Expert Opinion

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Delivery systems for hormone replacement therapy

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The steroid hormones used for hormone replacement therapy in the menopausal transition and postmenopause can be administered by several different routes using a variety of delivery systems. The conventional approach to administration has been oral, and this is still the standard against which other routes are compared. However, there is a steadily increasing research development and popularity for alternative systems. Such systems can be geared to ultra low-dose delivery for local vaginal effect or higher dosages for systemic effect. Different delivery systems have a range of attributes with varying appeal to different individual women. Such a range of choices can be important for acceptability and compliance. One of the most important attributes of many newer delivery systems is the potential to deliver hormones in a controlled manner over prolonged periods of time, allowing constant low dosages, as well as constant blood and tissue levels. They also have the potential for reducing side effects and metabolic effects. Transdermal, subdermal, intravaginal and intrauterine systems are particularly likely to undergo refinement and further development in the foreseeable future with subsequent increases in popularity.

Keywords: hormone replacement therapy, intrauterine delivery, estrogen, progestogen, transdermal delivery, vaginal bleeding

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1. Introduction

Following the menopause, ovarian secretion of steroid hormones falls dramatically [1]. This is most obvious in the case of estradiol, the main biologically active estrogen, which is the primary secretory product of mature ovarian follicles. Menopause occurs when the ovaries run out of follicles. During the 1 – 5 years prior to menopause, menstrual cycles become increasingly erratic due to the decline in responsive ovarian follicles [2]. During this menopausal transition, women may experience a range of troublesome symptoms primarily due to erratic or deficient secretion of ovarian estradiol. The most prominent of these symptoms are usually vasomotor symptoms, including hot flushes and night sweats [3]. Other ovarian steroid hormones may also change and some women experience a marked fall in circulating levels of testosterone, which may sometimes contribute to a fall in libido.

2. Menopausal physiology

In Western society, ~ 80% of women will experience menopausal vasomotor symptoms, with up to 50% finding one or more symptoms a problem [4]. Most women will only experience these symptoms for 1 – 2 years, but for 15 – 20%, these will persist for > 5 years [5]. An equally common but less well-recognised symptom of menopause is urogenital atrophy resulting in symptoms of vaginal dryness, vulval pruritus and superficial dyspareunia. This may also influence urinary symptoms, including dysuria, urgency and recurrent infections. Of postmenopausal women, 10 – 30% will experience effects of urogenital atrophy within the first or second decades after menopause [6,7], and this number may increase with age. Many women

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find these symptoms embarrassing and do not discuss them with their doctor.

In contrast to vasomotor symptoms, urogenital atrophy symptoms tend to persist and even worsen with time, with troublesome consequences for many women living > 30 years beyond menopause. These urogenital symptoms usually respond well to a low dose of local vaginal estrogen but do not always respond fully to systemic hormone replacement therapy (HRT). Anecdotally, ~ 10 – 15% of women using systemic HRT may benefit from additional vaginal estrogen, suggesting that different target organs may require different hormone exposure.

The onset of menopause is also associated with a range of metabolic changes that can influence bone, the heart, the vascular system, blood lipids, glucose and insulin metabolism, and liver function, as well as have some effects on the CNS, skin, teeth and eyes [8-14]. These changes vary considerably from one woman to another, and interact with changes due to general ageing.

The least controversial of these long-term effects involves an increase in the rate of bone mineral loss from the vertebrae and long bones following menopause, compared with the premenopausal phase of reproductive life. There is extensive literature on this well-researched topic [8]. More controversial is the effect of menopause on the heart and vascular system, especially when studied through changes in surrogate markers such as those for atherogenic lipids [10-12]. These changes include an increase in circulating levels of total cholesterol with a specific increase in low-density lipoprotein (LDL) cholesterol and fasting triglycerides, as well as a decrease in the high-density lipoprotein (HDL) subfraction 2. There is also an increase in another atherogenic risk marker, lipoprotein (a).

Changes in insulin secretion, sensitivity and elimination occur with the loss of ovarian function [12]. These changes may be of particular importance for women with other risk factors indicating the development of diabetes. The female body shape changes with the onset of the menopause transition with more fat deposition around the central abdominal region rather than the hips and thighs [13]. Some menopause-related changes in vascular fibrinolysis, vascular endothelial function and circulating coagulation factors may have subtle effects on risks of venous thromboembolism (VTE) and arterial vascular disease.

3. Concept of hormone replacement therapy

There is strong evidence to demonstrate that vasomotor symptoms improve greatly in most women during treatment with low doses of exogenous estrogen given by any one of a number of routes [15]. This indication is the main justification for the widespread use of HRT in modern clinical practice. However, a range of other indications have sometimes been recommended, including local vaginal treatment of urogenital atrophy, and systemic treatment for the prevention of osteoporosis and coronary artery disease [16,17].

This field has attracted great controversy over the past 3 – 4 years following the publication of a major American, randomised, controlled clinical trial; the Women's Health Initiative (WHI) in 2002 [18]. This very large trial demonstrated a small increase in absolute numbers of certain adverse events (arterial and venous thromboembolic events and breast cancer) in HRT users compared with placebo users. A number of important criticisms have been raised about the findings and the interpretation of the results of this trial [19,20], but nevertheless it has led experts in the field to re-evaluate the way in which HRT should be used.

