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Progestogen intolerance and compliance with hormone replacement therapy in menopausal women

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It is vital that we maximize compliance if patients are to receive the full benefits from hormone replacement therapy (HRT). One of the main factors for reduced compliance is that of progestogen intolerance. Progestogens have a variety of effects apart from the one for which their use was intended, that of secretory transformation of the endometrium. Endometrial effects vary between individuals and between different progestogens, leading to bleeding problems. Symptoms of fluid retention are produced by the sodium-retaining effect on the renin–aldosterone system. The nor-testosterone-derived progestogens can have adverse effects on skin, lipids, vasculature and insulin resistance. Negative mood effects are produced by most progestogens due to the effect on neurotransmitters via central nervous system progesterone receptors. Manipulation of the dosage and duration of progestogen, continuous administration of a low dose of progestogen and a reduction in the number of progestogenic episodes can be used to improve compliance. The progestogen and progesterone releasing coils and vaginal progesterone gel minimize systemic side effects and bleeding. Adverse effects can also be avoided by making use of the progesterone receptor-specific progestogens such as the pregnanes (e.g. cyproterone), nor-pregnanes (e.g. nomegestrol) and progesterone itself. Hysterectomy remains an option for the severely progestogen-intolerant woman. In the future, progestogen intolerance may not be an issue if selective oestrogen receptor modulators provide a complete alternative to HRT.

Key words: compliance/HRT/progesterone/progestogen/progestogen intolerance

Introduction

There is now much evidence that hormone replacement therapy (HRT) is important in the treatment and prevention of the immediate and long-term complications of the menopause (Chakravarti *et al.*, 1977; Ettinger *et al.*, 1985; Stampfer and Colditz, 1991). Despite this, compliance with HRT is poor. Progestogens are necessary for non-hysterectomized women on oestrogen therapy if endometrial hyperplasia is to be prevented (Sturdee *et al.*, 1978). However, progestogenic side effects and heavy, prolonged withdrawal bleeds can be significant problems in patients using HRT. This intolerance of progestogenic effects is one of the main reasons for poor compliance with HRT (Ferguson *et al.*, 1989; Studd, 1992), leading to high discontinuation rates (Barlow *et al.*, 1989) and reducing the cost-effectiveness of therapy (Cheung and Wren, 1992). There has also been anxiety that progestogens may produce metabolic disturbances, for instance, in cardiovascular risk markers, and that there may be an adverse effect on the risk of breast cancer. This review identifies the potential adverse effects of progestogens, discuss their pathogenesis and give an opinion as to how these effects can be avoided or at least minimized in order to improve compliance with HRT.

Adverse progestogenic effects

The effect common to all progestogens is that of inducing a secretory phase in the oestrogen-primed endometrium. However, depending on their derivation and dosage, progestogens may have androgenic and/or oestrogenic or anti-androgenic and/or anti-oestrogenic effects. Progestogens may also have mineralocorticoid and

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glucocorticoid-type effects (Table I). All of these effects are instrumental in determining the pathophysiology of adverse progestogenic effects. Figure 1 gives a classification of the various types of progestogens and their derivation from progesterone.

Endometrium

The effect of progestogens on the endometrium is mediated via a decrease in oestrogen receptors and an increase in the 17α-oxoreductase activity that converts oestradiol to oestrone. Progestogens inhibit mitotic activity, as shown by the decrease in the number of mitoses in both the glandular epithelium and stroma. They induce secretory transformation, with production of stromal oedema, pseudo-decidualization and glandular suppression. After a few weeks of progestogenic exposure, areas of superficial focal necrosis become apparent and in the long term the endometrium develops very suppressed glandular development, thin atrophic stroma and more generalized necrotic areas. A recent study demonstrated that high-dose progestogen exposure significantly decreased the number of microvessels and increased the number of dilated venules in endometrium when compared with controls (Song *et al.*, 1995). This finding suggested that progestogens suppress endometrial vasculature more than the non-vascular compartments of epithelium and stroma. Significant numbers of leukocytes are found in progestogen-exposed samples which appear to play an important role in the initiation or acceleration of progestational endometrial necrosis by the release of cytolytic and cell toxic molecules (Song *et al.*, 1996).

Progestogens are protective to the endometrium in a dose- and duration-dependent manner. The incidence of endometrial hyperplasia is reduced to 4% with 7 days of progestogen, 2% with 10 days and 0% with 12 days of progestogen if prescribed at an adequate daily dosage (Sturdee *et al.*, 1978; Paterson *et al.*, 1980). If cystic hyperplasia does occur with oestrogen therapy, it can be resolved with three courses of 21 days of progestogen in virtually all cases (Thom *et al.*, 1979). Despite these effects, the exact relationship between progestogens in HRT and bleeding patterns remains largely unknown. This is because of considerable interindividual variability (Lane *et al.*, 1983), complex oestrogen/progestogen interactions (Henderson *et al.*, 1988) and the absence of an appropriate animal model. These factors and the different plasma oestradiol concentrations with different doses or routes of administration explains why some patients experience problems with heavy, prolonged periods and endometrial hyperplasia, whereas the same duration, dose and type of progestogen would produce atrophy in another patient. A

