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Percutaneous estradiol gel with an intrauterine levonorgestrel releasing device or natural progesterone in hormone replacement therapy

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Abstract

Objective: To evaluate the bleeding patterns and clinical compliance associated with postmenopausal amenorrhea-inducing forms of hormone replacement therapy using either percutaneous estradiol-gel and a levonorgestrel-releasing intrauterine device or an oral/vaginal natural progesterone. *Methods*: Sixty postmenopausal women with an intact uterus were followed over 12 months in this open, non-randomised, parallel group study. All patients continuously received a gel containing 1.5 mg of estradiol daily. The women were divided into three groups on the basis of progestin administration. Twenty women (group I) had a levonorgestrel-releasing device (LNG-IUD) inserted at the beginning of the study. Twenty-one women (group II) received oral natural micronised progesterone (oral P) 100 mg daily during 25 calendar days each month, and 19 women (group III) used vaginal natural micronised progesterone (vaginal P) 100–200 mg daily during 25 calendar days each month (higher dose if spotting occurred). Clinic visits were at 0, 3, 6 and 12 months. Bleeding patterns were recorded by the patient in a diary and clinical compliance was evaluated at control visits during the treatment. Symptoms were recorded using a modified Kuppermann index. The serum estradiol concentration was determined at the 0, 6 and 12 month control visits. *Results*: 80% ($n = 16$) of the patients in the LNG-IUD group, 67% ($n = 14$) in the oral P group II and 53% ($n = 10$) in the vaginal P group were without bleeding at 12 months. Spotting was common during the first 3 months. Symptom relief was good in each group. The LNG-IUD did not cause any serious side-effects. Compliance was good for LNG-IUD and oral progesterone but not for vaginal progesterone. *Conclusions*: Percutaneous estradiol-gel associated with LNG-IUD is an appropriate method of hormone replacement therapy. The combination of oral natural progesterone with estradiol-gel is also useful, although bleeding episodes complicated the treatment in one third of the patients. The vaginal administration of natural progesterone was impractical due to bleeding disorders. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Progestin is used in hormonal replacement therapy (HRT) to eliminate the risk of endometrial hyperplasia and adenocarcinoma which is associated with the use of estrogen alone. When choosing the best progestin for combined HRT a progestin of minimal androgenicity is preferable with regard to lipid changes [1]. In this respect, natural progesterone is better than a 17-OH-progestin or 19-nortestosteroid derivative. Natural progesterone in its micronised form can be used orally or vaginally [2]. The oral administration of progesterone in cyclical or continuous fashion has been successfully used in HRT [3] while the vaginal route of progesterone has not yet been investigated for this purpose.

Because the endometrium is the only target of progestin in combined HRT, a direct endometrial form of administration of progestin would be optimal. Results from previous studies using intrauterine levonorgestrel-releasing devices (LNG-IUD) support this concept [4,5].

The aim of this study was to evaluate symptom relief and bleeding patterns in postmenopausal women treated daily with a percutaneous, estradiol (E2)-containing gel combined with LNG-IUD or micronised natural progesterone given orally or vaginally. Percutaneous estrogen administration was chosen as it effects liver metabolism less than does oral estrogen [6,7].

2. Materials and methods

Sixty volunteer menopausal women contacted through an advertisement in the local newspaper were recruited to the study in the Kainuu Central Hospital, Finland, which provides secondary care services to a population of 100 000 inhabitants. Eligible subjects had an intact uterus, no contraindications to HRT and serum follicle stimulating hormone (FSH) concentration more than 20 IU/l and the time from their last natural menstruation was at least 6 months. Former users of HRT ($n = 32$) underwent an at least 2-month wash-out period and also had FSH > 20 IU/l. The study design was approved by the ethical committee of the hospital.

In this open, non-randomised study, consecutive women were divided into three groups according to an alternating schedule in the order that they entered the study with the exception that an IUD (group I) was not inserted in nulliparous women ($n = 5$). If a nulliparous woman was allocated to group I (IUD), she was put in the next of the remaining two groups in turn. The eligibility assessment was performed before allocation to the treatment group. All women agreed to receive the treatment allocated.

The estrogen treatment was transdermal 17β-estradiol-containing gel (Estrogel®, Besins-Iscovesco, Paris, France), which contains 1.5 mg of estradiol per 2.5 g gel in all three groups. This daily dose releases 150 μg estradiol into the circulation. The regimens differed from one another in their type and route of progestin administration: in the first group ($n = 20$) an LNG-IUD (Levonova®, Leiras oy, Turku, Finland) was inserted at the beginning of the study. Paracervical blockade was used by insertion in three cases. The LNG-IUD releases 20 μg of levonorgestrel per 24 h for 5 years.

