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Intrauterine application of progestins in hormone replacement therapy: a review

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Key words: PROGESTIN, HORMONE REPLACEMENT THERAPY, INTRAUTERINE

ABSTRACT

The intrauterine application of progestins as endometrial protection against hyperstimulation by estrogen replacement therapy has been investigated in clinical trials since the early 1990s and one product has become available for this indication. This review considers the available published and presented reports on intrauterine use of progestin to date. Reports of 19 studies were reviewed. These studies included both peri- and postmenopausal women (826 in total), treated with different types of estrogens administered via various routes.

Progesterone was used in two small studies, while all other studies used different doses of levonorgestrel for periods ranging from 6 months to more than 5 years. Endometrial effects, bleeding profiles, systemic effects (symptoms and metabolic), as well as clinical experience, were considered and were comparable to other forms of continuous combined hormone replacement therapy (HRT).

It is concluded that the current evidence supports complete endometrial protection and a good safety profile.

The observed bleeding profiles appear favorable but have not yet been directly compared with other forms of continuous combined HRT. A favorable effect on serum lipids has been observed and also awaits direct comparative confirmation. Progestin-attributable side-effects, effects on bone and breast tissues and other systemic effects have not yet been studied.

Acceptance by patients has been good, while insertion did not present undue problems for the investigating physicians. Retention of the studied intrauterine systems has been very good.

Intrauterine use of progestins, especially levonorgestrel, by purpose-designed systems as part of combined HRT, is a new way of administration and carries good benefits, while some aspects require more clinical evidence.

INTRODUCTION

Natural progesterone and synthetic progestins were originally added to intrauterine devices with the aim of improving retention and improving contraceptive efficacy[1]. Beside progesterone, synthetic progestins such as norethindrone, medroxyprogesterone acetate and norgestrel and dydrogesterone were involved in early testing in animals and humans[1,2]. Later, progesterone, levonorgestrel and desogestrel have been studied as intrauterine applications for the indications of contraception and menorrhagia. As a result, there are currently two intrauterine products on the contraceptive market, containing progesterone and levonorgestrel, respectively, both considerably reducing menstrual blood loss. These products release a constant daily amount of active

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REVIEW

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drug from fluid- or polymer-based reservoirs, covered with membranes and mounted on frames similar to intrauterine devices which need to be inserted into the uterus through the cervical canal. The products loaded with progestin are often called intrauterine systems.

The use of intrauterine progestin as endometrial protection against endometrial hyperplasia in women using estrogen replacement has been a logical consequence of its suppressive effect on the endometrium, observed when used as a locally acting contraceptive. The suppression of endometrial proliferation and the induction of decidual changes in the stroma reflect the contraceptive action of locally administered progestins, whilst not interfering with ovarian activity. Clearly, the endometrial changes observed in fertile women would also be the desired protective effect in women taking exogenous estrogens around and after menopause.

Since the early 1990s, the intrauterine effect of the two compounds used in contraception, progesterone in a daily dose of 65 μg and levonorgestrel 20 μg, but also other, experimental systems releasing doses of 5 and 10 μg of levonorgestrel, have been studied in hormone replacement therapy (HRT).

To date, 19 clinical studies have been reported, either as journal publications, academic theses (17) and/or congress abstracts (10). Together, these studies have investigated 826 patients using intrauterine progestins as a component of continuous combined HRT for treatment periods ranging from 6 months to 12 years. These are tabulated in Table 1. Several of these trials included only a small group of treated women. Of the randomized controlled studies in the table, four used a sequential progestin reference treatment: Andersson[3,4] with 250 μg levonorgestrel, Boon[5] with 1 mg norethisterone acetate, Masters[6] with oral sequential levonorgestrel 75 μg, and Raudaskoski[7] and Timonen[8] with 5 mg medroxyprogesterone acetate. Six used as reference other continuous progestins, respectively oral and vaginal progesterone 100 mg[9–11], 1 mg oral norethisterone acetate[12,13], subdermal

Table 1 Published and presented studies with intrauterine progestin administration in HRT

