Levonorgestrel intrauterine system (LNG-IUS) with conjugated oral equine estrogen: a successful regimen for HRT in perimenopausal women

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BACKGROUND: This study was designed to assess the long-term efficacy (5 years) of the levonorgestrel-releasing intrauterine system (LNG-IUS) in protecting the endometrium from hyperplasia during estrogen replacement therapy in perimenopausal women. METHODS: Prospective, open, outpatient clinical trial in London and Oxford. Eighty-two women received oral conjugated equine estrogen 1.25 mg daily and LNG-IUS releasing 20 µg levonorgestrel per 24 h. Endometrial biopsy and histological assessment were performed annually. Endometrial thickness was measured by vaginal ultrasonography. RESULTS: Non-proliferative endometrium was present at the end of cycles 12, 24, 36, 48 and 60 in 98.6, 98.6, 95.5, 96.8 and 95.2% of the participants respectively. No endometrial hyperplasias were confirmed throughout a period of 60 cycles. The proportion of amenorrhoeic women increased from 54.4% at 12 cycles to 92.7% at the end of the study. The continuation rate per 100 women at 60 cycles was 79.84 (95% CI 71.0–88.6). CONCLUSIONS: The LNG-IUS with estrogen supplementation in perimenopausal women suppresses endometrial proliferation resulting in amenorrhoea and relieves vasomotor symptoms. The treatment regimen is well tolerated and provides an alternative strategy for perimenopausal women with the likelihood of increasing compliance.

Key words: bleeding/endometrium/hyperplasia/LNG-IUS/perimenopause

Introduction

HRT is an effective treatment for menopausal symptoms (Rymer and Morris, 2000), conserves bone mass and reduces the risk of osteoporotic fracture (Komulainen et al., 1998; Torgerson and Bell Syer, 2001; Writing Group for the Women’s Health Initiative Investigators, 2002).

Estrogen alone is well known to increase the risk of endometrial neoplasia and hyperplasia (Grady et al., 1995). This risk is reduced by the addition of progestogen with most studies examining oral administration (Weiderpass et al., 1999; Sturdee et al., 2000).

The levonorgestrel-releasing intrauterine system (LNG-IUS), releasing 20 µg/24 h levonorgestrel, has been shown to be a highly effective long-acting method of contraception (Luukkainen et al., 1986; Sivin et al., 1990; Andersson et al., 1994) and is known to induce endometrial glandular atrophy (Silverberg et al., 1986) and amenorrhea (Andersson et al., 1994). Furthermore, it is an effective treatment for excessive menstrual bleeding (Nilsson, 1977; Andersson and Rybo, 1990; Lethaby et al., 2000), a complaint which may be more common in the perimenopause (Hallberg et al., 1966).

Perimenopausal women, in addition to having vasomotor symptoms, may have difficulties in finding acceptable forms of contraception, particularly if they have contraindications to combined oral contraceptives or have excessive menstrual bleeding, making a copper-bearing intrauterine device inappropriate. Furthermore, they may wish to have a ‘no bleed’ HRT regimen, which cannot be achieved with either oral or transdermal delivery.

When this study was started, in 1992, the published data relating to the use of the LNG-IUS in perimenopausal hormone replacement were limited to 18 women followed for 12 months (Andersson et al., 1992). They showed that the LNG-IUS in combination with orally administered estradiol prevented endometrial proliferation and reduced uterine bleeding. Thereafter several studies have confirmed this, but predominantly in postmenopausal women (Raudaskoski et al., 1995; Suhonen et al., 1995ab1997; Suvanto-Luukkonen et al., 1997; Suvanto-Luukkonen and Kauppila, 1999; Varila et al., 2001). The only studies extending follow-up to 5 years have recruited postmenopausal women (Suvanto-Luukkonen and Kauppila, 1999; Varila et al., 2001).
The primary aim of the study was to investigate the long-term efficacy of the LNG-IUS to prevent the induction of endometrial hyperplasia and proliferation in perimenopausal women exposed to estrogen. Effects of this HRT combination on vaginal bleeding, continuation rate, menopausal symptoms and overall tolerability were also assessed.

Materials and methods

Subjects and ethical approval
Eighty-two perimenopausal women seeking medical treatment for their menopausal symptoms were recruited at the Margaret Pyke Centre in London and the Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford (41 at each centre).

The study (DE00651–91514) was approved by the independent local research ethics committees at the Middlesex Hospital (92/0037) and the Central Oxford Research Ethics Committee (2620). The initial planned study period of 24 cycles was extended to 60 cycles of 28 days. All subjects gave written informed consent. The first subject was screened for entry in November 1992 and the last LNG-IUS insertion was performed in May 1994. The last subject completed the 60 cycle visit in December 1998.