In the second, oral P, group ($n = 21$), a natural micronised progesterone 100 mg per day capsule with nutoil as a vehicle (Lugesteron®, Leiras Oy, Turku, Finland) was given orally during 1–25 calendar days. In the third, vaginal P, group ($n = 19$), natural micronised progesterone was administered vaginally during 1–25 calendar days. The daily dose was initially 100 mg in each case but was raised to 200 mg in 12 women due to irregular bleeding.

Clinical out-patient visits took place at 0, 3, 6 and 12 months. At each visit the patients were interviewed, their blood pressure was measured and a pelvic examination was performed. Clinical compliance and possible side-effects were regis-

Table 1
Baseline characteristics of the patients in the different treatment groups

	Group		
	LNG-IUD ($n = 20$)	Oral P ($n = 21$)	Vaginal P ($n = 19$)
Age (years):			
Median (range)	52 (47, 61)	55 (45, 66)	54 (45, 63)
BMI (kg/m^2)			
Median (range)	25.4 (19.8, 33.6)	25.1 (17.4, 36.5)	24.8 (19.2, 37.2)
Time since menopause (years) median (range)	1.9 (0.5, 8.3)	5.0 (0.5, 23)	3.5 (0.5, 15)
Former HRT users	11	12	9
Current smokers	3	2	2

All groups received percutaneous estradiol gel 1.5 mg daily continuously.
LNG-IUD, levonorgestrel-releasing intrauterine device.
Oral P, oral micronised natural progesterone 100 mg/day during 1–25 calendar days.
Vaginal P, vaginal micronised natural progesterone 100–200 mg/day during 1–25 calendar days.

tered. The women recorded any bleeding or spotting episode every day on a diary card. Diaries were checked at each clinic visit. Menopausal symptoms were registered before the treatment and at each clinic visit by using a modified Kupperman-index [8]. Every patient graded the severity of symptoms using a scale 0–3: 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe symptoms. The symptoms evaluated were hot flushes, sweating, insomnia, irritability, depression, vertigo, tiredness, joint-pain, headache, palpitation and dryness of the vagina. Scores for sweating, insomnia and irritability were multiplied by 2 and scores for hot flushes by 4, resulting in a maximum score of 51.

Blood samples for measuring the serum concentration of estradiol (E2) were taken before the treatment and at 6 and 12 months. Serum E2 values were measured using the 1244-056 DELFIA Estradiol kit (Wallac Oy, Turku, Finland). The intra- and inter-assay coefficients of variation for measurements of E2 are 10.2% and 9.7%, respectively.

The treatment groups were compared using descriptive plots and statistics. Pairwise differences in proportions between the groups (with 95% confidence intervals) were calculated for the comparison of the number of patients without bleeding at the 6th and 12th month of follow-up using the CIA (Confidence Interval Analysis) program [9].

3. Results

The groups were comparable with respect to body-mass index, smoking and former HRT-use, but the women in the IUD-group were on average 2–3 years younger and had had a shorter time since their last menstruation than did the women in the other groups (Table 1). There were three nulliparous women in the oral P and two in the vaginal P groups. All outcomes were compared between the groups both before and after excluding the nulliparas. As the results did not change essentially, we report the results for the original groups.

Nine patients discontinued the trial during the 12-month period: 2 in the LNG-IUD group (one woman due to abdominal pain caused by the IUD and another due to irregular vaginal bleeding), 3 in the oral P group (one woman due to vaginal bleeding, another due to breast tenderness and the third because of deep venous thrombosis) and 4 in the vaginal P group (two discontinuations were due to vaginal bleeding and the third because of a growing uterine leiomyoma. A fourth woman suffered from a successfully operated subarachnoidal hemorrhage). After the 1-year study 32 women wished to continue the study medication; 16 in the LNG-IUD group, 12 in the oral P group and only 4 in the vaginal P group.

The relief of climacteric symptoms was significant and similar in all groups during the treatment (Table 2).

Table 2
Symptoms in the three different treatment groups measured by the Kuppermann index (scores 0–51). Figures are medians and (quartiles)

Group	Time since start of treatment			
	0 months	3 months	6 months	12 months
E2-gel and LNG-IUD ($n = 20$)*	23 (19, 30)	7 (3, 8)	5 (1, 7)	7 (1, 10)
E2-gel and oral P ($n = 21$)*	20 (16, 28)	6 (2, 10)	2 (1, 7)	5 (1, 9)
E2-gel and vaginal P ($n = 19$)*	24 (17, 32)	9 (3, 17)	5 (1, 11)	8 (2, 19)

E2-gel, estradiol gel.
LNG-IUD, levonorgestrel-releasing intrauterine device.
Oral P, oral micronised natural progesterone.
Vaginal P, vaginal micronised natural progesterone.
*The number of patients at 12 months were 18, 19 and 15 in the 3 groups, respectively.