					Progestin		*Estrogen*	
First author	*Year*	*Menopausal status*	*n*	*Duration* (months)	*Type*	*Daily dose*	*Type*	*Daily dose*
Shoupe[20]	1991	post	10	6/12	prog	65 μg	CEE oral	0.625 mg
Andersson[3,4]	1992, 1996	peri	18	12	LNG	20 μg	E_2 oral	2 mg
Varila[19]	1993	post	40	12	LNG	20 μg	E_2 oral	2 mg
							E_2 patch	50 μg
Archer[21]	1994	post	7	18	prog	65 μg	CEE oral	0.625 mg
Raudaskoski[12,13]	1995, 1995	post	20	12	LNG	20 μg	E_2 patch	50 μg
Stuckey[15], Gutterridge[16]	1996	post	37	12	LNG	20 μg	estropipate	0.9 mg
Wolter Svensson[17,18]	1995, 1997	peri	108, 51	12	LNG	5, 10 μg	E_2 oral	2 mg
							E_2 patch	50 μg
Suvanto-Luukkonen[9–11]	1997, 1998, 1999	post	20	12, 24, 60	LNG	20 μg	E_2 gel	1.5 mg
Suhonen[22–24]	1995, 1997, 1997	peri, post	45	60	LNG	20 μg	E_2 implants	not stated
Boon[5]	1998	peri	100	12	LNG	20 μg	E_2 oral	2 mg
Suhonen[14]	1995	peri, post	10	12	LNG	20 μg	E_2 oral	2 mg
Hampton[25]	1996	peri	81	12	LNG	20 μg	CEE oral	1.25 mg
Panay[26]	1996	peri	44	12	LNG	20 μg	E_2 implants, oral, transdermal	various
Van der Pas[27]	1997	post	21	12	LNG	20 μg	E_2 patch	50 μg
Masters[6]	1998	post	89	12	LNG	20 μg	E_2 oral	2 mg
Rönnerdag[30]	1999	peri, post	7	144	LNG	20 μg	various	various
Raudaskoski[28]	1999	post	13	6	LNG	20 μg	E_2 patch	50 μg
Raudaskoski[7],Timonen[8]	1999	post	108	12	LNG	20 μg, 10 μg	E_2 oral	2 mg
Varila[29]	2000	post	48	24	LNG	10 μg	E_2 oral	2 mg

LNG, levonorgestrel; CEE, conjugated equine estrogens; E_2, estradiol; prog, progesterone

other, experimental
5 and 10 μg of
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have been reported,
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826 patients using
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rogestin reference
250 μg levonor-
ethisterone acetate,
tial levonorgestrel
id Timonen[8] with
cetate. Six used as
gestins, respectively
100 mg[9–11], 1 mg
e[12,13], subdermal

Estrogen	
Type	*Daily dose*
CEE oral	0.625 mg
E_2 oral	2 mg
E_2 oral	2 mg
E_2 patch	50 μg
CEE oral	0.625 mg
E_2 patch	50 μg
stropipate	0.9 mg
E_2 oral	2 mg
E_2 patch	50 μg
E_2 gel	1.5 mg
2 implants	not stated
E_2 oral	2 mg
E_2 oral	2 mg
CEE oral	1.25 mg
implants, ral, trans-dermal	various
E_2 patch	50 μg
E_2 oral	2 mg
various	various
E_2 patch	50 μg
E_2 oral	2 mg
E_2 oral	2 mg

levonorgestrel 15 μg[14], medroxyprogesterone acetate 2.5 mg[15,16], or compared two doses of intrauterine levonorgestrel: Wollter-Svensson[17,18] with 5 and 10 μg and Raudaskoski (1999)[7] and Timonen[8] with 10 and 20 μg. One study compared transdermal to oral estrogen in patients with a 20 μg levonorgestrel-releasing intrauterine system[19]. The remaining studies listed in the table were non-controlled[20–30].

From these studies, it has become clear that the endometrial effects of intrauterine progestin in women using estrogens for replacement therapy are identical to those seen in fertile women and that the safety profile is similar.

Pharmaceutical companies have developed and are developing intrauterine products to provide long-term local endometrial protection, which is associated with a favorable bleeding pattern, low systemic effects attributable to progestins and higher adherence levels. The intrauterine application allows choices of type, route of administration and dose of estrogens. Currently, one product releasing 20 μg of levonorgestrel for 5 years is commercially available in Finland, Denmark and Sweden, while marketing approval for this product has been obtained or is pending in several other countries. Several investigators have also reported favorable outcome of intrauterine progestins in the treatment of endometrial hyperplasia in postmenopausal women[31–33].

The different clinical and other effects of continuous combined HRT have been extensively reported. This review compares the reported effects of intrauterine progestin with those of other routes of administration of progestins, where relevant, whilst not replicating the entire body of available knowledge of the action and effects of progestins in HRT.

The various aspects highlighted will comprise the effects on the endometrium, bleeding profiles, subjective, metabolic and long-term clinical effects, insertion and patient acceptance. It will be shown that the current state of knowledge of intrauterine progestin administration, as available from published clinical trials, is not yet complete (although it is already fairly extensive).