At present, it is widely agreed that the primary indications for the use of HRT are vasomotor and related symptoms [21], and the local vaginal treatment of symptoms of urogenital atrophy. HRT delivery should generally be limited to 3 – 5 years unless troublesome vasomotor symptoms persist. There is considerable controversy about the possible use of HRT to try and prevent the bone loss that may lead to osteoporosis, to prevent the development of coronary artery atherosclerosis and myocardial infarction, and to prevent the development of degenerative CNS changes such as Alzheimer's disease. HRT is currently not recommended for these indications.

There is ongoing discussion as to what constitutes HRT; some experts take it to mean only conventional estrogen and progestogen delivery, but the authors have taken it to include any hormonal therapy acting through estrogen, progesterone or androgen receptors at this phase of life.

4. Routes of delivery

HRT steroids can be administered by a variety of routes. These include oral, intramuscular, subcutaneous, subdermal, transdermal, intranasal, intravaginal or intrauterine. Each route has different characteristics that have varying appeal to different women, and which may have specific advantages or disadvantages in particular clinical situations (Table 1). These systems can be designed to release varying dosages and combinations of estrogen, progestogen or androgen depending on the relevant indication.

In this review, oral administration has been considered as the standard route and other systems have been compared and contrasted with it.

A delivery system is generally regarded as a device designed to modify the release of a drug in a specific manner, usually at a controlled rate over a specific period of time. The comparator is usually taken to be the pattern of drug as it is released into the body following oral administration. The pharmacokinetic aim of delivery systems is usually to achieve steady release rates of drug (a zero order release), resulting in constant blood levels over prolonged periods of time. The clinical aim is for these characteristics to increase efficacy, convenience and acceptability, and at the same time reduce side effects and metabolic effects. No system is perfect and each of the HRT systems will have advantages for some women and disadvantages for others.

Table 1. Advantages and disadvantages of the different routes of systemic HRT administration.

Route	Advantages	Disadvantages
Oral	Easy to take Relatively quick absorption Familiar administration route for user Inexpensive May raise HDL cholesterol Variable dosing Can be used for estrogen and progestogens	Easy to forget daily dosing Fluctuation of systemic levels Side effects (e.g., nausea) Variable absorption First-pass metabolic effect on the liver Postmenopausal estradiol:estrone ratio May raise triglycerides
Transdermal patches	Easy to use Avoids daily dosing Steady systemic levels Estradiol absorbed unaltered No first-pass effect on liver metabolism Physiological estradiol:estrone ratio Reduces triglycerides Can be used for estrogen and progestogens Variable doses	Variable skin adherence Visible Variable absorption More expensive Does not increase HDL cholesterol Local skin irritation
Transdermal gel	Easy to use Invisible Steady systemic levels Estradiol absorbed unaltered No first-pass effect on liver metabolism Reduces triglycerides Less skin irritation than patches Physiological estradiol:estrone ratio Variable doses	Daily administration Messy Variable absorption More expensive Does not increase HDL cholesterol Progestogens cannot be administered by this route
Implants	Avoids daily dosing Estradiol absorbed unaltered No first-pass effect on liver metabolism Reduces triglycerides 6 – 12 monthly insertion Variable doses Physiological estradiol:estrone ratio Estradiol and testosterone can be used Estradiol levels in mean premenopausal range Bone conservation greater than with oral HRT	Invasive procedure May cause tachyphylaxis Does not increase HDL cholesterol Not immediately reversible Cannot be easily removed Estradiol can accumulate Risk of endometrial hyperplasia if long-term progestogens not given Variable hormone levels and duration of effect Occasional expulsion especially testosterone implants Bleeding or infection at insertion site
Nasal spray	Avoids first-pass effect on the liver Only transient rise in systemic estradiol Not visible Minimal estrogen side effects Familiar route of administration	Rhinitis/nasal symptoms Progestogen needs to be given separately Repeated dosing needed for symptom control
Vaginal ring	Lasts for 3 months Avoids daily dosing Steady systemic levels Estradiol absorbed unaltered No first-pass effect on liver metabolism Reduces triglycerides Physiological estradiol:estrone ratio	Inserted internally May be expelled Variable absorption Only one dose Does not increase HDL cholesterol Progestogens via another route

HDL: High-density lipoprotein; HRT: Hormone replacement therapy.

Hence, a wide range of choices can be valuable for women who have specific difficulties.

Non-oral routes of delivery are designed to avoid the large first-pass effect of drug through the mucosa of the small intestine, the portal system and hepatic lobules where substantial metabolism takes place. This metabolism influences the effective levels of circulating HRT steroids, as well as simultaneously influencing hepatic protein synthesis, lipid profile and bile composition (Table 2 and 3). Delivery by other routes should allow a much greater proportion of unchanged HRT steroid to reach the target tissues and should have less metabolic impact on the liver itself.

Table 2. Effects of different estrogen delivery methods on metabolic parameters in menopausal women.

	Oral	Transdermal	Nasal
Effects on lipoprotein metabolism			
Total cholesterol	Decreases	Decreases	Decreases
HDL cholesterol	Increases	Small increase	Increases
LDL cholesterol	Decreases	Decreases	Decreases
Lipoprotein (a)	Decreases	No effect	Decreases
Triglycerides	Increase (conjugated equine estrogens) Small increase (estradiol)	Decreases	No effect
Effects on coagulation			
Thrombogenesis	Increases (dose effect plus first-pass effect on liver)	No effect	No effect
Fibrinogen	Decreases		
Factor VII	Decreases		
PAI-1	Decreases		
Fibrinolysis	Increases	No effect	No effect
C-reactive protein	Increases	No effect	No effect
Endothelial function	Beneficial	Beneficial	
Effects on glucose and insulin metabolism			
Insulin resistance	Improves (except conjugated equine estrogens and ethinylestradiol)	No effect	No effect

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PAI: Plasminogen activator inhibitor.