Irregular vaginal bleeding was common in all groups during the first 3 months of the trial (Fig. 1). At 6 months, 15 (75% of the original group) in the LNG-IUD group, 13 (62%) in the oral P group and 8 (42%) in the vaginal P group were free of bleeding problems. The differences of proportions (in percent points with 95% confidence limits) between the groups were +13 (−15 to +41) between the LNG-IUD and oral P groups, +33 (+4 to +62) between the LNG-IUD and vaginal P groups and +20 (−11 to +50) between the oral and vaginal P groups. The numbers of patients at 12 months without bleeding were 16 (80%), 14 (67%) and 10 (53%), respectively. The differences of proportions between the groups were +13 (−13 to +40) between the LNG-IUD and oral P groups, +27 (−1 to +56) between the LNG-IUD and vaginal P groups and +14 (−16 to +44) between the oral and vaginal P groups. Vaginal bleeding appeared mostly in the form of spotting (Fig. 2).

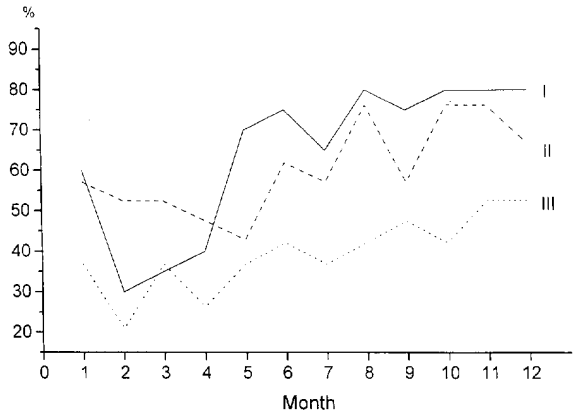

Fig. 1. The proportion of patients without bleeding by month of follow-up in the three groups. The proportions were calculated from the original group at each month. I, E2-gel and LNG-IUD; II, E2-gel and Oral P; III, E2-gel and vaginal P.

One woman in the LNG-IUD group had mild abdominal pain after insertion of the IUD. At 4 months her IUD was expulsed and a new IUD inserted the next day. She completed this study without further problems. Most of the women who used vaginal progesterone felt usage discomfort. Part of the medicine tended to be lost from the vagina as the capsule melted. Three women in the LNG-IUD group, three in the oral P group and two in the vaginal P group complained of disturbing breast tenderness. This side-effect was mostly transient, but one woman discontinued the study due to this discomfort.

Before treatment, the median serum E2 value was 70 pmol/l (range 40–290 pmol/l) in the entire study population. At 6 and 12 months the median (range) serum E2 values were 250 (50–1030) pmol/l and 210 (40–1050) pmol/l, respectively.

4. Discussion

The return of menstrual periods after menopause when using sequential estrogen-progestagen therapy is unacceptable to many