PREVENTION OF ENDOMETRIAL HYPERPLASIA

Until now, only two compounds have been used and tested in human intrauterine use in HRT – progesterone and levonorgestrel. The only reason to add progestin to estrogens in combination HRT is to protect the endometrium from overstimulation by estrogens, leading to hyperplasia and endometrial carcinoma. In several large studies[34,35], the risk of endometrial hyperplasia in postmenopausal women who still have their uterus and who were treated with unopposed oral estrogen, has been found to be 20% for the 1-year study[34] and 62% for the 3-year study[35], as compared to untreated controls.

In these studies, the same progestin, medroxyprogesterone acetate, was tested in different oral doses, both sequentially and continuously. One study included sequential progesterone. All treatments were shown to prevent hyperplasia adequately. The groups treated with continuous combined treatment showed an annual (and 3-year) incidence of hyperplasia of less than 1%, similar to non-treated controls. Other available continuous combined oral treatments, for instance containing various doses of estradiol and norethisterone acetate, have shown the same beneficial effects[36,37].

Transdermal estradiol, either with sequential or continuous transdermal norethisterone acetate in different doses, was also found to be very effective in protecting the endometrium[38]. Oral and transdermal continuous combined treatments have been shown to be associated with an incidence of endometrial hyperplasia of less than 1% per year.

All but one of the studies listed in Table 1 report on endometrial safety. The report by Rönnerdag[30] concerns very long-term clinical experiences of women who used three consecutive 20 μg levonorgestrel intrauterine systems for contraception, seven of whom were going through menopause during the 12-year observation period. No endometrial data are reported from this study. The remaining data have been obtained in both peri- and postmenopausal women: a total of 826 women who either used a progesterone intrauterine device releasing 65 μg per day (n = 17) or different doses of levonorgestrel: 5, 10 and 20 μg released from an intrauterine system (n = 809). The duration of treatment varied between 6 months and 5 years. The women used oral, subcutaneous or transdermal estrogens. All these studies report annual incidences of endometrial hyperplasia of 0%, as no cases were detected. Notwithstanding the somewhat fragmentary nature of the evidence, the degree of exposure appears sufficient to confirm endometrial safety for this application.

Clinical studies in HRT for postmenopausal women with a new intrauterine system releasing 10 μg of levonorgestrel have been reported, showing a similar incidence of low hyperplasia

(0%) over 1 and 2 years[7,29]. Intrauterine progestin appears to be a very effective way to protect the endometrium from hyperplasia induced by estrogen substitution.

MORPHOLOGICAL CHANGES

Morphological changes in the endometrium during treatment with exogenous natural progesterone and synthetic progestins have been studied fairly extensively. Concerning HRT, the well-known morphological effects of progestins, used to protect the endometrium from overstimulation by estrogens, have been described many times: glandular epithelial atrophy and decidualization of the stroma. The same tissue changes are seen with locally applied progesterone and levonorgestrel, the only two progestins studied in this context, and have been shown to be a result of the hormonal treatment and not from the device[39].

The same histological pattern, generally described as suppression of the endometrium, has been found in patients using progestins as part of HRT and in fertile women using an intrauterine system for contraception in doses from 10 to 30 μg of levonorgestrel per day for up to 7 years[40]. No damage to the uterine tissue could be detected, even after 7 years.

In HRT studies with intrauterine administration of levonorgestrel, all daily doses studied (5, 10 and 20 μg) produced the same strong endometrial suppression. The same morphological changes are seen with the continuous oral use of other progestins like levonorgestrel, medroxyprogesterone acetate and norethisterone. Subcutaneous levonorgestrel implants, releasing 15 μg of levonorgestrel per day, did not produce the typical endometrial suppression in a 1-year study, but no hyperplasia was observed[14]. Oral or vaginal progesterone in a dose of 100 mg did not produce hyperplasia either[9–11].

BIOCHEMICAL MARKERS AND GROWTH FACTORS

Receptor concentrations, enzymatic activity, DNA synthesis as well as ultrastructure detected by electron microscopy have all been established as markers for the effects of progestins on the endometrium, including potency and dose response. Endometrial growth factors have been identified as part of the mechanism of action of systemic progestins on the endometrium, and also in intrauterine administration[41–45].

Insulin-like growth factor 1 (IGF-1) promotes endometrial epithelial cell proliferation. Its binding protein (IGFBP-1), counteracting the stimulatory effects of estrogens and found in the late secretory-phase endometrial stroma in cycling women and in the pregnant decidua, has been studied in the intrauterine application of levonorgestrel and has been found to be a strong marker of progestin effect, both in contraception and in HRT. In contrast, oral or vaginal progesterone in a daily dose of 100 mg for 25 days per calendar month did not produce biochemical proof of IGFBP-1 activity, nor a histological picture consistent with progestin activity. Conversely, IGFBP-1 activity is absent in endometrial carcinoma[46,47].

