, serum estradiol levels do not predict therapeutic response due to interindividual differences in pharmacodynamic effects. Consequently, menopause guidelines recommend individualization of estradiol dose to ensure that all women who choose to use MHT can reap the health benefits and avoid the harms of over-treatment and under-treatment.[11-13]

Despite the emphasis on individualized care,[11–13] little guidance exists concerning ***how*** to tailor transdermal estradiol dose to the individual, to ensure that optimal levels are achieved. For most medications, a "treat-to-target" strategy is used to inform dose decisions. For example, statins and antihypertensive drugs are titrated to reach lipid and blood pressure target levels for the prevention of cardiovascular disease. Concerning estradiol, there is no universally agreed-upon target level or therapeutic range for serum estradiol in MHT users,[14] and blood tests can be unreliable because levels fluctuate and different assays have distinct reference ranges and performance characteristics.[15] Consequently, "treating to target" is not routinely recommended, and the dose is usually titrated to symptom response. However, in the absence of symptoms or if symptoms persist, measurement of serum estradiol concentration is sometimes helpful.

While many publications acknowledge that estradiol levels are sometimes useful in women using transdermal estradiol, none make recommendations regarding how to interpret and act on the results.[14,16–19] Others do not offer guidance at all,[20] or actively discourage blood monitoring, citing lack of evidence for improved patient outcomes and cost considerations.[21,22] The lack of clarity around the role of blood testing and recent dose-related controversy has caused considerable confusion for clinicians.[21,23] Many women in the United Kingdom have reported difficulty accessing the treatment they need in the National Health Service (NHS).[24] A recent All-Party Parliamentary Group Inquiry found that many General Practitioners (GPs) lack the tools needed to provide individualized menopause care, which has contributed to variation in quality of care (a "postcode lottery"), and negatively impacted the lives of many menopausal women.[25]

The purpose of the present manuscript is to provide evidence-based guidance regarding how to tailor transdermal estradiol dose to the individual, to support clinician prescribing and facilitate patient-centered menopause care. Specifically, our objectives are (1) to review the indications for measurement of serum estradiol concentration in perimenopausal and postmenopausal women using transdermal estradiol, (2) to discuss the challenges involved in the interpretation of blood results, according to the clinical context and the method used for estradiol quantitation, (3) to offer practical suggestions for estradiol dose titration based on currently available evidence, and (4) to emphasize the need for a "personalized medicine" approach in which estradiol dose and formulation are customized according to women's unique characteristics and needs.

BASIC PRINCIPLES AND DOSE CONSIDERATIONS

For most women, estradiol dose decisions are clinically guided. For treatment of moderate-to-severe vasomotor symptoms, therapy should be initiated using a low-to-medium dose. If using patches, the recommended starting dose is 25 mcg/24 h (eg, Climara, Estradot, Estraderm MX), 37.5 mcg/24 h (eg, Vivelle Dot, Minivelle), or 50 mcg/24 h (eg, Evorel).[26–31] The dose should be uptitrated every 12 weeks, for example, in 25 mcg/24 h patch increments, until symptom relief is achieved (usually with doses of 50-100 mcg/24 h).[31,32] If using 0.06% estradiol gel, the usual starting dose is 1 pump daily, increased in 1 pump increments every 12 weeks until symptoms abate (usually with doses of 2, 3, or 4 pumps daily).[33,34] Side effects (eg, bleeding, mastalgia, bloating, nausea, headaches) are common after treatment initiation, especially in younger women, but usually subside over time or can be managed by changing the dose, preparation, regimen, or route of administration.[35–37]

If patients with menopause at the usual age (above 45 y) achieve symptom relief using licensed doses, it is not necessary to routinely check their hormone levels. In the United Kingdom, between 1 and 4 pumps of 0.06% Estrogel daily (1.25 g gel/0.75 mg estradiol per actuation) are licensed to treat estrogen deficiency symptoms in postmenopausal women,[34] but 1 pump daily is the only regulator-approved dose in the United States.[33] In both the United Kingdom and the United States, estradiol patches in doses ranging from 25 to 100 mcg/24 h are licensed to treat menopausal vasomotor and genitourinary symptoms.[26–31] Transdermal sprays are also available that deliver 1.53 mg estradiol per metered dose spray; 1 to 3 sprays daily are licensed to treat menopausal vasomotor or estrogen deficiency symptoms.[38,39]