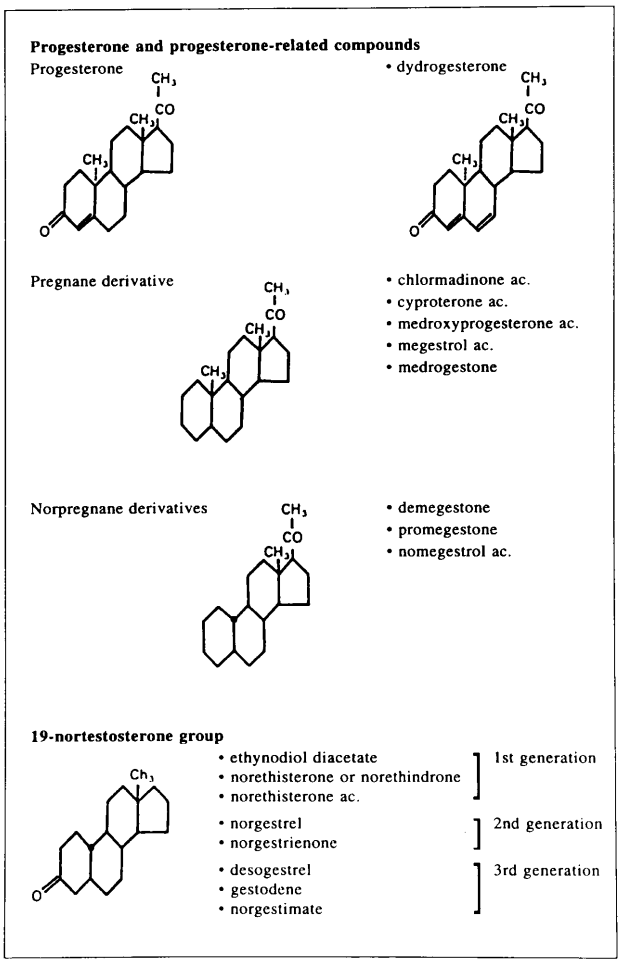

Figure 1. Chemical classification of progestogens.

recent study has demonstrated that, broadly speaking, there appear to be two endometrial bleeding responses to sequential HRT, one with a mean cycle length of 29 days (late bleeders) and another with a cycle of shorter duration (early bleeders). The latter group appears to have less variability in cycle length and bleeding of shorter duration. No significant differences were demonstrable between the two groups in terms of past history or physical characteristics, except that early bleeders included more smokers. It was postulated that smoking could led to bleeding problems due to a hypo-oestrogenic state (Habiba *et al.*, 1996).

Mineralocorticoid activity

Most of the physical symptoms associated with progestogen intolerance, such as oedema, weight gain, bloating and migraine, may be due to the mineralocorticoid-like effect of progestogens. It was originally thought that progestogens acted like progesterone, which enhances the renin–aldosterone cascade by acting as a precursor (Oelkers *et al.*, 1974). However, it

may be that progestogens produce their effect by competing for the mineralocorticoid receptor. This effect can lead to retention of sodium and fluid gain during the progestogenic phase.

Androgenic effects on skin

Effects such as acne, greasy skin and darkening of facial hair tend to occur mainly with the 19-nortestosterone derivatives, which can have androgenic effects due to their relatively strong binding affinity for the androgen receptor. Progesterone and dydrogesterone and nor-pregnane derivatives have no androgenic effects. Pregnane progestogens, particularly medroxyprogesterone, have mild androgenic effects, as their binding of the androgen receptor is a little higher than that of progesterone (Rozenbaum, 1996).

Lipids and lipoproteins

There has been anxiety that the beneficial effects of oestrogen replacement therapy on the risk of cardiovascular disease are attenuated by the need to add progestogen in non-hysterectomized women. This has arisen partly from data showing that the nor-testosterone-derived C_{19} progestogens used in monotherapy lead to unfavourable lipid changes. In a study by Farish *et al.* (1986), postmenopausal women treated with 5 mg per day of norethisterone had a significant drop in high-density lipoprotein (HDL_2 and HDL_3) concentrations. In contrast, the C_{21} progestogens appear to have no significant effects on lipoprotein metabolism when used in moderate or low dosages (Barnes *et al.*, 1985). The net result of oestrogen and progestogen combinations in HRT appears to depend on the balance between these steroids, as well as the type of progestogen used. Progesterone and dydrogesterone seem to have no effect (Siddle *et al.*, 1990), whereas medroxyprogesterone may have an effect, depending on the dose of oestrogen. The C_{19} progestogens such as norethisterone and levonorgestrel can oppose the increases in HDL (Whitcroft *et al.*, 1994), but Jensen and Christiansen (1987) showed that increasing the dose of oestrogen led to a dose- dependent rise in HDL. In the 3 year Postmenopausal Estrogen Progestin Interventions (PEPI) trial (Miller *et al.*, 1995), oestrogen alone or in combination with a progestogen improved lipoprotein and lowered fibrinogen concentrations without detectable effects on post-challenge insulin concentrations or blood pressure. There were no long-term adverse effects of added progestogen, especially when adequate doses of oestrogen were given. This may be most important in improving the lipid pattern to decrease the risk for cardiovascular disease. Recent data from the Nurses Health Study (Grodstein *et al.*, 1996) have also shown that the addition of progestogen does not attenuate the cardiovascular benefits of oestrogens.

Vascular effects

The modifying effects of progestogens on pulsatility index have been studied as an indication of cardiovascular risk. Hillard *et al.* (1992) examined the effects of progestogens on resistance to flow in 12 postmenopausal women. The pulsatility index (PI) was higher during the oestrogen/progestogen phase than during the oestrogen-only phase but remained lower than before treatment. Marsh *et al.* (1994) also showed an increase in mean uterine artery PI, of 30%, during the norethisterone phase of combined therapy but that this change was short lived, with the PI falling within 4 days of the progestogen being stopped. Encouragingly, long-term studies on oestrogen and progestogen co-medication have not demonstrate any marked decrease in blood flow in comparison with oestrogen-only therapy (Samsioe and Astedt, 1996).

Table I. Summary of psychological and physical and metabolic effects of progestogens

Psychological	Metabolic	Physical
Anxiety	Adverse lipid changes	Acne
Irritability	Increased insulin resistance	Greasy skin
Aggression	Increased vascular resistance	Abdominal cramps/bloating
Restlessness		Fluid retention
Panic attacks		Weakness
Depressed mood		Headaches
Poor concentration		Dizziness
Forgetfulness		Breast tenderness
Lethargy		??Breast cancer
Emotional lability		

Insulin resistance

The addition of progestogen to oestrogen therapy may produce adverse effects on glucose and insulin metabolism. In a study by Godsland *et al.* (1993), levonorgestrel addition to conjugated equine oestrogens led to a decrease in insulin sensitivity. Non-androgenic progestogens may avoid adverse changes of progestogens on vascular resistance. Work by Stevenson (1996) using cyclical dydrogesterone with oral oestradiol suggested an improvement in insulin resistance. Such a regimen, using a non-androgenic progestogen, would be particularly indicated for women with diabetes mellitus.