Furthermore, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), as well as fibroblast and endothelial growth factor (FGF, VEGF), have been identified in the cycling endometrium[45]. VEGF is of special interest, as it may be related to the unscheduled bleeding and spotting seen in the first 3–6 months in women on continuous combined HRT[48]. There is still no clinically relevant explanation for this type of unscheduled, and undesired, bleeding.

It is likely that further endocrine and paracrine factors involved in endometrial regulation have yet to be identified.

DOSE EFFECTS

Since the 1980s, investigators have studied the minimum effective doses, relative potency and best treatment regimen of progestin administration in HRT, by morphological, biochemical and molecular biological techniques[49–52]. The histological changes have been quantified[38] and ultrastructural changes detected by electron microscopy[43,52]. In endometrial DNA synthesis, nuclear and cytosol estradiol receptors are decreased by progestins in the presence of estrogens in postmenopausal women[49,50,52]. Progestins stimulate the activity of the enzymes, estradiol dehydrogenase and citric dehydrogenase, thus increasing estrogen metabolism in the endometrium. The increased activity of these enzymes has, in the case of some progestins, been considered supraphysiological in the doses used[49,50,52]. Based on these morphological and biochemical parameters, relative potencies and minimum effective doses of progestins, such as progesterone, norethisterone, dydrogesterone, medroxyprogesterone acetate and levonorgestrel, have been proposed. All recommended dose levels

and progestins have been proven to achieve endometrial safety.

Clinical studies in HRT for postmenopausal women with a new intrauterine system releasing 10 μg of levonorgestrel per day have recently been reported[7,29]. These studies reported a similar level of endometrial protection (no hyperplasia at all) and a similar pattern of endometrial suppression to that seen with higher (20 μg) or lower (5 μg) doses.

The *in vivo* daily release of levonorgestrel (and progesterone) by intrauterine systems or devices is calculated from the amount of active substance left in systems removed at certain time points in the designed period of use of the products in question. The outcome of these calculations is then considered together with the observed *in vitro* release of active product to establish appropriate correlation[53]. For obvious reasons, it is not possible to measure *in vivo* release directly.

Until now, no dose response could be identified for levonorgestrel in the doses used in HRT studies (5, 10 and 20 μg), since all three showed equally strong endometrial suppression[7,17].

In a contraception study comparing the effects of 20 μg of levonorgestrel to those of 2 μg, it was observed that only the higher dose inhibited DNA synthesis[54].

In view of the long-term safety of the intrauterine levonorgestrel treatments, the dose locally applied is only one and perhaps not the most important factor, as acceptance by patients and physicians largely depends on (absence of) bleeding and spotting, progestin-attributable subjective side-effects and metabolic changes, such as serum lipid profiles and breast cell stimulation.

Intrauterine and subcutaneous use of levonorgestrel in HRT, with a daily released dose of 20 and 15 μg, respectively, was associated with serum levels of about 20% of those seen with 150 μg of oral levonorgestrel[14].

Serum levels of levonorgestrel show great interindividual variation[55] and can, for that reason, not be considered a reliable marker of the effect on the endometrium, at least not in repeated oral dosing. The levonorgestrel serum concentrations with intrauterine use, however, vary little over time of use[53]. In fertile women, the uterine tissue concentrations of levonorgestrel applied locally were found to be 158 times higher than with oral levonorgestrel, underlining the high local dose of levonorgestrel[53]. Until now, there is no definite proof that the low serum levels of levonorgestrel seen with intrauterine administration are associated with a reduction in subjective side-effects that can be attributed to the progestin.

Two recent studies, comparing the serum lipid profiles in postmenopausal women using oral estrogens and 10 or 20 μg of levonorgestrel delivered by the intrauterine system, found that lipid profiles with the lower dose, as expressed by HDL-cholesterol increase over time, were more favorable. A similar potential benefit was not observed by Raudaskoski[13] with the combination of transdermal estrogen and 20 μg levonorgestrel delivered in the uterus. Further studies are needed to confirm the dose responses when using intrauterine levonorgestrel and estrogens delivered via various routes and doses.

For better bleeding control (see later), perimenopausal women may require the higher dose of 20 μg[3,17,56]. Estrogen dose and route of administration are of equal importance[36], as well as other factors. In summary, the endometrial effects of progesterone and levonorgestrel administered directly to the endometrium in HRT are qualitatively the same as seen with other routes of administration and with other progestins. With intrauterine administration, the locally active dose is higher than with other routes of administration, while the total delivered dose is much lower, leading to similar and strong endometrial suppression in the doses studied to date.