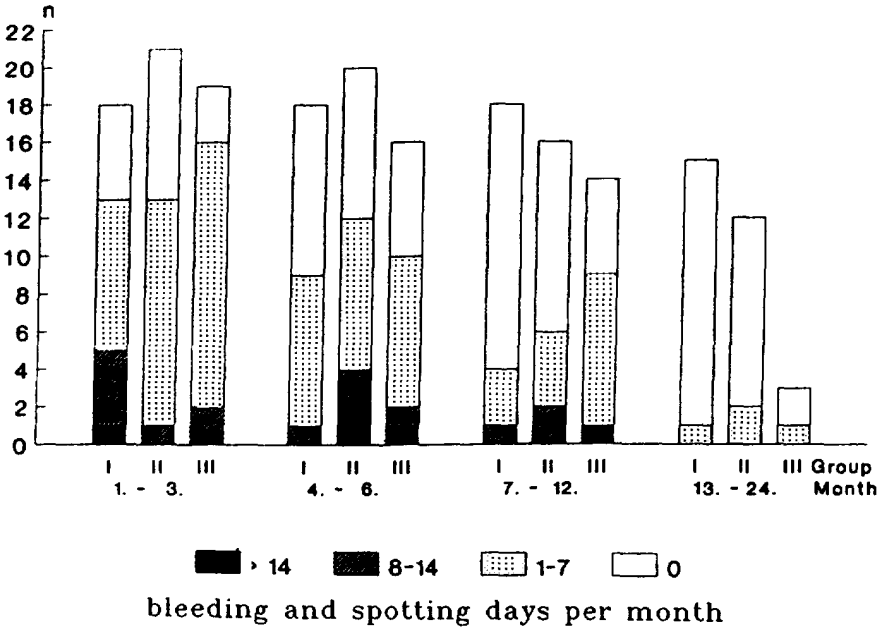

Fig. 2. Bleeding and spotting days per month in the three different groups. Groups: I, E2-gel and LNG-IUD; II, E2-gel and Oral P; III, E2-gel and vaginal P.

women. Therefore there is a great need for amenorrhea-inducing regimens of HRT [10]. This was the main reason why we have evaluated the usefulness of three different forms of combined HRT, aimed to induce amenorrhea.

The use of E2-containing gel did not cause any significant side-effects and was well accepted by our patients. The range in serum E2 concentrations was wide. Scott et al. [11] also found a considerable interindividual variation in serum E2 concentrations after the administration of E2-gel, but individual serum concentrations remained quite stable.

The 80% rate of patients without bleeding in patients with an LNG-IUD at 12 months is comparable with previous findings [4,5] suggesting that the LNG-IUD is a practical aid for counteracting estrogen-induced endometrial stimulation. The present clinical observations on endometrial behavior agree well with findings in our histopathological and immunohistochemical studies on the endometrium of these women [12]. The study showed that natural progesterone in our regimen was weak to prevent proliferative changes in each case. In addition, the endometrium of the women exposed to natural progesterone did not express insulin-like growth factor-binding protein-1 (a marker of endometrial response to progesterone) whereas this phenomenon was seen in the endometrium of each woman bearing LNG-IUD.

Spotting appeared frequently during the first 3–6 months but then gradually diminished. LNG-IUD did not cause any remarkable side-effects and its compliance was good. According to our observations, women who still suffer from bleeding problems at 6 months should consider some other form of HRT. The women in the IUD-group were somewhat younger and had had a shorter time since menopause as compared with the other groups. In that respect, they would have been expected to have more bleeding or spotting than women in the other two treatments, but on the contrary, the bleeding profile was best in the IUD-group.

Two thirds of the women using oral progesterone in our study did not complain of any bleeding at 12 months. This result is not as good as that (81%) observed by Faguer et al. with

almost similar therapy [13]. In their treatment regimen, however, administration of both E2-gel and progesterone was restricted to calendar days 1–25 whereas we had such a break for progesterone only in order to upregulate progesterone receptors. This may partly explain the difference of the bleeding disorders between the two studies. A more likely explanation, is a strict bleeding registration, as even a small sign of spotting was marked on the files. The bleeding disorder of the women in our study was mostly spotting. It is also possible that the absorbed dose of E2 remained relatively low in some women which allows the endometrium to escape from hormonal control. There is evidence in the literature to show that a relatively small estradiol dose is frequently associated with bleeding problems. For example, the combination of oral conjugated estrogen (0.625 mg daily) and continuous oral medroxyprogesterone (2.5 or 5.0 mg daily) induced amenorrhea in only approximately half of the women [14]. Oral progesterone combined to percutaneous estrogen seems to be useful regarding clinical compliance and bleeding profiles although endometrial suppression was not as strong as with LNG-IUD [12].

Natural progesterone is well absorbed from the vagina into the circulation [15–17]. Consequently vaginal progesterone cream has been used beneficially in the treatment of endometrial hyperplasia [18]. The present observation of a good endometrial efficacy in only 53% of women using vaginal progesterone is in strong contrast with previous observations obtained from mostly premenopausal women. It seems likely that progesterone in the postmenopausal women was not adequately absorbed. Indeed, the patients reported that some of the medicine came out of the vagina as the suppository melted. This drawback might be caused by the anatomical and functional changes of the vagina caused by childbearing, delivery and menopausal transition. At least partly due to this, postmenopausal women did not wish to continue this form of treatment while the women in the other two groups wished to continue their study medication. A more appropriate form of vaginal tablet would be desirable if the vaginal administration of progesterone is required in continuous HRT.

In conclusion, E2-gel gave good symptom relief with minimal side-effects. LNG-IUD seems to be effective in endometrial control in amenorrhea-inducing forms of HRT. Oral natural progesterone is also useful for this purpose whereas vaginal natural progesterone gave neither an adequate endometrial control or compliance.

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