In the United Kingdom, both estradiol gel and estradiol patches are approved for the prevention of osteoporosis, but in the US, patches are the only transdermal formulation licensed for this purpose. For the prevention of osteoporosis, the minimum doses with proven efficacy are 14 mcg/24 h (Menostar), 25 mcg/24 h (eg, Vivelle Dot, Climara) and 50 mcg/24 h (eg, Estradot, Estraderm MX, Evorel).[26–29,31,40] Modest improvements in bone density in postmenopausal women treated with 14 mcg/24 h have only been demonstrated for older women aged 60-80 years.[40] Doses of at least 100 mcg/24 h are recommended to prevent bone loss in younger women with premature ovarian insufficiency (POI).[41] If using gel, the usual starting dose is 1.5 mg estradiol daily (eg, 2 pumps 0.06% gel daily), but the lowest effective dose for the prevention of osteoporosis is not known.[34] Higher doses are likely to be needed for younger women with POI.[41]

When is the measurement of serum estradiol helpful?

Blood tests are not needed to diagnose menopause in women aged above 45 years because the diagnosis is clinical (based on age and amenorrhea >12 months).[20] Blood tests cannot be used to inform dose decisions when the estradiol concentration is in the normal range, because a single measurement does not reflect cumulative target tissue exposure or tissue sensitivity. And finally, blood tests are not informative in women using oral estradiol, because a significant proportion of the administered dose is metabolized to estrone and estrone sulfate during first-pass through the liver.

However, in the menopause clinic, measurement of serum estradiol can be helpful in the following scenarios:[16,17,42]

- To aid the diagnosis of premature ovarian insufficiency (POI, menopause below 40 y) or early menopause (menopause between ages 40 and 45 y).
- To ensure that estradiol levels are in the therapeutic range in women with premature and early menopause, especially if they have no or minimal menopausal symptoms and/or underlying comorbidities (eg, osteoporosis) or risk factors for chronic disease (eg, obesity or diabetes).
- To screen for poor transdermal absorption if there is inadequate symptom relief after initiating transdermal estradiol and/or after increasing the dose.
- To help distinguish between persistent menopausal

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symptoms and side effects of MHT (eg, headaches, bleeding, mastalgia, bloating, negative mood symptoms).

Blood tests may also be helpful when asymptomatic postmenopausal women above 45 years are using MHT solely for bone protection, to ensure that therapeutic levels are achieved (discussed further below); and to reassure women with persistent menopausal symptoms and low estradiol levels on the highest licensed dose that a higher off-label dose is likely to be safe.

How is serum estradiol measured?

In clinical practice, immunoassays and gas or liquid chromatography/tandem mass spectrometry (GC-MS/MS or LC-MS/MS) are used to measure serum estradiol concentration.[15,43] Both are subject to technical issues and limitations that may give rise to erroneous results.[15,44] It is therefore essential that clinicians understand the different methodologies used, and the inherent limitations of each, to enable accurate interpretation of blood test results and inform treatment decisions.

Early immunoassays used radioisotope labeling (radioimmunoassay, RIA) and included one or more purification steps to remove potential cross-reacting and interfering substances from the sample before estradiol quantitation ("indirect" or "conventional" RIA).[15,43,44] Because the purification steps were laborious and costly, "direct" RIAs that measure estradiol directly (without the preceding purification steps) were developed in the 70s and 80s.[15,43,44] The subsequent development of new technologies, including chemiluminescent and enzymatic labeling, enabled automation, which further increased throughput, and therefore direct enzyme-based chemiluminescent immunoassays are widely used today.