BLEEDING PATTERNS

Continuous combined HRT has been developed to ensure ongoing endometrial protection, to avoid the systemic peak and trough effects of oral cyclical progestin administration, and to provide 'bleed-free' HRT to women who do not desire the regular withdrawal bleedings associated with sequential progestin administration. Vaginal bleeding associated with HRT regimens tested in clinical trials is generally classified as scheduled (withdrawal bleeding with sequential HRT) or unscheduled. Unscheduled bleeding associated with continuous combined regimens is usually documented as the number of days of unscheduled bleeding during treatment, or as numbers of subjects who experience this inconvenience, and the proportion of subjects who are retrospectively classified 'bleed-free' or who have amenorrhea at the end of the 1st year of treatment.

There are several difficulties in interpreting and comparing the many studies which analyze bleeding. Often, bleeding is distinguished from spotting, the latter not requiring sanitary protection. This definition is subject to the cultural perception

of woman-users and, consequently, continuation of therapy is probably different in the presence of similar bleeding patterns. For this reason, the degree of inconvenience, which is key to treatment acceptance and adherence, remains unknown. In addition, analytical methods vary from study to study, especially in the way amenorrhea is defined: sometimes as a proportion of subjects for every month[21,36,57], as the proportion of subjects without any bleeding during month 11 of a 1-year study[9] or as a similar proportion that did not experience any bleeding during the 90 days preceding the 12-month time-point[14]. The proportion of subjects who are defined as amenorrheic retrospectively (or bleeding free, that is, spotting excluded) after 12 months of treatment is considered an important parameter for the ability of a treatment to control unscheduled bleeding, but should be considered together with the proportion of subjects prematurely discontinuing (before 12 months) a clinical trial because of bleeding problems. Finally, it should be kept in mind that all interpretation is based on self-reported data from trial subjects.

The published and presented clinical trials on intrauterine progestin administration (progesterone 65 μg, levonorgestrel 5, 10 and 20 μg) in HRT included both perimenopausal and postmenopausal women using different doses of estrogens as tablets, patches, gel, or subcutaneous implants. In perimenopausal patients, 1-year amenorrhea proportions (all definitions) varied from 34 to 83%, but, in postmenopausal subjects, the variation was less great: 59%[27] to 83%[29].

In the one study comparing two doses of levonorgestrel (5 and 10 μg) together with either oral (2 mg estradiol valerate) or transdermal estrogen (estradiol 50 μg per day) in perimenopausal women, no difference was observed between levonorgestrel dose levels and routes of estrogen administration as concerns 1-year amenorrhea rates: both about 60%[17]. Andersson[3] achieved an even higher level of amenorrhea, 83%, in patients using 2 mg of estradiol orally with 20 μg levonorgestrel intrauterine. On the other hand, Hampton[25] and Boon[5] achieved lower 1-year amenorrhea rates: 34 and 38% in perimenopausal women using either 1.25 mg conjugated equine estrogens or 2 mg of oral estradiol hemihydrate together with 20 μg levonorgestrel intrauterine per day.

In postmenopausal women, Suhonen[14] found no difference in amenorrhea rates (72%) at 1 year with two different doses of subcutaneous estradiol. Suuvanto-Luukkonen[9] obtained a similar outcome of 80% with transdermal estradiol (gel).

Raudaskoski[7] and Varila[29] observed 1-year amenorrhea rates of over 70%.

These 1-year rates, observed in clinical trials, compare well with those observed with other forms of continuous combined HRT in postmenopausal women: between 60 and 90%[36,56–58], although some investigators reported lower rates[59].

Bleeding and spotting during the 1st year of treatment are the other parameters usually documented either as number of days, sometimes taken together as defined episodes, and/or number of subjects experiencing bleeding or spotting during a particular period. The combination of both analyses is useful as it is well known that a small number of subjects with prolonged bleeding and/or spotting can bias the outcome, especially in smaller studies. With intrauterine progestin treatment, most postmenopausal trial subjects experienced bleeding (mostly of the scanty type) and spotting during the first 3 months of treatment, strongly decreasing until 6 months and after[7,9,12,22,29]. The per patient number of bleeding and/or spotting days varied between 5 and 25 over the first 3 months. Three of these studies allow direct comparison with subdermal levonorgestrel[14], which produced a less favorable bleeding pattern, oral or vaginal progesterone[9] which also performed less well than intrauterine levonorgestrel, or two different doses of intrauterine levonorgestrel (10 and 20 μg), which produced similar results[7]. The remaining study[12] compared combinations of transdermal estrogen 50 μg and intrauterine levonorgestrel to oral estradiol 2 mg and oral norethisterone acetate, rendering comparison difficult. However, the bleeding profile seen with intrauterine treatment was similar to that observed in the other studies.