Negative mood effects

Progesterone receptors are found in the caudate, cerebellum, cortex, habenula, hippocampus, hypothalamus, olfactory lobe, lamina terminalis and area postrema (Maggi and Perez, 1985). Limbic system functions, which subserve emotion and behaviour, can therefore be influenced by circulating reproductive steroids such as progesterone and progestogens. There is evidence that progesterone and progesterone metabolites affect a number of central nervous system (CNS) transmitter systems to bring about mood changes, and these effects can be extrapolated to the progestogens in HRT (Backstrom *et al.*, 1996).

Progesterone metabolites and the $GABA_A$ receptor

The γ-aminobutyric acid A ($GABA_A$) receptor usually has anti-anxiolytic properties. It has been suggested that pregnenolone sulphate, a progesterone metabolite, may have antagonistic properties leading to inhibition of the $GABA_A$ receptor, thus producing negative mood effects.

Effect of progesterone on monoamine turnover and metabolism

Progesterone and progestogens have been shown to increase the metabolism and turnover of monamines in the rat brain. Also, platelet monamine oxidase activity has been shown to decrease in the luteal phase. These effects could theoretically produce negative mood changes.

Serotonin system

Studies have shown that the serotonin uptake and content of platelets is significantly lower in the premenstrual phase in patients diagnosed with premenstrual syndrome (PMS) compared to controls. There is also evidence for the beneficial effects of serotonin re-uptake inhibitors on PMS symptoms. It is therefore possible that symptoms related to the progestogenic component of HRT are in part due to actions on the serotonin system.

Other transmitter systems

Pregnenolone sulphate appears to have an action at the *N*-methyl-D-aspartate (NMDA) receptor, which is part of the excitatory CNS, but the role of the receptor in the hormonal effects on mood is still unclear.

The times in a woman's life when oestrogen concentrations are low, i.e. postpartum and in the perimenopause, or when progesterone concentrations are high, i.e. premenstrually, is when the greatest excess of depression occurs. There are indications that it is the high luteal phase progesterone concentrations which exacerbate PMS symptoms such as depression and mood swings. This is supported by the fact that abolition of ovulation with GnRH analogues or percutaneous oestrogens alleviates symptoms. Certain women appear to be sensitive to the production of negative mood changes by progestogens. Cullberg (1972) showed that women who had previously suffered from PMS reacted badly when taking oral contraceptives. This suggests that women with PMS are more sensitive to hormonal provocation than women without. There are also some endocrine indications the hypothalamo-pituitary unit is more sensitive to ovarian hormones in women with PMS than in controls (Backstrom *et al.*, 1985). This is important, as it suggests that it would be possible to predict which patients would experience negative mood changes during oral contraceptive use and HRT.

There are reports relating negative mood changes during HRT to the addition of progestogens in sequential therapy. The symptoms occur soon after progestogens are commenced and last for a couple of days after progestogens are ceased (Hammarback *et al.*, 1985). Holst *et al.* (1989) showed that the progestogen component of combined preparations can have negative mood effects, especially depression, anxiety and cognitive impairment. Magos *et al.* (1986) demonstrated psychological PMS-type effects of norethisterone in postmenopausal women and showed that these changes appear to be dose dependent, with the 5 mg dose causing more severe symptoms than the 2.5 mg dose (Figure 2). Magos *et al.* regarded the addition of cyclical progestogen to continuous oestrogen therapy as 'a model for the aetiology of PMS.' The similarity of progestogenic side effects to PMS symptoms was confirmed by Smith *et al.* (1994). In contrast to all these studies, Marslew *et al.* (1991) found that two types of 19-nortestosterone and hydroxyprogesterone progestogens caused only mild adverse effects but the only negative mood effect assessed was that of irritability.