Table 3. Effects on metabolism with the addition of progestogens to oral estrogen therapy.

	Androgenic progestogen	Non-androgenic progestogen
Lipoprotein effects		
LDL cholesterol	No effect	No effect
HDL cholesterol	Decreased rise	No effect (except MPA attenuates estrogen-induced rise)
Triglycerides	Decreased rise	No effect
Effects on glucose and insulin metabolism		
Insulin resistance	Increase (reduced adverse effect with transdermal androgenic progestogens)	No effect (except MPA, which increases insulin resistance)

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MPA: Medroxyprogesterone acetate.

5. Different delivery systems for hormone replacement therapy

Different delivery systems exhibit a wide range of attributes affecting drug pharmacokinetics, endogenous pharmacodynamic responses and clinical performance. Individual systems are discussed below.

5.1 Oral

Oral HRT is the most commonly chosen route of administration by women. It is an acceptable way of delivering drug therapy and has been available for the last 50 years. In women with a uterus, estrogen is combined with progestogen. Depending on the dose, the estrogen component alleviates most vasomotor and some urogenital symptoms,

Table 4. Estogens and progestogens available or trialled in hormone replacement therapy.

Preparation	Estrogen	Progestogen	Androgen
Oral	Conjugated equine estrogen Estradiol valerate Estradiol Estradiol/estriol Estropipate	Norgestrel Norethisterone acetate Medroxyprogesterone acetate Dydrogesterone Drospirenone	
Oral gonadomimetic	Tibolone		
Transdermal	Estradiol	Norethisterone Levonorgestrel	Testosterone
Gel	Estradiol		Testosterone
Implant	Estradiol		
Nasal spray	Estradiol		
Intrauterine		Levonorgestrel	
Vaginal ring (low and systemic doses)	Estradiol	Progesterone	
Vaginal gel/pessaries		Progesterone	
Vaginal creams and pessaries	Estriol Estradiol Conjugated equine estrogens		

and some progestogens (especially norethisterone and medroxyprogesterone acetate) provide additional control for vasomotor symptoms. However, the main role of the progestogen is to ensure endometrial protection. Oral HRT can be given cyclically; in a long cycle regimen or as a continuous combined preparation.

Cyclical HRT regimens contain estrogen throughout the cycle with progestogens for 10 – 14 days resulting, in a regular withdrawal bleed each month.

Licensed long-cycle HRT preparations contain estrogen for 70 days with additional progestogen in the last 14 days. This is followed by 7 days of placebo tablets. Some clinicians in the UK make up long-cycle formulations with continuous estrogen and 12 – 14 days of progestogen every 2 – 3 months. These regimens are particularly useful for perimenopausal women who poorly tolerate progestogens; however, long-term endometrial safety has not yet been defined.

Postmenopausal women taking continuous combined HRT receive daily estrogen and progestogen throughout the month. In the first few months, irregular vaginal bleeding or spotting is not uncommon, but 80 – 90% are amenorrhoeic by the sixth month. [22] These women particularly welcome this break from bleeding, as recent evidence suggests that taking continuous combined HRT reduces the incidence of endometrial cancer [23].

Hysterectomised women need only to take estrogen alone as a hormone replacement because endometrial protection by a progestogen is not required. It must be remembered, however, that those potential users who have undergone endometrial ablation or subtotal hysterectomy, where there is a possibility of endometrium being present in the stump of the cervix, should be prescribed combined HRT.

Table 4 shows the different estrogens and progestogens contained in HRT preparations. The doses and regimens vary to allow the clinician to tailor the preparations to the needs of individual women. Most oral HRT preparations are quickly absorbed in the upper gastrointestinal tract, reaching maximum levels systemically 2 – 4 h after administration. There is no accumulation of most of these hormones, with the lowest levels being reached by 8 – 12 h, and, therefore, once-daily dosing is appropriate [24]. Following the discontinuation of HRT no exogenous hormones can be measured after 3 – 4 days, although some metabolites of the conjugated equine estrogens (which cannot easily be measured) may persist a little longer. Absorption may vary between individual women, particularly if they suffer from malabsorption or if they are taking liver enzyme-inducing drugs, such as carbamazepine or phenytoin.

Relatively high doses of HRT need to be given orally to ensure similar systemic levels to those provided by transdermal and percutaneous HRT preparations. This may result in some women complaining of nausea. Such side effects may be improved either by lowering the estrogen dosage or changing the route of HRT administration.

Micronised estradiol and other oral estrogen preparations are absorbed through the gut wall and transported via the portal system to the liver where they are metabolised and conjugated, finally being excreted in the bile. It is here that much of the estrogen is converted to estrone, a biologically weaker estrogen than estradiol. Following the menopause, the ratio of estrone to estradiol changes so that estrone and estrone sulfate become the dominant circulating estrogens. This initial high estrogen load on the liver and its resultant metabolism is often referred to as the 'first-pass effect' [25], and may be associated with undesirable side effects in some women, mainly related to

elevated protein synthesis (Table 2 and 3). Some side effects of the first pass, such as an increase in HDL and a decrease in total cholesterol, are desirable.