Of the four studies in perimenopausal women[3,5,17,25], only one compared two continuous progestin treatments: two doses of intrauterine levonorgestrel[17]. Andersson[3] and Boon[5] compared intrauterine levonorgestrel to sequential norethisterone acetate 1 mg and the remaining study had no reference group. The bleeding profiles observed by Wollter-Svensson with either levonorgestrel dose or administration route of estrogen (transdermal or oral) were similar and comparable to the profiles found in postmenopausal women with frequent bleeding and spotting during the first 3 months, strongly declining afterwards, confirming the earlier findings of Andersson[3,17]. Although Hampton[25] and

Boon[5] reported lower amenorrhea rates than did the other studies, the bleeding and spotting profiles found over the first year were similar in the reported studies.

The number of years elapsed since menopause is considered predictive of the amount of unscheduled bleeding on continuous combined HRT, with cut-off points being 3 years[58] or 5 years[56], when disturbances are less frequent. In the published studies on intrauterine levonorgestrel, no sharp distinction can be made between peri- and postmenopausal women, since results in perimenopausal subjects are not consistent, but both groups respond to different doses in the same way as do postmenopausal women in trials with other forms of continuous combined HRT.

Other factors implicated in postmenopausal women have been type of previous HRT, dose of progestin (with higher doses associated with less bleeding[60,61]), and of estrogens, a lower dose leading to less bleeding problems[3,60], or the dose ratio estrogen/progestin[36].

None of these factors, with the local dose of progestin being very high, as well as body weight[36,56], has been observed so far as having great impact on bleeding profiles associated with intrauterine levonorgestrel. Raudaskoski[12] observed that a smaller uterine size was associated with more unscheduled bleeding in subjects with intrauterine treatment, suggesting a mechanical factor.

Despite initial research into the role of multiple growth factors (like VEGF) and other relevant biochemical factors in the endometrium[62,63], unscheduled bleeding during HRT, often from atrophic endometria, remains unexplained and basic research into components of the human endometrium other than epithelium and stroma, has not been extensive.

Studies in monkeys have confirmed the 'functional' (i.e. non-receptor-mediated) antiestrogenic effect of progesterone receptor modulators, such as antiprogestins, and some of these compounds were observed to have an inhibiting effect on endometrial blood vessels (spiral arteries), quickly leading to amenorrhea[64,65]. This may represent an interesting future lead.

Currently, intrauterine administration of progestins in humans, mainly studied with levonorgestrel, appears to be associated with bleeding patterns similar to those observed with other forms of continuous combined HRT regimens in postmenopausal women. Further studies are needed to confirm the apparent suitability of intrauterine levonorgestrel treatment for both peri- and postmenopausal patients and independent of the dose and route of administration of the estrogen component.

SYSTEMIC EFFECTS: SUBJECTIVE SYMPTOMS

The side-effects attributed to progestins in HRT are generally considered to be similar to those of the premenstrual syndrome in fertile women and are divided into physical and psychological effects. A history of premenstrual syndrome appears to be predictive of these symptoms when taking HRT, although with great individual variation[66].

It has been suggested that the psychological effects (mood changes, etc.) are more associated with the progesterone derivatives (such as medroxyprogesterone acetate) while the nortestosterone derivatives (like norethisterone and levonorgestrel) would be more linked to the physical symptoms, such as headache and the various symptoms of fluid retention due to the aldosterone effect, but there is no conclusive evidence for this. A dose–response relationship has been observed by Rozenberg[58] for norethisterone acetate in a large study involving two doses of either sequential or combined treatment. A similar effect had been seen by Magos[67] and Panay[26]. In the latter study, patients were switched from oral to intrauterine treatment (20 μg of levonorgestrel), resulting in a lower incidence of side-effects attributable to progestins.

Nand[68] reported a lower incidence of these side-effects when comparing continuous medroxyprogesterone acetate to sequential treatment with medroxyprogesterone acetate, but Rozenberg[58] did not find this for sequential norethisterone acetate. This aspect of HRT is quite likely to be a key factor in adherence to HRT, yet it is poorly and incompletely studied.

The lower systemic availability with intrauterine progestin administration should in theory, and in view of the data on dose–response, lead to a lower incidence of progestin-related side-effects. The presently available reports on intrauterine progestin in HRT scarcely mention side-effects except for Wollter-Svensson[17], who claims fewer side-effects, but it is unclear what is meant and on what evidence this is based.

The pooled 1-year discontinuation rate (as far as data on this were provided) of the studies in Table 1 appears to be 10% for patients (n = 406) on any intrauterine progestin treatment and 17%

for those on non-intrauterine progestin ($n = 189$). The drop-out rates because of bleeding were 3 and 5% respectively and 6 and 11% for other adverse events. The overall discontinuation rates, undoubtedly partly related to the more permanent and physician-controlled nature of intrauterine treatment, are lower than, for instance, observed by Rozenberg[58]: 28 and 30% for low- and high-dose combined transdermal treatments. In the latter study, bleeding was the reason for drop-out in 7% of patients and other side-effects also in 7%[58].