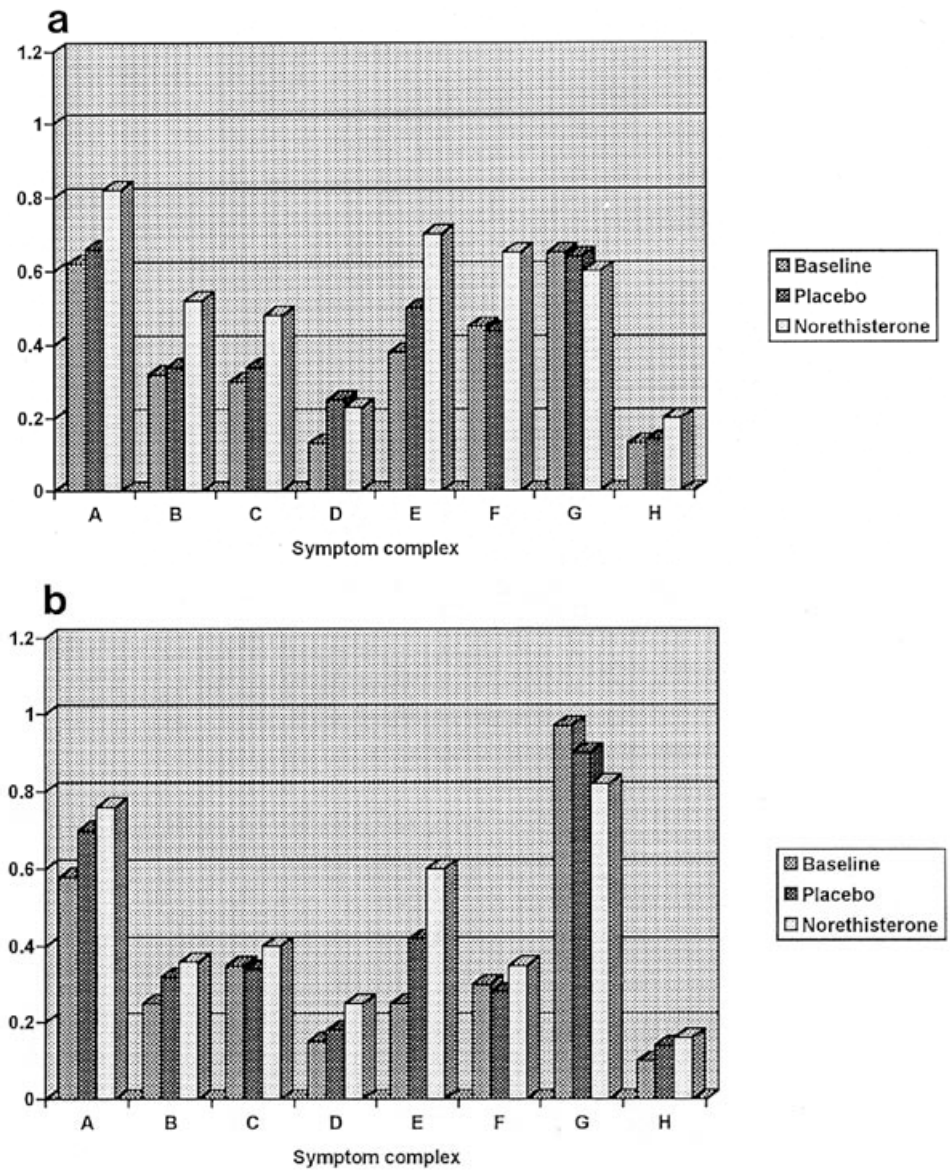

Figure 2. (**a**) The production of premenstrual syndrome (PMS)-type symptoms in women without a uterus receiving cyclical placebo and 5 mg of norethisterone each month. Adapted from Magos *et al.* (1986). (**b**) The production of PMS-type symptoms in women without a uterus receiving cyclical placebo and 2.5 mg of norethisterone each month. The symptom clusters A–H represent the groups of the Moos premenstrual distress questionnaire. A = pain, B = concentration, C = behavioural change, D = autonomic reactions, E = water retention, F = negative affect, G = arousal, H = control.

Breast cancer

The effect of progestogens on breast cancer risk is still controversial and the data are incomplete. Some workers claim that progestogens may have a beneficial effect and others claim an adverse effect. Progestogens do seem to enhance the mitotic activity of normal breast epithelial cells (Persson, 1996). However, in the latest update of the Nurses Health Study of 725 550 women with 1935 newly diagnosed cases of breast cancer, there was no difference in the relative risk of breast cancer in those using oestrogens alone, oestrogens and progestogens, or progestogens alone (Colditz *et al.*, 1995). It is clear that we need more long-term data to obtain conclusions about the effects of progestogens on breast cancer risk.

Prescribing for the progestogen-intolerant woman

Most practitioners commence HRT with a proprietary sequential regimen, usually oral. About 20% of women will have significant progestogen intolerance, with about half this number having serious effects which will prevent them from continuing with treatment. Many progestogen-induced side effects will resolve within a reasonable trial

period of 2–3 months. Patients should therefore be counselled appropriately and given encouragement if drop-out rates are to be improved (Nachtigall, 1990). Low continuation rates with HRT could be due to a lack of interest from practitioners in finding a suitable progestogenic regimen for their patients. A recent survey showed that ever use of HRT was as high as 55% in menopausal female doctors (Isaacs *et al.*, 1995), which suggests that lack of interest may be greater in male doctors.

If symptoms do not resolve or are severe, a number of possible actions may be taken to deal with the side effects directly. Attention is also being focused on how we can best avoid or improve the delivery of progestogens to minimize adverse effects, improve the benefit/risk ratio of HRT and thus maximize compliance. Recent developments in progestogens and HRT regimens have provided a greater scope for avoidance of adverse progestogenic effects.

Physical side effects

Side effects related to fluid retention, such as oedema and bloating, may respond to a mild diuretic such as 25 mg of either spironolactone or hydrochlorothiazide (Gambrell, 1995). The diuretic should be given in the last week of added progestogen. In the future it may be possible to substitute an anti-mineralocorticoid-type progestogen such as Drospirenone (Oelkers *et al.*, 1995) to counteract fluid retention problems. Breast tenderness may either be aggravated or relieved by added progestogen. If it is aggravated, the addition of an androgen (e.g. a 100 mg testosterone implant every 6 months) may occasionally ameliorate breast tenderness. Headaches are unlikely to occur if oestrogens are used continuously, but if they do occur during the progestogenic phase they may be improved by the addition of a mild diuretic or an androgen. It must not be forgotten that nuisance progestogenic side effects such as bloating and breast tenderness and headaches will be better tolerated if the physician prepares the woman, offers a solution and helps to put the problem into perspective.

Dose and duration of progestogen

Manipulation of the dosage and duration of progestogen administration in sequential HRT is of value and has been practised for many years. In the 'Consensus Statement on Progestin Use in Postmenopausal Women' in Florida (1988) it was deemed important to individualize the length of progestogen treatment because of potential metabolic effects and symptomatic complaints (Table II).

Negative mood effects may develop whilst a patient is receiving progestogens. Also, it may be felt that they are predisposed to developing negative mood effects because of a past history of severe PMS or a bad reaction to the contraceptive pill. The minimum recommended duration of progestogen required to prevent endometrial hyperplasia completely is 12 days (Sturdee *et al.*, 1978). However, if a patient is progestogen intolerant the duration of progestogen can be reduced to 10 or even 7 days per month. This will increase the risk of endometrial hyperplasia, particularly if implants are being used, so it will be necessary to have a lower threshold for endometrial sampling should there be any suspicious bleeding. Heavy/prolonged bleeding may also be a problem with the shorter duration of progestogen.