Tibolone is a synthetic steroid, often referred to as a gonadomimetic or tissue-specific preparation, that is taken orally. Tibolone has never been delivered by routes other than oral. It cannot be classified as either an estrogen or progestogen because of its tissue-selective action. Following administration, it is rapidly converted into three metabolites: 3α- and 3β-hydroxy-tibolone, which have estrogenic effects, and the δ(4)-isomer, which has progestogenic and androgenic effects. Tibolone is effective in treating vasomotor symptoms, preventing bone loss and produces the following changes in metabolism [26]: it has no effect on LDL cholesterol but does decrease triglycerides. It has also been shown to significantly lower lipoprotein (a) and decrease HDL cholesterol. Whether these effects are of any clinical relevance is not known.

5.2 Transdermal and percutaneous systems

5.2.1 Patches

Both estrogen and certain progestogens can be administered transdermally in cyclical and continuous combined regimens (Table 3). The advantages of delivering HRT transdermally have been summarised in Table 1. Much lower doses of hormones can be given via the skin, as this approach circumvents first-pass liver metabolism by delivering the drug directly into the bloodstream. A number of patches have been studied with reservoir formulations marketed first, followed by matrix preparations. Different amounts of estradiol are contained in these patches (estradiol 25 – 100 µg/day) for symptom control, and these patches are changed once- or twice-weekly. The size and shape of patches vary, with those containing estrogen and progestogen being available in just one dose, limiting prescribing choice.

Transdermal delivery occurs mainly by passive diffusion of lipid-soluble substances through lipophilic spaces between keratinised cells of the stratum corneum [27]. Both estrogen and progestogens are dissolved either in a reservoir gel or within the adhesive of a matrix patch. Ethanol in the reservoir patches enhances estradiol delivery through a rate-limiting membrane and through the skin (e.g., 30% ethanol can increase estradiol flux by 20-fold when compared with an equivalent but aqueous formulation) [28]. How is this achieved? The ethanol increases the solubility and diffusivity of estradiol with the first property being the most important. A similar approach has been taken for the transdermal delivery of levonorgestrel (LNG) using ethyl acetate as the delivery vehicle and enhancer [29]. In the immediate phase following application of a reservoir patch, the flux of the estradiol is proportional to the flux of alcohol that is transported across the skin; much faster than the hormone. As a consequence, depletion of ethanol in the reservoir leads to higher saturation of the drug and, finally, a decline in transdermal estradiol delivery. Therefore, reservoir patches must be changed twice-weekly and produce a very rapid rise

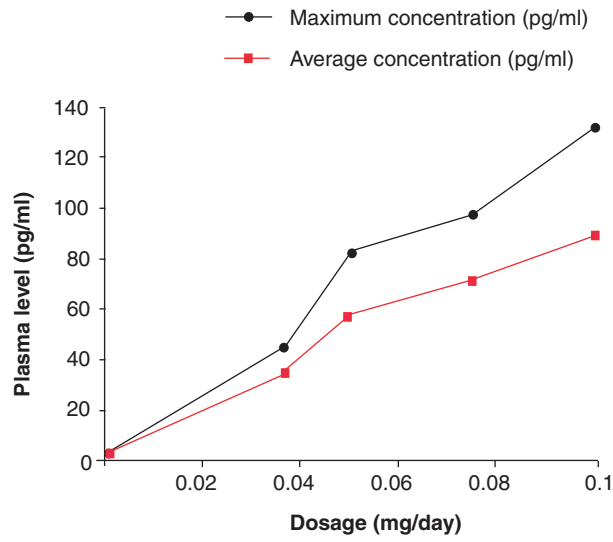

Figure 1. Near linear effect of different patch strengths on plasma concentration of estradiol. Reproduced from WATKINSON AC: The pharmacokinetics of drug delivery systems in hormone replacement therapy. *J. Br. Menopause Soc.* (2001) **7**:105-108 [24], with the permission of the Royal Society of Medicine Press on behalf of the British Menopause Society.

in estradiol (within 3 – 4 h) followed by a slower rise at 48 h, and a gradual fall to low levels at 96 h [30-34].

Matrix patches do not contain ethanol, with the rate of drug delivery being fairly constant over the application period. The rate and duration of the drug delivery depends on the estradiol content of the adhesive matrix and the unit area of the system in contact with the skin. The new dot matrix patches exhibit enhanced estradiol delivery from a smaller surface area.

Different patch sizes and strengths correspond with a near linear effect on the plasma concentration of estradiol, but levels of absorption vary from individual to individual (Figure 1). The rate of drug delivery is controlled in matrix patches by diffusion through the skin rather than by the use of a rate-limiting membrane as in reservoir patches. Mean serum estradiol levels of 90 – 120 pmol/l can be expected with 50-µg patches, and 180 – 210 pmol/l with 100-µg patches.

The steady release of estradiol transdermally results in an estradiol to estrone ratio, which is similar to that seen in the premenopausal women. Whether this ratio is of importance in symptom control, or the result of metabolic effects induced by transdermal administration of estrogen, is not known. What is known, however, is that different estrogen and progestogen delivery methods affect the metabolic parameters in menopausal women differently (Table 2 and 3). Although there are no outcome data available, most clinicians tend to choose a transdermal preparation for diabetic women who often suffer from dyslipidaemia. There is also some evidence

to suggest that transdermal estradiol/norethisterone combinations increase insulin sensitivity [35]. More recently, data have suggested that transdermal administration of estradiol has no effect on VTE risk when compared with a small increased risk with oral estrogens [36]. Different types and doses of oral estrogens may differentially alter VTE risk [37].