At present, no conclusion can be drawn and adequate comparative studies are needed to prove the hypothesis that intrauterine progestin is associated with a lower level of attributable side-effects.

METABOLIC SYSTEMIC EFFECTS: SERUM LIPID PROFILES

Many published reports on HRT have included investigation of serum lipid profiles. Of the studies with intrauterine progestin listed in Table 1, eight considered serum lipids, and reported changes over time (from baseline) and compared effects between different treatments[4,5,8,10,13,15–20,29]. The main selected results of these eight studies are summarized in Table 2. The subjects treated with intrauterine progestin are broken down according to menopausal status, type and dose of progestin and type and dose of estrogen, resulting in 11 distinct treatment groups. Apart from the early small study with intrauterine progesterone[20], the progestin used in all studies was levonorgestrel, in three doses: 5 µg ($n = 26$), 10 µg ($n = 134$) and 20 µg ($n = 252$). The concomitant estrogen was mostly administered in oral form, with some 40 subjects treated with transdermal estrogen. The interpretation of the outcome should be carefully made, as there may be underlying methodological differences, particularly for appropriate pre-study wash-out (where stated, mostly of 8 weeks' duration), definition of menopausal status and adjustment for compliance with the estrogen therapy.

In most studied groups, levels of total serum cholesterol and low-density lipoprotein (LDL) cholesterol decreased. Results for high-density lipoprotein (HDL) cholesterol were diverse, ranging from increase to decrease. Triglycerides remained unchanged (see Table 2).

Table 2 Serum lipid changes from baseline to 12 months in subjects on hormone replacement therapy with intrauterine progestin: selected studies

Population studied	*Progestin type and dose/day*	*Estrogen route and dose/day*	*Total cholesterol*	*LDL cholesterol*	*HDL cholesterol*	*Triglycerides*
Peri, $n = 175$	20 µg LNG $n = 118$	E_2 2 mg oral[4,5]	↓↓	↑↓	↓↔	↔↔
	10 µg LNG $n = 31$	E_2 2 mg oral[18]	↓	↓**	↑***	↑
	5 µg LNG $n = 26$	E_2 mg oral[18]	↓*	↓**	↑***	↔
Post, $n = 245$	20 µg LNG $n = 132$	E_2 patch 50 µg $n = 20$[13]	↓***	↑*	↓***	↔
		E_2 gel 1.5 mg $n = 20$[10]	↔	↔	↔	↔
		estropipate 0.9 mg $n = 37$[15]	↓*	↓*	↓	—
		E_2 2 mg oral $n = 55$[8]	↓***	↓***	↔	↔
	10 µg LNG $n = 103$	E_2 2 mg oral[8,29]	↓***↓***	↓***↓***	↑***↑***	↔↔
	65 µg progesterone $n = 10$	CEE 0.625 mg oral[20]	—	↓	↑	↔

↑ signifies increase, ↓ decrease and ↔ no change. Each arrow represents one study.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. No annotation: no p values for changes from baseline. LDL, low-density lipoprotein; HDL, high-density lipoprotein; E_2, estradiol; LNG, levonorgestrel; CEE, conjugated equine estrogens

From the presently available results and with the limitations of interpretation, it appears that intrauterine levonorgestrel, when used in lower doses, attenuates, in a very limited way, the 'beneficial' effect of oral estradiol on serum lipids. For additional clarification of the presently inconsistent data obtained with transdermal estrogens and estrone, more subjects need to be studied.

Several studies have shown 'blunting' of the serum lipid changes caused by estrogens when continuous progestins were added[58,69–72]. All these studies found decreases of LDL cholesterol and small or no significant increase or decrease in serum HDL cholesterol, with some indications of a dose–response relationship. Less 'blunting' seemed to occur with the lower doses of levonorgestrel. In studies where conjugated estrogens were used, triglycerides increased, and less so with medroxyprogesterone acetate[69]. Estradiol used with norethisterone acetate[58] caused less increase of serum triglycerides and, with higher doses of norethisterone acetate, produced a decrease. With intrauterine levonorgestrel, no significant changes in serum triglycerides were seen, irrespective of dose and route of estrogen administration. Cardiovascular health, for which lipids are believed to be markers[73,74], although their meaning may be doubted by others[75], has not been studied more specifically with intrauterine progestins.

OTHER EFFECTS

One study with intrauterine levonorgestrel has looked at glucose metabolism[28]. Transdermal estrogen plus intrauterine levonorgestrel 20 μg, when compared to transdermal estradiol alone, did not change serum levels and insulin resistance, but produced less insulin sensitivity, suggesting a limited impact as compared with other regimens[69,71].