However, direct immunoassays use small volume samples, typically 0.1-0.2 mL, and lack sensitivity at low concentrations (generally <30 pg/mL or <110 pmol/L).[43,45] Consequently, they cannot be used to accurately quantify estradiol in postmenopausal women with estradiol levels typically <30 pg/mL.[46] Further, failure to remove cross-reacting and interfering substances reduces assay specificity. Cross-reacting substances are molecules or compounds that structurally resemble estradiol and can therefore also bind to the assay antibody, leading to falsely elevated results. Examples include estradiol metabolites (including unconjugated, sulfated, and glucuronidated estrogens), exogenous estrogens/metabolites in MHT, and some drugs used to treat breast cancer (fulvestrant, anastrozole, and exemestane).[15,44] In a study that measured serum estradiol in postmenopausal women treated with oral estrogen (micronized estradiol or conjugated equine estrogen), levels were up to 10-fold higher when measured using direct versus indirect RIA, suggesting large cross-reactivity between the assay antibody and estradiol metabolites, and equine estrogens/ metabolites.[47] In women treated with transdermal estradiol, the metabolite concentrations are much lower, and there is likely to be closer agreement between estradiol levels measured using the two different methods.

Interfering substances alter estradiol-antibody binding in the assay, and also cause mostly false high results. Examples include heterophile antibodies, biotin (used in over-the-counter supplements to promote skin, hair and nail health, and in some medications), and red blood cells and lipids in hemolyzed and lipemic samples, respectively.[44,47] False low results are less commonly encountered in clinical practice but may occur, for example, if insufficient buffer is used to displace estradiol from albumin and sex hormone–binding globulin before quantitation.[44]

Conversely, gas or liquid chromatography (GC or LC) coupled with mass spectrometry (MS) has high sensitivity and specificity, and enables more accurate and precise measurement of serum estradiol, especially at low estradiol levels.[15,43,48] However, mass spectrometry is also subject to limitations (eg, lack of standardization, complex and technically demanding—requires a highly skilled technician, low throughput, high cost) and is not always available.[15]

Because MS is not widely available (and expensive), estradiol is measured using immunoassays in $>99\%$ of clinical laboratories in the United States, and mass spectrometry in $<1\%$.[49] Similarly, in the United Kingdom, most labs currently measure estradiol using direct immunoassay.[14] Although direct immunoassays are considered unreliable, they can provide clinically meaningful results in the menopause clinic at high concentrations,[15] and when used to screen for poor transdermal absorption; a level of <55 pg/mL or thereabouts in a patient with persistent menopausal symptoms is sufficient to confirm that the dose is inadequate and/or poorly absorbed, and a higher dose can be safely tried. Further, most factors that give rise to erroneous results cause falsely elevated levels, and overestimation increases as estradiol levels increase.[48] In other words, high levels may be true or spurious, but a low level is likely to be true (albeit inaccurate), and in the presence of menopausal symptoms signals a need for a higher dose (or change in formulation).

In other contexts, for example, when measuring serum estradiol concentration in children to assess pubertal development, or to assess treatment efficacy in women with breast cancer using aromatase inhibitors, analytical accuracy is critical.[43,50,51] Accuracy is also critical in research, for example, to establish reference intervals for estradiol in perimenopausal and postmenopausal women, and to study relationships between estradiol levels and risk of diseases in postmenopausal women. When high sensitivity and specificity are needed, liquid or gas tandem mass spectrometry is the gold standard with high validity for measuring serum estradiol concentration.

What is a "low" estradiol level?

Due to the limitations of the different methods used to measure serum estradiol concentration in women with low levels, there is currently no generally agreed-upon reference interval for estradiol in postmenopausal women.[15] Nor is there consensus concerning a suitable

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therapeutic range for serum estradiol in postmenopausal women using MHT.[14] The results of dose-finding studies in which women received oral estrogens, mainly CEE and synthetic estrogens, cannot be extrapolated to women using transdermal estradiol because different estrogenic substances and their metabolites have different chemical structures and biological effects.[52] However, an approximate lower threshold or target range that allows for interindividual differences in clinical response can be surmised from the available literature, which can be used to guide dose titration in certain scenarios, listed above.

In an early study, 50 postmenopausal women with frequent hot flashes were randomized to receive a 25, 50, 100, or 200 mcg/24 h estradiol patch, or placebo.[53] With the exception of placebo, all patch doses significantly increased serum estradiol concentration in a dose-dependent manner to means of 18, 38, 73, and 100 pg/mL, respectively. Significant reductions in hot flush frequency were observed in women using ≥ 50 mcg/d patches, although clinical response was variable. Linear regression revealed a 50% reduction in hot flush frequency when levels approximated 61 pg/mL (~225 pmol/L), and a theoretical 100% reduction in hot flush frequency at levels of around 122 pg/mL (around 450 pmol/L).