There are specific side effects in some users of HRT patches. The most common reaction is local skin irritation or allergic response in 15 – 40% of women using reservoir patches [33,38,39] and in < 10% in matrix-patch users. This is either a reaction to the ethanol or the adhesive in the patch, and regular changing of the site of the skin patch may reduce this problem; however, occasionally, women need to opt for a different HRT delivery system. Some women report that the patches adhere poorly, especially if they exercise regularly or live in a humid climate. Adhesion seems to be superior with the matrix patches [40]. A percutaneous gel delivery system can be a useful alternative for all patch users with these side effects. However, they would need to take additional progestogen orally, vaginally or via an intrauterine system.

At the present time, licences are being sought in a number of countries for testosterone matrix patches used to treat 'androgen deficiency' in oophorectomised women [41]. These have been shown to significantly increase satisfying sexual activity and sexual desire, while decreasing personal distress. The exact role of these patches in managing postmenopausal libido problems has not yet been defined, but demand from consumers is likely to grow.

5.2.2 *Percutaneous spray*

An intriguing new concept for transdermal delivery of a precisely metered dose of estradiol (Acrux Company) uses a simple and neat hand-held spray pump and absorption enhancers based on well-studied sunscreen technology [42]. This system has considerable appeal as an alternative system for daily administration of estradiol or combined HRT, using technology that produces remarkably constant daily blood levels [42,43]. The same company has developed a low-dose transdermal testosterone delivery system using the same technology for treatment of postmenopausal loss of libido. Both of these systems are currently in Phase III clinical trial development.

5.2.3 *Percutaneous gel*

A number of percutaneous, alcohol-based, steroid-delivering gel systems containing estradiol have been developed and marketed over the last 10 years [44]. Most gels release between 1.5 and 3 mg of estradiol per day (depending on the volume applied), and these generally need to be applied every 24 h over the lower abdomen, thighs or upper arms to insure a steady release. Absorption does vary between women and is proportional to the surface area of application. Administration of these gels increases the serum estradiol level close to the mid-follicular phase levels seen in the normal menstrual cycle (120 – 400 pmol/l), and takes 2 – 5 min for absorption to be complete [45]. Unfortunately, there are no licensed progestogen/combination HRT percutaneous gels available, with progestogen having to be given (if required) by another route. Progesterone transdermal creams may be bought via the internet or privately, but are not licensed in the UK or most other countries as quality assurance and efficacy data are insufficiently available. The use of progesterone or progestogen creams is not recommended.

Some women find these gels are messy and report that it takes time for the gel to be absorbed. Local reactions and allergies do sometimes occur, but less often than in either matrix or reservoir-patch users. One study suggested that just 1.7% of women discontinued therapy because of skin irritation [44].

5.3 Injectable preparations

Injections of estrogenic preparations, or combinations of estrogen and progestogen esters or estrogen and androgen esters, have been used anecdotally for many years for the relief of perimenopausal symptoms in women still requiring contraceptive reassurance (e.g., estradiol valerate combined with norethisterone enantate). Most of these preparations are no longer used as they suffer from a short duration of action and need frequent injections, resulting in high early blood levels and a variable duration of action [46]. Several small studies in the 1980s suggested that depot medroxyprogesterone acetate may be an alternative to estrogen therapy [47,48]. It was found to reduce menopausal symptoms when compared with placebo, and was equally effective as estrogen in menopausal symptom control. More recent controversy suggesting that high-dose parental progestogens have a deleterious effect on bone mineral density makes this preparation alone unsuitable for perimenopausal women [49]. However, in combination with estrogen as a once-monthly injection it may offer contraception, protection of the endometrium and vasomotor symptom control for this group of women [50].

5.4 Subdermal and subcutaneous systems

Estrogen and testosterone implants are one of the oldest non-oral technologies and were first used in 1938. These biodegradable, crystalline pellets are inserted into the subcutaneous fat and, like other transdermal and percutaneous delivery methods, avoid the first-pass metabolic effects, keeping the physiological estradiol:estrone ratio of > 1. Overall menopausal symptoms are controlled for ≥ 6 months, although there is wide individual variation.

Estradiol implants contain 25, 50 and 100 mg of estradiol, and the testosterone implants have 100 mg of testosterone. After insertion, there is an initial peak then a slow fall over time with endometrial stimulation having been reported ≤ 43 months following estradiol implant administration [51]. Ongoing release of estradiol may, therefore, increase the risk of endometrial hyperplasia and cancer in those with a uterus. For these women there is a need to continue cyclical progestogen for 10 – 14 days each month until no further withdrawal bleeds occur.

Table 5. Advantages and disadvantages of the different routes of local estrogen administration.

Preparation	Advantages	Disadvantages
Creams and pessaries (estriol 0.01%, 0.1% CEE)	Ease of use Effective for urogenital atrophy May give added lubrication Estriol safe in low-dose maintenance Can be used in women with previous breast cancer and venous thromboembolism	Messy Need to follow dosing regimen May cause local reaction CEE cream in recommended dosing regimens may cause endometrial hyperplasia
Vaginal tablets Estradiol 25 µg (Vagifem®; Novo Nordisk)	Ease of use Preferred by users Effective for urogenital atrophy Safe in low-dose maintenance Can be used in those with previous breast cancer and venous thromboembolism	Need to follow dosing regimen
Vaginal ring Estradiol 8 µg (Estring®; Pharmacia)	Avoids daily regimen Safe in long-term use Lasts for 3 months Steady low dose of estrogen May be used in infirm Relative ease of use Effective for vaginal atrophy	Worn internally May be expelled May be felt during sex

CEE: Conjugated equine estrogens.