Concerning the effect on bone, intrauterine levonorgestrel 20 μg was associated with a larger increase in bone mineral density at the femoral neck, as compared with medroxyprogesterone acetate 2.5 mg[28].

Other metabolic effects and effects on target organs like the breast have not yet been studied.

CLINICAL ASPECTS

While the use of intrauterine devices and hormone releasing intrauterine systems is common in fertile women who want contraception, their use as the progestin part of combined HRT is still novel in clinical practice. With the increasing use of the 20 μg levonorgestrel system for contraception extending into the late premenopause, acceptance by subsequent HRT users is expected to grow. As with the long-term intrauterine contraceptive application, use in HRT will require conscientious counselling of patients by their physicians concerning bleeding patterns, other potential side-effects, the procedures of insertion and removal and the occurrence of unexpected bleeding during use once a no-bleed status has been achieved.

The available reports from the clinical studies in Table 1 show a high continuation rate at 1 year (90%), and a low drop-out because of bleeding problems and adverse events (3 and 6%). This high adherence level can be seen as a positive acceptance by HRT users of this new way to administer progestin, although the more physician-controlled nature of the treatment and the specific clinical trial situation have to be considered.

The feasibility of intrauterine levonorgestrel treatment in HRT depends on whether it is possible to insert the system through the cervical canal, if cervical stenosis is present, and whether the uterine size is sufficient to keep the system in a fundal position and prevent it from being expulsed. Both can be limiting factors in peri- and postmenopausal women, especially when they are nulliparous.

Some of the clinical studies listed in Table 1 have collected fragmentary and limited clinical information on a variety of parameters: patient selection, insertion success, ease of insertion, pain, the use of dilatation and local anesthesia and the rates of expulsion. Investigators have rated the ease of insertion but this should be interpreted with some caution. Patient selection might exclude nulliparous women and those from whom an endometrial biopsy could not be taken because of cervical canal stenosis. Especially in the older studies, patients were in some trials pretreated with estrogens for periods ranging from 1 to 3 months. The use of cervical canal dilatation and/or local anesthesia, when applied before insertion, will render insertion easier. In the published reports, the investigators rated the insertion of 20 μg levonorgestrel and the 65 μg progesterone systems as 'easy' in 46–90% of postmenopausal and in 80% of perimenopausal patients. Systems with a lower levonorgestrel dose, which are smaller in diameter, were evaluated as easy to insert in 78% of postmenopausal

patients. The use of cervical canal dilatation and/or local anesthesia, recorded in two studies, is given as 25% of insertions in postmenopausal women and 10% in perimenopausal subjects, both with the 20 μg levonorgestrel system.

In the same way, the use of anesthesia has an impact on the experience of pain by the patients during insertion. Where data are provided, 10–25% of patients reported moderate pain, while 5–10% experienced severe pain.

Expulsion rates are provided in most publications and, from the present data, the observed 1st year rates were 4% in perimenopausal study subjects, 2% for each of the larger and smaller levonorgestrel systems used. In most cases, the expulsed systems were replaced. From the limited experience in postmenopausal patients, an expulsion rate of 1% (20 μg levonorgestrel systems only) is apparent.

As far as they are mentioned, the local adverse events that may be attributed to the intrauterine systems are abdominal pain and vaginal discharge. In none of the trials, published or presented, did pelvic inflammatory disease occur.

CONCLUSION

Intrauterine administration of progestin in HRT has been investigated (mainly with levonorgestrel), over a period of 10 years. It has become clear that this long-term variant of continuous combined HRT provides good endometrial protection with sustained strong endometrial suppression and no hyperplasia in all doses studied. Other aspects have been studied to various degrees, requiring more clinical studies, especially bleeding patterns in early postmenopausal women, who would otherwise probably be treated with sequential rather than continuous combined HRT. Bleeding patterns observed so far with intrauterine levonorgestrel appear promising in terms of amenorrhea rates at 1 year, but direct comparison is lacking as yet.

Metabolic effects appear favorable in terms of limited or no attenuation of beneficial estrogen effects in all doses, especially in the lower ones. Additional data, however, are needed from the use of non-oral estrogens together with intrauterine levonorgestrel.

Progestin-attributable side-effects, which are also likely to be less frequent with the low systemic burden of levonorgestrel released *in utero*, remain an objective for comparative studies.

The effects on bone mineral density and breast epithelium have not been studied sufficiently until now. Clinical experience from the studies indicates good patient satisfaction, as seen from the high rates of adherence with few side-effects, and suggests ease of use, certainly in parous women, and good retention rates. All these are likely be supportive for good patient compliance with this new way of administering progestins in HRT.

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