In a subsequent report, de Lignieres[54] concluded that the optimal estradiol concentration for relief of menopausal symptoms and prevention of bone loss is 60-150 pg/mL (220-550 pmol/L), based on a mean serum estradiol concentration of 100 pg/mL (367 pmol/L) in a normal 28-day menstrual cycle, the absence of cyclical symptoms (eg, bloating, mastalgia, fatigue, low mood, and headaches) in the mid-follicular phase when serum estradiol levels approximate 60-150 pg/mL (~220-550 pmol/L), and the results of early dose-finding studies. Due to interindividual variation in estradiol pharmacokinetics and pharmacodynamics, De Lignieres[54] emphasized that it was unlikely that any standardized unique dose would produce optimal levels in all women, and therefore "efforts for individual titration are mandatory to improve clinical compliance and actual efficacy on a long term."

Concerning bone health, there is a dose-dependent effect of estrogens on bone turnover and bone mineral density (BMD).[55] Mean serum levels increase with dose, and a significant positive correlation between serum estradiol concentration and bone density has been observed in studies in which women received oral estradiol,[56] and estradiol implants.[57]

Dose-dependent bone protective effects may be less consistent in women using transdermal estradiol because there is substantial interindividual variation in transdermal absorption; dose doesn't reliably predict serum level, and around 1 in 3 women may not achieve therapeutic levels using licensed doses.[9,58,59] In a review of 14 studies that measured bone density at various sites in postmenopausal women treated with transdermal estradiol for between 1 and 3 years, bone loss was mainly observed in women with mean levels <55 pg/mL (<200 pmol/L; three of four studies, dose range 1-4 pumps 0.06% gel daily or equivalent), gains were mainly observed in women with mean levels >110 pg/mL: (>400 pmol/L; three of four studies, dose four pumps 0.06% gel daily or equivalent), and both losses and gains were observed in women with mean levels 55-110 pg/mL (200-400 pmol/L; losses in three studies, gains in three studies, doses of two or four pumps 0.06% gel daily or equivalent).[60] Factors, including the timing of blood sampling, the surface area of gel administration, interindividual differences in transdermal estradiol pharmacokinetics and pharmacodynamics, and the different assay methods used, are likely to account for the discrepant findings.

Low and ultralow transdermal estradiol doses (and levels) have been shown to maintain and/or modestly improve bone density in some studies,[61–64] but the number of nonresponders increases as dose decreases.[55] In studies in which women received doses ≤ 50 mcg/24 h patch, or equivalent, up to one third of women failed to respond (lost bone density).[61–64] Bone losses were more frequently observed at the hip and in younger women,[62–64] consistent with studies in which lower-than-standard doses of conjugated equine estrogen failed to prevent bone loss in younger women following oophorectomy.[65,66] This likely reflects more rapid rates of bone loss in the menopause transition versus older women far from menopause; higher estradiol doses (and levels) are typically required in women with premature ovarian insufficiency and early menopause to achieve full symptom relief and optimal bone mineralization.[67]

In summary, "dose doesn't predict level doesn't predict clinical response," and it is not possible to know or predict the threshold or optimal level for an individual that will effectively relieve symptoms and prevent bone loss. If taken to relieve symptoms, the transdermal estradiol dose should be titrated to symptom response. In the absence of symptoms, clinicians must titrate the dose to a "target level" for optimal clinical efficacy. If using direct immunoassay to measure serum estradiol, aiming >55 pg/mL (>200 pmol/L) or thereabouts seems likely to maintain bone density for most women, but younger women and women with established osteopenia or osteoporosis may benefit from higher levels (closer to 100 pg/mL, or ~400 pmol/L). Levels >55 pg/mL will most often be achieved with patch doses of 50-75 mcg/d, or 2-3 pumps 0.06% gel daily, but some women will achieve levels >55 pg/mL using lower doses, and others will require higher +/− off-label doses (Table 1).