If heavy/prolonged bleeding occurs on sequential therapy and pathology has been excluded, it may be necessary to use a longer duration or more androgenic progestogen to control the bleeding. This will need to be balanced with the physical/psychological side effects produced by the progestogen.

Table II. Minimum doses (mg/day unless stated otherwise) of progestogen given orally in hormone replacement therapy as endometrial protection (taken for 12 days per month)

Progestogen type	Dose (mg/day)
Micronized progesterone	200
Dydrogesterone	10
Medroxyprogesterone	5
Norethisterone	1
Norgestrel	150 µg
Cyproterone	1

Continuous combined regimens

A smaller dosage of progestogen given on a daily basis should theoretically produce fewer progestogenic side effects and amenonorrhoea with an atrophic endometrium, which should be more acceptable to postmenopausal women (Magos *et al.*, 1985; MacLennan *et al.*, 1993). Irregular vaginal bleeding in ~40% of women is common during the first 3 months of treatment, leading to high drop-out rates. Those who continue treatment over 6–9 months can expect high rates of amenorrhoea with minimal side effects, thus resulting in good rates of compliance (Figure 3).

Three oral preparations of continuous combined therapy are now available that can be used if bleeding is not desired by the woman, assuming it has been at least 1 year since her last menstrual period or if HRT has been used for at least 1 year. This makes it less likely there will be breakthrough bleeding, although it may take 3–6 months for bleeding to settle.

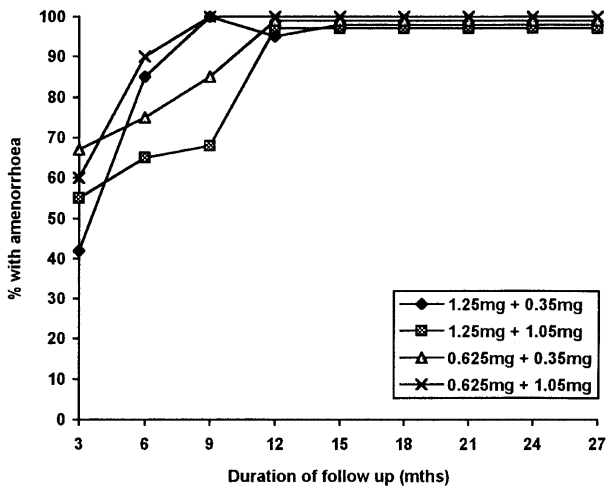

Figure 3. Percentage of patients with amenorrhoea among women receiving oral conjugated oestrogens (0.625–1.25 mg) and low-dose progestogen (norethisterone, 0.35–1.05 mg) continuously. Adapted from Magos *et al.* (1985). The first dose given for each symbol in the inset box refers to the amount of conjugated oestrogens administered and the second dose to the norethisterone administered.

For patients experiencing negative mood effects on sequential therapy, continuous combined therapy may be used to reduce the daily dose of progestogen, but this may produce constant low-grade PMS-type symptoms, as may tibolone.

Quarterly regimens

Long cycle HRT reduces to a minimum the number of progestogenic episodes, withdrawal bleeding and progestogenic side effects. Despite there only being four cycles per year, the rates of endometrial hyperplasia appear to be comparable to sequential regimens after 1 year of treatment (Ettinger *et al.*, 1994). The disadvantage of this regimen is that a relatively high dosage of progestogen is required (20 mg of medroxyprogesterone acetate daily for 14 days in one proprietary preparation) per progestogenic episode. This can lead to severe progestogenic side effects when the episode does occur, associated with heavy and/or prolonged withdrawal bleeding. Nevertheless, this provides an effective regimen for some patients, particularly as the prolonged unopposed oestrogenic phase allows for the beneficial effects of unopposed oestrogen on cardiovascular risk and CNS without the possible attenuating effects of progestogen. It is possible that this regimen may also be useful in depressed perimenopausal women who are progesterone/progestogen intolerant.

Non-oral progestogens

Levonorgestrel intrauterine system

The levonorgestrel intrauterine system (LNG IUS) consists of a plastic T-shaped frame with a steroid reservoir around the vertical stem of polydimethylsiloxane containing 52 mg of levonorgestrel released at a rate of 20 μg per day (Figure 4). It has been shown to be effective at controlling endometrial hypertrophy by suppressing endometrial growth (Silverberg *et al.*, 1986). After a few weeks the endometrial glands atrophy, the stroma becomes swollen and decidual, the mucosa thins and the epithelium becomes inactive. As a result of the suppression caused by the local release of hormone, also mediated by the regulatory action of high local concentrations of progestogen on endometrial oestrogen receptors, the endometrium becomes unresponsive to oestrogen (Luukkainen *et al.*, 1986). In the past few years, workers have also shown that the LNG IUS can prevent endometrial proliferation in perimenopausal women using oral transdermal or subcutaneous oestradiol (Andersson *et al.*, 1992; Raudaskoski *et al.*, 1995a; Suhonen *et al.*, 1995).

The plasma concentrations achieved by the LNG IUS are lower than those seen with the LNG implant, the combined oral contraceptive or the mini-pill (Weiner *et al.*, 1976; Diaz *et al.*, 1987; Kuhnz *et al.*, 1992). Also, unlike oral contraceptives, the concentrations with the LNG IUS do not display peaks and troughs. It is therefore postulated that using the LNG IUS, rather than an oral progestogen, to prevent endometrial hyperplasia would be an ideal way of avoiding progestogenic side effects in women being treated with oestradiol patches and implants for the menopause. Even with the lower, more constant, concentrations of progestogen released by the LNG IUS, some women still seem to experience adverse progestogenic effects. These can be both physical (e.g. oedema, headache, breast tenderness, acne) and metabolic [decreased low-density lipoprotein (LDL) concentrations; Raudaskoski *et al.*, 1995b]. The physical effects have been shown to subside after the first few months of usage (Nilsson *et al.*, 1986). Work recently completed in our unit showed that adverse progestogenic effects and severity of bleeding were reduced to a minimum when patients who were progestogen intolerant and thus were using mainly oestradiol implants, even with relatively high serum oestradiol concentrations, were switched from oral progestogens to the LNG IUS. Endometrial suppression was uniform, with no cases of endometrial proliferation or hyperplasia at 1 year and a >50% rate of amenorrhoea at this time (Panay *et al.*, 1996; Figure 5a and b).