In practice, most gynaecologists reserve this formulation for hysterectomised women with problematic vasomotor symptoms. Whilst receiving estrogen implant therapy, serum estradiol levels rise to the premenopausal range of 400 – 600 pmol/l. Ideally, levels should be monitored before each new implant is administered to avoid the development of tachyphylaxis (supraphysiological estradiol blood levels in the presence of a recurrence of menopausal symptoms) and to guide the next appropriate dose of estradiol to be inserted.

Subdermal testosterone implants have been used extensively for androgen replacement therapy in hypogonadal men but their use in women has been more controversial. Some evidence suggests that these implants are of benefit to oophorectomised women with loss of sexual desire and low serum testosterone levels, and should be given in conjunction with estrogen to reduce the incidence of androgenic side effects [52]. These can occur if serum estradiol and, therefore, sex hormone-binding globulin levels are low. Most clinicians recommend monitoring testosterone levels before each insertion and use 50- to 100-mg implants that achieve testosterone levels of 1 – 2.5 nmol/l.

Second-generation, non-biodegradable estradiol implants are also being developed. These contain estradiol in a polydimethylsiloxane matrix covered by a thin polydimethylsiloxane rate-limiting membrane [53]. The major advantages of this technology are to provide lower, more constant serum levels of estradiol, thereby reducing the problems of symptom recurrence with high, declining levels of estradiol and tachyphylaxis.

5.5 Vaginal systems

5.5.1 *Conventional local systems*

Systemic and local estrogen therapies have been shown to relieve symptoms of vaginal atrophy, with symptoms recurring after the cessation of therapy. Local estrogen therapy is often preferred as it is highly effective in improving the quality of the vaginal epithelium in atrophic vaginitis, without the systemic side effects sometimes associated with oral and non-oral HRT preparations. Women with a past history of breast cancer or VTE are often denied local estrogen therapies; however, recent data suggest that this concern is unfounded [54].

The vaginal epithelium is a good surface for rapid and efficient absorption of estrogens and progestogens. Local estrogen therapy can be administered as tablets, pessaries, creams or via a vaginal ring as described in Table 5. The continuation of low-dose, maintenance estrogen therapy is poor because health professionals often prescribe vaginal creams that are messy, cause discomfort and require daily to weekly self-administration [55]. Health professionals continue to voice concerns about the long-term endometrial safety of low-dose, local estrogen application, although there is growing evidence to support its long-term safety (with the exception of conjugated equine estrogen cream) in the dosage regimens recommended [56].

Although estrogen-containing creams and pessaries have been available for many years for local treatment of estrogen deficiency symptoms, it is only in the past decade that modern technologies have been applied to the development of precise steroid release from slow-release tablets and vaginal rings [57]. Much relevant research on the characteristics of steroid release and vaginal absorption has come from the development over the past 30 years of progestogen only and combined estrogen–progestogen vaginal rings for contraception [57].

5.5.2 *Vaginal slow-release estradiol tablets*

These tablets have been designed to release the low dosage of 25 µg of estradiol slowly during a 24-h period from a

hydrophilic gel (Vagifem®, Novo Nordisk). These tablets are placed high in the vagina using a simple applicator. Dosage of a single tablet is usually recommended daily for women presenting with untreated urogenital atrophy, and after 14 days the dosage frequency is reduced to once- or twice-weekly.

The estradiol primarily acts locally on the vaginal epithelium with some local diffusion into the pelvic tissues. During 12 months of treatment, serum levels of estradiol (from 15 to 36 pmol/l) and total estrone (from 1.1 to 1.7 nmol/l) increased slightly and significantly, but remained within the normal postmenopausal range [57]. Biological and clinical indicators (vaginal atrophy, dryness, dyspareunia and epithelial maturation index) confirmed a substantial reversal of urogenital atrophy, and the urogenital component of health burden is significantly improved. No cases of endometrial hyperplasia were found in this study, although slight endometrial thickening (from 2.5 to 2.7 mm) occurred and four episodes of slight breakthrough bleeding were recorded in 59 users treated over 12 months [58].

5.5.3 *Constant low-dose estradiol vaginal ring*

This ring consists of a steroid-containing core, a thick nonbiodegradable polymer sheath (to give it form and flexibility) and a rate-limiting, outer polymer membrane (Estring®, Pharmacia). It is designed to release estradiol at a constant rate of 5 – 10 µg/day (mean 8 µg/day) over a 3-month period. Serum estradiol increased from 16 to 25 pmol/l over a 12-month period [57]. The drug loading of the core mainly controls the lifespan of the device. The release rate of estradiol is so low that endometrial proliferation does not occur and a progestogen is not required in those women with a uterus. Release characteristics are close to a zero order.

Clinical performance of this ultra-low dose ring is very similar to that of 25-µg estradiol vaginal tablets administered every second or third day over a 1-year period [58]. Indeed, the two systems are almost indistinguishable in their clinical effects, except that breakthrough bleeding is even less common with this vaginal ring compared with the vaginal tablets. Both systems produce a high level of relief from atrophic urogenital symptoms and all objective signs of atrophy, including vaginal mucosa pallor, petechiae, friability, dryness and mucosal cytological maturation indices, improve greatly.

The clinical benefits of Estring are equal to those of vaginal estrogen creams (such as conjugated equine estrogen given in a 2-g dosage every second to third day). Most women express a clear preference for the convenience, lack of messiness and efficacy of the vaginal ring compared with creams [55,59].