Therapeutic levels are likely to have been grossly overestimated in studies that used direct immunoassay to quantify serum estradiol in MHT users, for the reasons discussed. There are limited data to inform the optimal level or target range when measured using more accurate methods. In postmenopausal women not using MHT, estradiol levels <25 pg/mL (92 pmol/L) are associated with a significant decrease in BMD, and a significant increase in Fracture Risk Assessment Tool (FRAX) score, when measured using LC-MS/MS.[70] Aiming for a serum estradiol concentration of >25 pg/mL (>92 pmol/L), therefore, seems reasonable, but younger women and/or

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TABLE 1. Mean estradiol concentrations in healthy postmenopausal women using regulator-approved transdermal estradiol formulations/doses, measured using direct immunoassay[29,31,33,38,68,69]

Estradiol formulation	Prescribed dose	Estradiol dose (mg/d)	Mean serum estradiol concentration (C_{avg} ± SD) (pg/mL)	Mean serum estradiol concentration (C_{avg} ± SD) (pmol/L)
Vivelle-Dot (ETS)	1 patch twice weekly	0.025	—	—-
	1 patch twice weekly	0.0375	34 (± 10)	125 (± 37)
	1 patch twice weekly	0.05	57 (± 23)	209 (± 84)
	1 patch twice weekly	0.075	72 (± 24)	264 (± 88)
	1 patch twice weekly	0.10	89 (± 38)	327 (± 140)
Evorel (ETS)	1 patch twice weekly	0.025	26 (± 10)	96 (± 35)
	1 patch twice weekly	0.05	47 (± 19)	173 (± 68)
	1 patch twice weekly	0.075	74 (± 44)	271 (± 161)
	1 patch twice weekly	0.10	104 (± 63)	382 (± 232)
Divigel (0.1% estradiol gel)	1 foil packet daily	0.25	9.8 (± 9)	36 (± 33)
	1 foil packet daily	0.5	21.0 (± 31)	77 (± 114)
	1 foil packet daily	1.0	30.5 (± 25)	112 (± 92)
Estrogel (0.06% estradiol gel)	1 pump daily	0.75	28.3 (N/R)	104 (N/R)
	2 pumps daily	1.5	68.1 (± 27.4)	250 (± 101)
	3 pumps daily	2.25	—	—-
	4 pumps daily	3.0	102.9 (± 39.9)	378 (± 147)
Evamist (transdermal spray)	1 spray daily	1.53	19.6 (± 9.6)	72 (± 35)
	2 sprays daily	3.06	30.7 (± 13.2)	113 (± 48)
	3 sprays daily	4.59	30.9 (± 9.3)	113 (± 34)

C_{avg}, the average estradiol concentration at steady state; ETS, estradiol transdermal system; N/R, not reported.

Mean levels > 55 pg/mL (> 200 pmol/L) are achieved with patch doses of ≥ 50 mcg/d, or ≥ 2 pumps 0.06% gel daily. Mean levels > 55 pg/mL (> 200 pmol/L) are not achieved with licensed doses of Divigel or Evamist.

The SDs are wide, especially at higher doses. For example, the coefficient of variation (SD/ mean) for mean estradiol concentration in women wearing an Evorel patch ranges from 38% (0.025 mg/d patch) to 61% (0.1 mg/d patch). In other words, there is substantial variability in dose-specific estradiol concentration. A large number of women have values below the mean and may not achieve levels needed to relieve menopausal symptoms and maintain bone density, even with higher licensed doses.

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those with risk factors for osteoporosis may need higher levels. If in doubt, serial BMD measurements may help guide dose decisions and support individualized care.

What factors influence serum estradiol levels in postmenopausal women using transdermal estradiol?