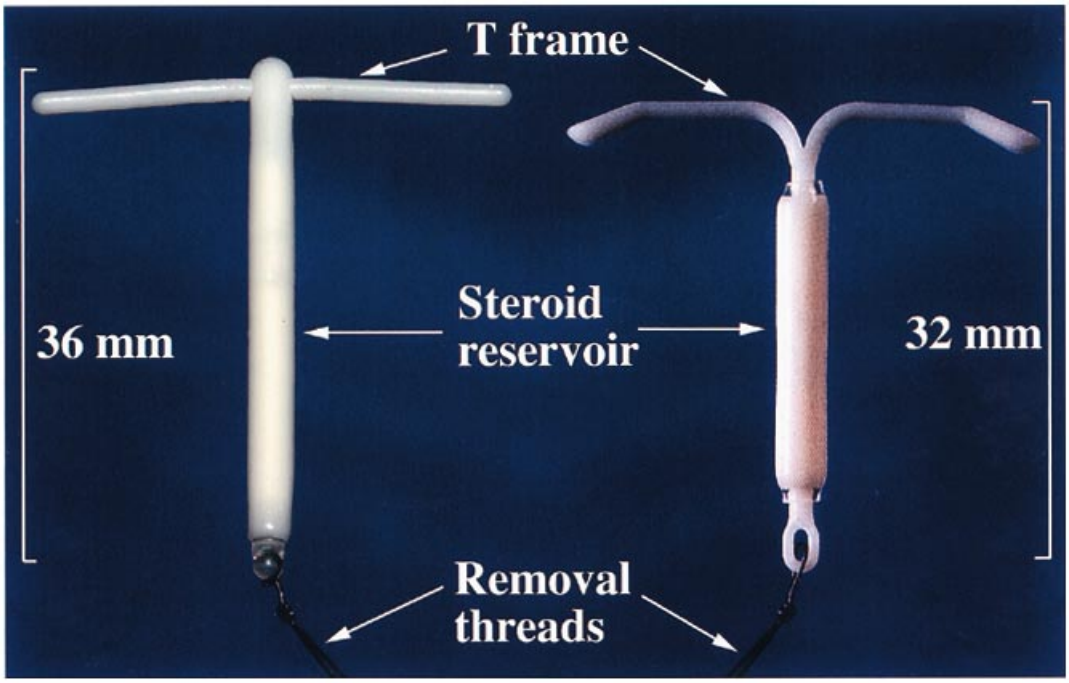

Figure 4. Levonorgestrel (right) and progesterone (left) releasing intrauterine systems are shown.

The progestogen intrauterine system is licensed for use as progestogenic opposition in HRT in Finland but it is only licensed in the UK for contraception at present. Its use in the HRT context should therefore be restricted to hospitals for now, where monitoring of the endometrium can be carried out with scans and biopsies.

Progestasert® intrauterine progesterone system (PIPS)

The Progestasert® intrauterine progesterone system (PIPS; Figure 4) consists of a polymeric T-shaped platform with a reservoir containing 38 mg of progesterone released at a rate of 65 μg per day. Results of two recent studies (Shoupe *et al.*, 1991; Archer *et al.*, 1994) indicate that the PIPS also suppresses endometrial proliferation in postmenopausal women taking 0.625 mg of oral conjugated oestrogen daily. Shoupe *et al.* (1991) reported a progestational effect of the system on the endometrium after 12 months; prior to the study, biopsy had shown a proliferative endometrium. Studies of plasma hormone concentrations, menstrual patterns and blood chemistry in various patient groups demonstrated no systemic effects of the PIPS, even on the progesterone-sensitive hypothalamic–pituitary–ovarian axis (Tillson *et al.*, 1975). It is therefore postulated that using the PIPS, rather than an oral progestogen, to prevent endometrial hyperplasia would be an ideal way of avoiding adverse progestogenic effects in women being treated with oestrogen replacement therapy. Studies are currently being conducted to confirm this hypothesis and the PIPS is only available on a trial basis in a few centres at present.

Vaginal gel

Studies are currently ongoing (e.g. that of Casanas-Roux *et al.*, 1996) to confirm the safety of progesterone vaginal gel for use as progestogenic opposition for oestrogen replacement therapy. This product would in theory be an ideal way of avoiding progestogenic adverse effects with minimal, if any, systemic absorption of the most physiological 'progestogen'. Like the progesterone intrauterine system, it would act locally to prevent endometrial hyperplasia, which is at present the major role for progestogen in HRT.

Transdermal progestogens

The avoidance of first-pass metabolism should in theory produce fewer adverse metabolic and physical effects, particularly if natural progesterone is used. Unfortunately, the steroid mass required for endometrial transformation would necessitate the use of an unacceptably large patch. The one existing progestogen patch using norethisterone provides satisfactory secretory transformation. Studies of the combination patch show it to be well tolerated, with only minimal differences in the physical, psychological and metabolic scores obtained in the oestradiol-only and oestradiol/norethisterone treatment phases (Ellerington *et al.*, 1992).