5.5.4 *Higher dose estradiol-releasing vaginal rings*

Several rings have been developed by the Population Council, to release estradiol at doses of 50 – 200 µg/day, producing serum estradiol levels of 180 – 400 pmol/l [57,60]. Again, release rates are close to a zero order and usually designed to last at least 3 months of continuous intra-vaginal use. These systems produce good to excellent relief of menopausal vasomotor symptoms, decrease in serum follicle-stimulating hormone levels, reduction of total and LDL cholesterol, and increased maturation of vaginal epithelial cells [60]. Vaginal discomfort, slippage or spontaneous expulsion can sometimes occur but overall satisfaction and acceptability of the ring are high, as described in Box 1. These higher-dose estrogen-releasing rings should only be used in hysterectomised women unless an oral or intrauterine progestogen is given.

Box 1. Attributes of vaginal ring systems for delivery of hormone replacement therapy.

- Great flexibility of steroid content and release rates
- Flexibility of different steroids and combinations
- Convenience of long duration of action
- Easy insertion and removal for most women, and under the control of the woman
- Estradiol at moderate doses is readily absorbed through the vaginal epithelium and yields physiological serum ratios of estradiol to estrone
- Avoidance of the skin irritations seen with transdermal patches
- Low incidence of side effects (generally lower than equivalent oral systems)
- Some partners may be aware of the ring during sexual intercourse but this is rarely a concern
- Slippage or spontaneous expulsion sometimes occur, mainly during defaecation
- Repeated expulsion is very uncommon
- High acceptability for many women, provided that they are comfortable about touching their genitalia

5.5.5 *Combined estradiol-progesterone menopausal vaginal rings*

The Population Council has also developed combined estradiol and progesterone rings for systemic HRT delivery; this time for women who still have a uterus [57,61]. Dosage release can be designed to ensure good clinical performance and endometrial protection. Systems currently under development release daily doses of estradiol of 150 – 225 pmol/l and progesterone of 10 – 15 nmol/l.

5.5.6 *Vaginal progestogen gel*

Natural progesterone is rapidly metabolised when taken orally. A sustained-release vaginal gel has been developed containing 4 and 8% of micronised progesterone in 1.1 g of gel supplied in single-use vaginal applicators. The base is in a water-in-oil emulsion containing polycarbophil, which rate limits the absorption of progesterone owing to the gel's bioadhesive properties. Therefore, one full applicator of this gel is required on alternate days for a period of ≥ 12 days out of each month of estrogen exposure. These progesterone vaginal gels prevent estrogen-induced endometrial stimulation with lower plasma progesterone levels than

other systemic routes of administration but can be messy for the user [62].

5.6 Intrauterine systems

The concept of intrauterine delivery of a progestogen for HRT is a relatively novel one, yet it is probably the most logical route for progestogen administration for this indication [63]. The only rationale for giving a progestogen for HRT is to counter the effect of unopposed estrogen on the endometrium and prevent excessive proliferation, hyperplasia and adenocarcinoma. Hence, direct delivery into the uterine cavity makes good sense, especially as lower doses (than oral routes) can be used, and may avoid many of the side effects of systemic progestogen use in some women.

Preliminary experience with intrauterine delivery of a progestogen as a component of HRT came with studies of the intrauterine levonorgestrel-releasing system (LNG-IUS), Mirena® (Schering), which was originally developed as a highly effective contraceptive [64,65]. This system releases ~ 20 µg/day of LNG into the uterine cavity, a proportion of which is absorbed into the systemic circulation, although most acts locally within the endometrium, uterus and pelvis. Measurable levels of LNG reach the systemic circulation, but these are usually less than those achieved with low-dose LNG-only minipills. The system is designed to last 5 years. The LNG-IUS delivers a relatively high local concentration of LNG, sufficient to effectively suppress endometrial proliferation in the continuing presence of systemically delivered estrogen for HRT [65]. The LNG renders the endometrium thin and atrophic, and this effect is much greater than that seen with oral or systemic progestogen administration [66,67].

The systemically absorbed component of intrauterine LNG has no detectable effects on carbohydrate metabolism, coagulation parameters or liver enzymes, but may have subtle effects on lipids equivalent to those seen with low-dose oral LNG or norethisterone acetate [68]. The main disadvantage of this is the initial breakthrough bleeding and spotting that are common in the first few months after insertion. This initial breakthrough bleeding is a 'nuisance-value symptom', which carries little or no health risk, and is usually followed within 3 – 6 months by complete amenorrhoea.

The 20-µg LNG-IUS has high acceptability as the long-acting progestogen component of HRT but a second-generation slimmer device releasing only LNG 10 µg/day may have even greater acceptability in HRT users [69]. This newer device is still on clinical trial, but is easier to insert and still provides ample LNG dosage to effectively protect the endometrium [68]. It is designed to provide relatively constant LNG release for ≥ 3 years. This system has great promise for providing long-term endometrial protection in women using continuous systemic estrogen by transdermal patch, for example [66].

5.7 Intranasal systems

In the last 5 years, we have seen the launch of nasal sprays delivering estradiol systemically. The pharmacokinetics of this delivery system are very different from any other route of administration, with estradiol being rapidly absorbed through the nasal mucosa reaching maximal levels after 10 – 30 min and returning to postmenopausal levels within 12 h. A dose of estradiol 300 µg gives a peak serum level of 1400 pg/ml, but over a 24-h period systemic exposure is similar to taking a 2-mg estradiol tablet or 50-µg/day patch [70].