Factors that influence serum estradiol concentration in postmenopausal women using transdermal estradiol include transdermal dose and compliance; factors affecting absorption (surface area and site of application, ethnicity, age, skin physiology—eg, adiposity, hydration, capillary density, inflammation)[71–73]; factors affecting estradiol distribution, metabolism, and excretion (eg, caffeine, smoking, alcohol, exercise, comorbidities, and polypharmacy); diurnal and seasonal variation in endogenous estradiol levels;[74,75] and factors related to the physicochemical properties of the formulation used.[71,76] When measuring serum estradiol concentration in transdermal estradiol users, the following factors must also be considered: timing of dose application relative to blood sampling (eg, estradiol levels peak 4-5 h after gel and patch application, but 18-20 hours after spray application),[77,78] timing of washing and/or exercising and/or sunscreen use relative to dose application (gel and spray),[73,79] use of tight clothing (eg, moisture-wicking fabrics designed to draw sweat away from the skin may also absorb residual gel if donned too soon after administration), skin contamination (gel and spray),[80] and assay-related factors.[15]

In clinical practice, an inadequate dose and/or poor absorption are common causes of low levels (improve with higher doses and/or a change in formulation). Nondose-related factors, for example, skin contamination (gel or spray) and analytical errors, may be more likely to account for high levels.[9]

Are blood tests helpful in perimenopausal women?

Blood tests are not recommended to diagnose perimenopause because serum estradiol levels fluctuate and can be misleading.[20] A low estradiol level plus an elevated follicle-stimulating hormone (FSH) confirms the clinical diagnosis, but normal levels don't exclude the diagnosis.

The reference range for serum estradiol in perimenopausal women has not been defined. In a study that measured serum estradiol in 588 premenopausal women using liquid chromatography-tandem mass spectrometry, serum estradiol ranged from 5.51 to 3582.90 pmol/L (~1.5-976 pg/mL).[81] The median concentration was 372.6 pmol/L (~100 pg/mL), consistent with the mean estradiol level of 367 pmol/L reported in earlier studies using direct RIA.[54] Compared with premenopausal women, estradiol levels can sometimes be up to 30% higher in perimenopausal women due to dysregulation of the hypothalamic-pituitary-ovarian axis and/or luteal-out-of-phase (LOOP) events.[82] In other words, levels may intermittently peak at >4,000 pmol/L (>1,000 pg/mL) in perimenopausal women. In MHT users, there will be an additive effect, which accounts for the wide range in serum estradiol levels encountered in clinical practice, especially if measured using a direct immunoassay.[9]

Neither immunoassay nor mass spectrometry distinguishes between endogenous and exogenous estradiol, which makes normal and high levels in perimenopausal women difficult to interpret. For example, a high estradiol level in a perimenopausal woman using transdermal estradiol may be a normal mid-cycle level, spurious (for the reasons listed above), or it may indicate that the dose is too high.

Therefore, blood tests are of limited value in perimenopausal women using transdermal estradiol. Persistent symptoms and low levels (measured on days 3-5 of the menstrual cycle when endogenous estradiol levels are usually low) suggest poor absorption (or suboptimal compliance), but normal and high levels are generally unhelpful.

What should I do if the level is low?

MHT users with persistent menopausal symptoms and a low estradiol level (~<55 or <200 pmol/L if measured using direct immunoassay; ~<25 or <90 pmol/L if measured using mass spectrometry) can be offered a higher dose or a change in formulation. Patient preference is key.

Patients should be reviewed after 3 months, and further dose adjustments may be needed if there are ongoing symptoms. If levels are still subtherapeutic and/or not improving, a change in formulation is likely to be necessary. If levels have improved but symptoms persist, alternative causes should be considered.[83,84]

Is there a maximum dose?

There are no long-term safety data concerning higher than regulator-approved doses of estrogen. However, "poor absorbers" using high and/or off-label transdermal doses to achieve normal estradiol levels are unlikely to be at greater risk of harm versus "good absorbers" who achieve normal levels using licensed doses.

Consequently, menopause society guidelines do not set arbitrary limits on dose, but recommend that the **lowest effective** dose is used to relieve symptoms and/or protect bones.[11–13] The lowest effective dose may be an off-label dose for up to 1 in 4 women using transdermal estradiol.[9]

What should I do if the level is high?

High levels (eg, >150 or 550 pmol/L) are not uncommon, especially in gel users and/or if measured using direct immunoassay without preceding purification steps.[9]

If a postmenopausal woman found to have a high level is clinically well, the test should be repeated before adjusting the dose. Women using gel or spray should be advised to avoid applying estradiol to their arm the night before or morning of the blood test (the inner thigh may be used instead), and to wash their hands thoroughly after dose application to reduce the risk of skin contamination.[80]

If a high level is confirmed on repeat testing, the dose

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should be gradually reduced (eg, in 1 pump increments every 4-6 wk) until levels normalize. If menopausal symptoms recur, women can continue to use the higher dose. It may be necessary to liaise with laboratory staff if there is a discrepancy between an estradiol level and the clinical picture, for example, to check whether the sample was hemolysed or lipemic, and/or to check for interference.[44]

Are high estradiol levels harmful?