Subcutaneous/injectable progestogens

In theory, levonorgestrel silastic implants and injectable depot progestogens could also be used as progestogenic opposition to avoid the first-pass hepatic effect. From the

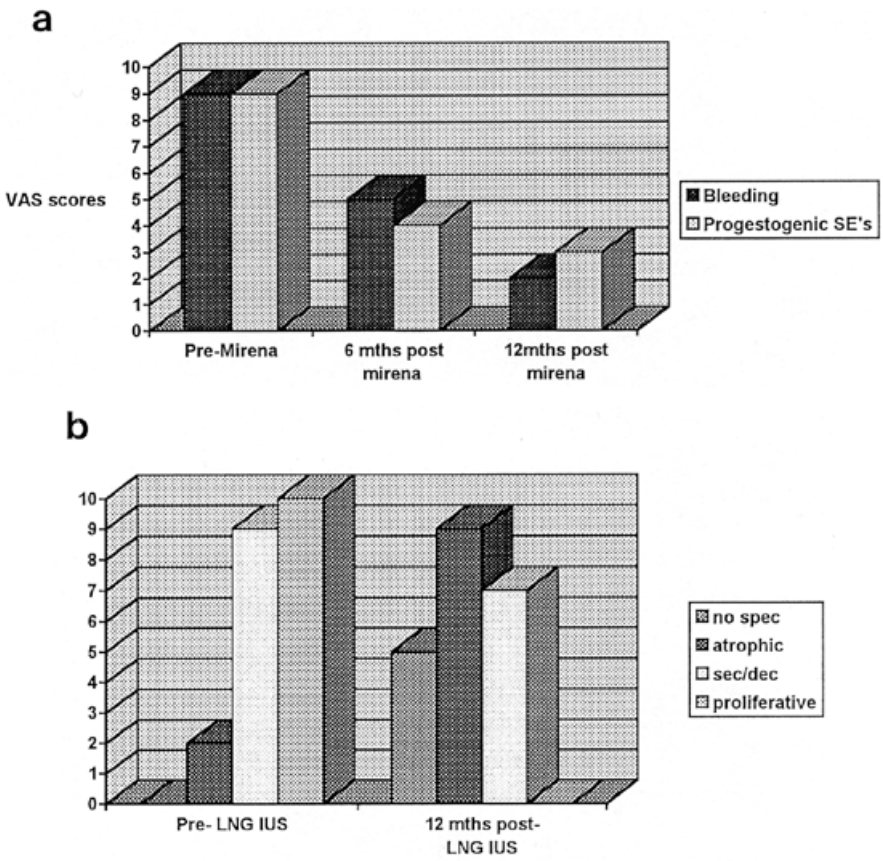

Figure 5. (**a**) Visual analogue scales (VAS) of global progestogenic side effects and bleeding severity in women using oestrogens with the levonorgestrel intrauterine system (LNG IUS) for progestogenic opposition. (**b**) Effect of LNG IUS on endometrium after 1 year. Adapted from Panay *et al.* (1996).

experience of family planning these progestogens are usually well tolerated. However, endometrial monitoring would have to be carried out to ensure suppression. Also, there may be little metabolic advantage to using these progestogens: because of their androgenic effects, there are still adverse changes in lipid profiles. It is astonishing that so little work has been done on the value of these much used preparations in HRT menopause regimens.

Alternative progestogens/progesterone

Depending on their derivation, progestogens may have different physical, psychological and metabolic effects. Non-androgenic progestogens and progesterone have the best physical effects, although they are not devoid of psychological effects. Anxieties about adverse lipid changes, increased vascular resistance and increased insulin resistance may be an issue in the patient who has either pre-existing cardiovascular disease or who develops cardiovascular disease whilst receiving HRT. In these patients it would be wise to use at the outset, or change to, progesterone itself or a less androgenic type of progestogen. Therefore, these progestogens are currently being incorporated into HRT regimens wherever possible in preference to those that are more androgenic.

Progesterone

Oral micronized progesterone has been developed to overcome absorption problems that meant in the past it had to be given by injection, vaginally or rectally. Unlike many oral progestogens, side effects are uncommon with progesterone administration. Dalton (1977), using low-dose progesterone for the treatment of PMS, claims not to have detected any adverse effects in 40 women treated over 10 years for PMS. Oral micronized progesterone, 300 mg per day for 12 days each month, or progesterone suppositories, 25 mg twice daily for 12 days, can be used as progestogenic opposition.

Recently, interest has been generated in exploring the potential of natural progesterone cream derived from plant sources, including wild yam, where it is found in its precursor form, diosgenin. Nutritionists and some doctors claim that it is sufficient in itself to provide relief of short- and long-term menopausal problems, including reversal of osteoporosis. Unfortunately, the bone data have been collected only from a few uncontrolled cases. This cream

certainly does appear to have minimal adverse effects, and anecdotally some patients do seem to derive benefits of increased energy, libido and improved skin. However, prospective, randomized, placebo-controlled studies are necessary to confirm the claims of its benefits; these have not yet been performed. It would also be interesting to see whether it could used as progestogenic opposition for oestrogen therapy.

Pregnane and nor pregnane progestogens

The pregnane cyproterone acetate (CPA) has recently been incorporated into HRT regimens because of its low incidence of side effects. In a study by Koninckx *et al.* (1993), 1 mg of CPA for 10 days per cycle proved to be the optimum dosage as a sequential regimen with 2 mg of oestradiol valerate, providing adequate endometrial protection and minimal adverse effects. The underused norpregnanes, such as promegestone and nomegestrol, are devoid of androgenic or of any adverse metabolic effects and, being potent progestogens, provide satisfactory endometrial protection (Rozenbaum, 1996).

Third-generation nortestosterone derivatives, e.g. desogestrel, gestodene

The third-generation nortestosterone-derived progestogens were developed in an attempt to minimize undesirable androgenic effects. These newer progestogens have a much higher selectivity ratio than the older ones. Some workers have demonstrated the beneficial effects of desogestrel as progestogenic opposition in terms of side effects and effect on lipids (Saure *et al.*, 1993). However, recent data concerning use of these preparations in combination with ethinyl oestradiol in the combined pill have suggested that users of the older second-generation pills had half the risk of thromboembolic disease. Although the data have been much criticized and are probably irrelevant to their usage in HRT, development of these progestogens for opposition in HRT has been suspended.