Nasal administration of estradiol produces a reduction in the Kupperman index and, in the occurrence of menopausal symptoms, as early as the second week of treatment. As it avoids hepatic first-pass metabolism, pulsed estrogen therapy also has a favourable action on the lipid profile, and is neutral with regard to clotting factors, angiotensinogen and insulin levels [71]. The effect of pulsed estrogen therapy on bone has been assessed in both the short and the long-term. Bone turnover, as measured by markers of resorption and formation, was normalised to premenopausal levels after 3 months of treatment at a dose of 300 µg/day [72].

Nasal symptoms occasionally occur and include itching, rhinorrhoea and sneezing. Most of these are mild in intensity and in clinical trials led to treatment discontinuation in ~ 3% of patients [73]. Unlike other non-oral HRT therapies, for those women who continue to complain of vasomotor symptoms with intranasal estradiol therapy, systemic levels are difficult to monitor, with alteration of dose not always leading to an improved clinical effect.

5.8 Transmucosal (sublingual) systems

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed directly through the oral mucosa enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. Hormones have been formulated for transmucosal delivery by using a cyclodextrin base, which is water soluble and is not absorbed [74]. Sublingual micronised estradiol, progesterone and testosterone have been studied. Short-term administration of sublingual estrogen to menopausal women with cardiovascular disease has been shown to produce coronary and peripheral vasodilation, reduction of vascular resistance and improvement in endothelial function [75]. Further studies of sublingual administration of estrogen are needed to clarify the most beneficial regimen [76].

6. Conclusions

Different non-oral HRT delivery systems offer women some advantage over conventional oral administration of the HRT steroids. These advantages come particularly through the convenience of long-acting delivery, often with more constant, lower dosing, and the use of 'natural' steroids (such as estradiol, progesterone and testosterone). There is usually no fear of forgetting a daily pill with the long-acting systems, and even with some of the daily systems, there are improved

pharmacokinetics, which provide a much greater margin of error for dosing. Many of these systems are under a woman's personal control, so that she can cease medication or have a break as desired.

Systems can often be designed to provide a range of different doses or steroid combinations to meet different needs. And, of course, each system has its own range of positive and negative attributes, which will influence the appeal and popularity of a system for different women and particular ethnic cultures.

7. Expert opinion

The direction of future HRT use will be greatly dependent on the resolution of current arguments, partly scientific and partly political, on potential risks and benefits of the long-term use of conventional systemic HRT. There is sound evidence from the WHI study (which only addressed one specific combined preparation) that some older postmenopausal women are at slightly increased risk of developing breast cancer, venous thrombosis and stroke when using systemic continuous combined HRT compared with current non-users [18]. These risks are very small in absolute terms. However, interpretation of the vast amount of scientific data on HRT is complex and controversial, and there is a real need to identify those women who will benefit, or be harmed, by particular HRT preparations (or related drugs).

There will undoubtedly be a continuing need for the development of more effective and safer ways of delivering menopausal HRT. The majority of those needing these new systems will be women requiring prolonged treatment for troublesome vasomotor or vaginal symptoms, or those with special risks or needs. Compliance is a major problem for many women using HRT over prolonged periods of time, and compliance difficulties may be an important cause of breakthrough bleeding. Longer acting systems may have an important role in ameliorating the common breakthrough bleeding problem.

Oral delivery is traditional and popular, but it is likely that delivery systems of various types will become much more popular as the general community becomes more familiar with them, and as more flexible choices become available. The disadvantage of multiple choices is that they are very expensive to develop when long-term usage data are required. Nevertheless, small variations in dosage combinations and type of delivery can sometimes make a big difference to clinical response.

It is anticipated that research and development of HRT delivery systems will proceed along the four pathways described below.

7.1 Refinement of present established systems

These refinements will be focused specifically on improved ease of delivery, improved convenience, improved pharmacokinetics, longer action and fewer side effects (in particular, breakthrough bleeding).

7.2 Progressive development of new systems that are currently in clinical trial

Numerous refinements can be predicted with most of these systems. There are likely to be particular benefits for the future development of superior subdermal implants, menopausal vaginal rings and purpose-designed intrauterine systems. To use as an example, there is a need for alternative intrauterine progestogen-releasing systems, which contain different progestogens (from the currently available LNG) and which have different shapes (which may minimise spontaneous expulsions).

'High-tech' delivery system approaches have the potential for substantial benefit to many women, especially for long duration of action but they need to be developed carefully, tested thoroughly and provided by well-trained health professionals to a well-informed public.

7.3 Exploration of new hormone combinations

This may include exploration of new molecules, which have more specific actions or act on different combinations of hormone receptors to produce more tailored actions. This research may include molecules that are not well-absorbed orally or are rapidly metabolised during absorption.

7.4 New concepts

This area is the least easy to predict because it will depend greatly on ongoing basic research. Two possible developments in this area are the intrauterine delivery of a progesterone receptor modulator (e.g., as mifepristone or asoprisnil) [77,78] or an angiogenesis inhibitor [79] (most current angiogenesis-inhibiting molecules are too toxic for use in this situation). These molecules may be useful adjuncts to prevent the breakthrough bleeding that is common in women using combined estrogen-progestogen HRT.

Another concept, which may be pursued in the future, is the tailored delivery of estrogen-receptor modulators, such as raloxifene, which may actually reduce a woman's risk of being diagnosed with breast cancer [80], while also providing some other benefits to the postmenopausal woman.

All of these concepts will eventually be influenced by the burgeoning database of genetic information, which will become more and more precise in predicting benefits, risks and side effects of specific diseases and treatments for individual women. However, this is many years away.

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