A small percentage of women—around 3% based on very limited data—may only achieve symptom relief with higher estradiol levels (> 477 pg/mL or > 1,750 pmol/L).[85] Women with severe psychological symptoms and/or surgically menopausal women are more likely to benefit from higher doses/ levels.[85,86] Higher doses/levels are also sometimes used to suppress endogenous cycles and relieve cyclical symptoms in perimenopausal women with severe premenstrual syndrome and premenstrual dysphoric disorder.[86,87]

There is a lack of long-term safety data concerning the use of high transdermal estradiol doses when used to achieve higher estradiol levels. Potential health risks include endometrial cancer, breast cancer, and tachyphylaxis—a re-emergence or worsening of menopausal symptoms despite ongoing treatment with MHT at a previously effective dose.

Unopposed estrogen therapy significantly increases the risk of endometrial hyperplasia and cancer.[88] Intuitively, women using high estradiol doses to achieve higher levels for clinical effect should therefore use a high progestogen dose for endometrial protection, but there are no data to inform the optimal progestogen dose in this scenario. Further, as with estradiol, progestogen pharmacokinetics and pharmacodynamics are highly variable; the same duration, dose, and type of progestogen in combined MHT regimens may cause endometrial atrophy in some women but hyperplasia in others.[36,89,90] And finally, high progestogen doses can cause side effects that limit use (eg, low mood, hypersomnolence, and mastalgia),[36] and may increase breast cancer risk.[91,92] Of note, use of body-identical progesterone in combined MHT regimens for up to 5 years has not been shown to increase breast cancer risk in observational studies.[93,94]

Consequently, progestogen dose should be clinically guided and tailored to the individual to ensure adequate endometrial protection while avoiding unnecessary progestogen exposure.[11–13] If using high transdermal estradiol doses to achieve higher levels for clinical effect, a proportionate increase in progestogen dose is recommended to ensure adequate endometrial protection.[95] A proportionate increase in progestogen dose is not necessarily needed if women are 'poor absorbers' with low or normal estradiol levels. Other factors to be considered include: progestogen type (synthetic vs. body-identical), regimen (sequential or continuous-combined) and route of administration; bleeding patterns (eg, light vs. heavy withdrawal bleeds in sequential MHT users, the presence of unscheduled bleeding); risk factors for endometrial hyperplasia and cancer (eg, obesity); the likelihood of progestogenic side effects (based on past use); and patient preference. If a high progestogen dose is recommended but not tolerated or desired, the endometrium should instead be monitored at regular intervals (eg, an annual transvaginal ultrasound scan).

Concerning breast cancer, observational study data reveal a small increase in breast cancer risk in estrogen-only and combined MHT users that increases with duration of use, but not with estrogen dose.[96] In a recent meta-analysis that pooled data from five placebo-controlled RCTs, breast cancer incidence was lower in hysterectomised women randomized to estradiol-alone MHT formulations (estradiol, estradiol valerate, or ethinyl estradiol), but the difference was not statistically significant (21 cases among 1,618 women randomized to estrogen-only MHT vs. 30 cases among 1,176 women randomized to placebo, 1.3% vs. 2.6%, RR = 0.63, 95% CI: 0.34-1.16, $P = 0.15$).[97] High estradiol doses are therefore unlikely to increase breast cancer risk, irrespective of serum levels, but larger RCTs with greater statistical power are needed to assess breast cancer incidence in women treated with body-identical estradiol.