Anti-mineralocorticoid progestogens, e.g. drospirenone

Drospirenone, chemically related to 17α-spironolactone, with approximately eight times its anti-mineralocorticoid activity, has recently been used in combination with ethinyl oestradiol. Unlike traditional oral contraceptives, there was a small decrease in body weight and blood pressure (Oelkers *et al.*, 1995). In the future, progestogen-intolerant women using HRT who suffer from an increase in body weight, oedema and breast tenderness may benefit from the development of anti-mineralocorticoid progestogens.

Table III. Progestogen intolerance and compliance with hormone replacement therapy (HRT): summary of general principles

General principle	Explanation
Progestogens are necessary in non-hysterectomized women receiving HRT	Prevention of endometrial hyperplasia
Progestogenic symptoms are common	1. Bleeding problems
	2. PMS-like side effects
	3. Metabolic side effects
Poor compliance with HRT leads to complications	1. Short and medium term, e.g. vasomotor, genitourinary
	2. Long term, e.g. osteoporosis and cardiovascular disease
Poor compliance due to progestogen intolerance can be improved in a number of ways	1. Dealing with side effects directly
	2. Reducing dose/duration of progestogen
	continuous combined HRT
	quarterly HRT
	progestogen & progesterone intrauterine systems, vaginal progesterone gel
	transdermal progestogen
	subcutaneous/injectable progestogen
	3. Changing type of progestogen, e.g. more to less androgenic or
	to progesterone itself
	4. Avoiding progestogen altogether
	short-term unopposed oestrogens
	tibolone/bisphosphonates
	hysterectomy
	bisphosphonates
	selective estrogen receptor modulators

Table IV. Progestogen intolerance and compliance with hormone replacement therapy (HRT): management options for specific progestogenic problems

Symptom/disturbance	Action
Heavy/prolonged bleeding	Increase dose/duration progestogen
	Use more androgenic progestogen
	Long cycle/continuous combined HRT
	Progestogen/progesterone intrauterine system (IUS)
Progestogenic side effects	Diuretics (fluid retention symptoms)
(physical/psychological)	Androgens (breast/headaches/libido)
	Decrease dose/duration progestogen
	Less androgenic progestogen(physical)
	More androgenic progestogen(psychological)
	Long cycle HRT
	Progestogen/progesterone IUS
	Hysterectomy + unopposed oestrogen
	Unopposed oestrogen + endometrial sampling
Metabolic side effects	Less androgenic progestogen
(lipids/insulin resistance etc.)	Long cycle HRT
	Progestogen/progesterone IUS

Alternatives to progestogens/progesterone

Unopposed oestrogen replacement therapy

There will be a few patients for whom it will not be possible to find suitable progestogenic opposition. In these cases, the option of very low dose unopposed oestrogens needs to be considered. In a non-hysterectomized woman the risk of endometrial hyperplasia will be high, depending on the dose. Endometrial sampling must therefore be performed on at least an annual basis with a baseline sample to exclude initial pathology. If hyperplasia develops and progestogens are not tolerated, then either treatment should be stopped, or a progestogen coil could be inserted, or even hysterectomy should be considered.

Tibolone

Tibolone, a synthetic gonadomimetic compound with oestrogenic, progestogenic and androgenic properties, provides the user with bleed-free HRT. In the non-hysterectomized woman who cannot tolerate progestogens, particularly sequentially, this compound may be better tolerated. Studies have demonstrated adequate relief of climacteric symptoms coupled with low rates of breakthrough bleeding and good endometrial suppression with this compound over many years of follow up (Genazzani *et al.*, 1991; Rymer *et al.*, 1993; Ginsberg *et al.*, 1995). The effect of tibolone on lipids is inconsistent with an adverse, lowering effect on HDL cholesterol but a beneficial, lowering effect on total and LDL cholesterol and lipoprotein a (Rymer *et al.*, 1993; Milner *et al.*, 1996).

Hysterectomy

Hysterectomy with adequate oestrogen replacement may have to be considered if other actions fail and the women wishes to continue using HRT (Studd, 1995). This procedure should not be regarded as a last chance failure because it provides the convenience of long-term uncomplicated HRT as well as curing any painful periods, PMS and menstrual migraine. Thus, compliance is excellent and in our recent study of 200 consecutive hysterectomies, reviewed 2–5 years after surgery, 98% were still taking oestrogens (Studd, 1996).

Bisphosphonates

The bisphosphonates provide an option for the progestogen-intolerant woman who wishes to have HRT solely for the benefit of treating osteoporosis. Although not licensed for skeletal protection there is no reason, apart from cost and possible side effects, why these drugs could not be used for osteoporosis prophylaxis.

Selective oestrogen receptor modulators, e.g. droloxifene, raloxifene

These drugs possess both oestrogenic and anti-oestrogenic properties. The aim is to develop one which is selectively oestrogenic in the skeletal, cardiovascular and central nervous systems, whilst possessing anti-oestrogenic effects in the breast and endometrium. Data are still not complete for all parameters in any of these drugs, but one which fulfils all the desirable criteria may well provide the answer to

many of the problems associated with HRT in general and of progestogen intolerance specifically.

Conclusions

Progestogen use is essential in the non-hysterectomized woman using anything but very short-term oestrogen replacement therapy. Intolerance of progestogenic side effects remains a major obstacle to the maximization of patient compliance with HRT. This review has highlighted the adverse effects that progestogens can produce and discussed possible ways of minimizing these effects to improve compliance (Tables III and IV). Premenstrual-type effects and bleeding problems can often be dealt with by changing the type of progestogen, the dose or the duration. Continuous combined preparations are useful and intrauterine progestogen and progesterone systems will become more commonly used in HRT regimens. Hysterectomy remains an option for the severely progestogen-intolerant woman in whom other regimens have not succeeded. For the present, research continues into the development of more selective progestogens, improved regimens and sophisticated delivery systems. In the future, compliance could be maximized by development of the ultimate selective oestrogen receptor modulator, which would be devoid of side effects, have good oestrogenic effects on the skin and skeletal, cardiovascular and central nervous systems and anti-oestrogenic effects on endometrial and breast tissue.

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