Finally, use of high +/− off-label transdermal estradiol doses has led to concerns about the possible risk of tachyphylaxis.[98] Concerns that high-dose estradiol may cause tachyphylaxis are based on a single study published in 1990, in which estradiol levels were measured in 1,388 women treated with subcutaneous estrogen implants (pellets).[85] Subcutaneous implants are usually inserted every 6 months, but 3% of study participants reported that their symptoms returned after just 4 months, and needed more frequent implant insertions. Regular, four-monthly insertions were associated with higher estradiol levels (> 1,750 pmol/L or > 476.7 pg/mL), but these women did not have true tachyphylaxis because symptom control was achieved with the higher (more frequent) doses and levels. The authors concluded that "higher doses may be necessary to achieve symptom control in some women" and **did not** consider this to be an example of tachyphylaxis, but the study has since been repeatedly cited as evidence for this phenomenon.

Given that most women using high-dose transdermal estradiol are "poor absorbers" with low or normal serum levels, the risk of tachyphylaxis is not usually a concern. There is a theoretical risk if women are using high doses to achieve higher levels, but there are no data to support an association between high estrogen doses and possible tachyphylaxis.

CONCLUSION

In conclusion, MHT is the most effective treatment option for troublesome menopausal symptoms and has long-term health benefits. Compared with oral estradiol, transdermal formulations have a superior safety profile and are increasingly used. However, there is substantial interindividual variation in serum estradiol concentration in transdermal estradiol users, even among women using the same dose and formulation. Consequently, the trans-

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TABLE 2. Summary of clinical recommendations for tailoring estradiol dose to the individual to ensure that optimal estradiol levels are achieved in postmenopausal women using transdermal estradiol.

Summary of clinical recommendations
Tailor transdermal estradiol dose to the individual according to clinical response +/− blood levels, and be aware that the lowest effective dose may be an off-label dose for some women.
Measure serum estradiol concentration to confirm absorption if women have persistent menopausal symptoms after initiation of MHT and/or after increasing the dose.
Consider measuring serum estradiol concentration for postmenopausal women using MHT for bone protection, especially in the absence of menopausal symptoms.
Consider measuring serum estradiol concentration for younger postmenopausal women (below 45 years), especially in the absence of menopausal symptoms.
Consider measuring serum estradiol concentration to distinguish side effects from persistent menopausal symptoms.
Be aware of the limitations of the methods used to measure serum estradiol in clinical practice.
If using immunoassay to monitor estradiol levels in asymptomatic women, aim for 55-160 pg/mL (approx. 200-600 pmol/L) - but always "treat the patient, not the result."
If using mass spectrometry to monitor estradiol levels in asymptomatic women, aim for levels > 25 pg/ml (~> 90 pmol/L)—but always "treat the patient, not the result."
It is not necessary to routinely increase the progestogen dose if "poor absorbers" are using high transdermal estradiol doses to achieve normal estradiol levels. However, women with unscheduled bleeding should be offered a higher progestogen dose, or the levonorgestrel-containing intrauterine system (LNG-IUS), after exclusion of endometrial pathology. Women with risk factors for endometrial cancer may also benefit from a higher progestogen dose.
Be aware that some women may only achieve symptom relief with higher estradiol levels. Offer women using high estradiol doses to achieve high estradiol levels for clinical effect a higher progestogen dose (or the LNG-IUS), or regular endometrial surveillance.

LNG-IUS, levonorgestrel intrauterine system; MHT, menopausal hormone therapy.

Recommendations are based on the best currently available evidence.

dermal estradiol dose must be tailored to the individual to maximize benefits and minimize risks. Dose is usually titrated to symptom response, and blood tests are not routinely indicated. However, measurement of serum estradiol concentration is sometimes helpful. Mass spectrometry is the best method for measuring estradiol levels, but it may not be available.

More research is needed to define the therapeutic or target range for serum estradiol that will achieve relief of vasomotor *and* other menopausal symptoms, and protect against the development of osteoporosis (at both the lumbar spine *and* hip) *and* other long-term morbidities (eg, diabetes and cardiovascular disease), in different patient populations (eg, in different ethnic groups, perimenopausal women, women with POI). Until such data are available, there are sufficient data from available studies to inform a pragmatic approach to dose optimization and facilitate patient-centered menopause care (Table 2). Ensuring that all women achieve optimal estradiol levels, including women who absorb estradiol poorly across the skin, is likely to improve quality of life for many women, reduce chronic disease morbidity and all-cause mortality,[99–101] and have economic benefits for both individuals and society in the long term.[102–104]

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