Inclusion/exclusion criteria
Symptomatic perimenopausal women with intact uteri aged >40 years, with or without the need for contraception, were selected for this study if they had experienced a minimum of three menstrual periods in the preceding year, with no amenorrhoea for ≥6 months and FSH level of >15 IU/l. Women aged ≥48 years with menopausal symptoms did not need to have FSH value of >15 IU/l to qualify for this study. A menopausal symptom chart was used at entry and at cycles 12 and 24; analysis was performed on hot flushes, night sweats, vaginal discomfort (dryness or pain on intercourse) and mood disturbances (tense or wound up, feeling unhappy or depressed).

Subjects had to be free from conditions that could potentially interfere with the study treatment or otherwise complicate participation in the study, e.g. congenital anomaly or uterine leiomyoma distorting the cavity (identified by pelvic ultrasonography), presence or past history of pelvic infection, current vaginal or cervical infection, history of ectopic pregnancy, undiagnosed abnormal uterine bleeding within the preceding 6 months, deep vein thrombosis, thromboembolic disorder or cardiovascular accident, history or current clinical evidence of endocarditis or cardiac disease, history of hormone-dependent or any other active malignancy or current abnormal cervical cytology comparable to CIN 1 confirmed by colposcopy. Women were excluded if they had received estrogen or progestogen therapy during the preceding 6 months; a 12-month wash-out period was required after an estrogen implant. The use of the LNG-IUS during the preceding 12 months was also prohibited.

Treatment regimen
The levonorgestrel-releasing intratubercine system (Mirena®, Levonova®) has a polyethylene T-shaped body. A cylinder, containing a mixture of 52 mg of levonorgestrel and polydimethylsiloxane, is mounted around the vertical stem of the T-body. The sustained daily release of levonorgestrel is 20 μg.

The LNG-IUS was inserted during days 4–10 of the menstrual cycle. If inserted at other times, pregnancy was excluded first. The doctor performing the insertion assessed the procedure as easy or difficult; if difficult, further details were recorded. The subject scored the insertion procedure with respect to pain as no, mild, moderate or severe.

The oral conjugated equine estrogen preparation (Premarin®) was used at a dosage of 1.25 mg/day continuously starting on the day of LNG-IUS insertion, with the option to change the preparation if clinically indicated for persistent estrogenic side-effects. At first the dose of Premarin® was reduced to 0.625 mg/day and, if the symptoms persisted, an alternative oral estrogen formulation was tried: Progynova® containing 1 and 2 mg estradiol valerate or Zumenon® containing 2 mg and 4 mg estradiol hemihydrate.

Safety data
The following screening laboratory tests were performed on venous blood samples: fasting glucose, insulin, sodium, potassium, creatinine, FSH, urea, chloride and bicarbonate. Subjects were also screened for chlamydial infection. Urinary pregnancy tests were performed if appropriate. Other baseline parameters recorded were relevant medical history, height, body mass index and the findings of a general physical examination.

Following study entry, visits were scheduled at 6 weeks, 6 months and 12 months and 6-monthly to 60 months. Weight and blood pressure were checked at each visit. Pelvic examination was performed at screening, entry, 6 weeks, then 6-monthly for the first two years and annually thereafter. Pelvic ultrasound, endometrial biopsy, cervical cytology, breast examination and haemoglobin estimation were performed at baseline and annually. Liver function tests, total protein, albumin and globulin were performed at 0, 24 and 60 months. Mammography was performed prior to study entry if not performed during the preceding 12 months; repeat mammography was performed every 2–3 years. With the exception of mammography all tests were repeated in cases of premature termination.

Endometrial biopsy and assessment
Endometrial biopsy samples were obtained using Pipelle de Cornier suction curettage. All samples were analysed for hormonal status and pathology using standard classification. Endometrial ultrasonography replaced histology if an insufficient sample was obtained. A double layer endometrial thickness of ≤6 mm was classed as non-proliferative; a thickness of >6 mm constituted a proliferative sample. Women with endometrial hyperplasia, polyp or carcinoma were excluded. Endometrial histology was classified as: atrophic, inactive, secretory, proliferative, hyperplastic and 'other pathology'. In some tables a category of non-proliferative, consisting of atrophic, inactive and secretory findings, was used. One pathologist performed the primary reading of all samples. After the onset of the study the European Union Committee for Proprietary Medicinal Products (CPMP) advised the use of double reading of samples by two independent pathologists. All samples were subjected to secondary reading in line with CPMP guidance. The independent pathologists agreed on all histological diagnoses. Had there been disagreement, the opinion of a third pathologist would have been sought; the independent findings of the third pathologist, generated without reference to previous records, would have been used to produce a definitive result.

Diary data, symptom and bleeding record
Intake of estrogen tablets and concomitant medications, bleeding (any bloody vaginal discharge requiring the use of pads or tampons) and spotting (any vaginal discharge not sufficient to require sanitary protection) were recorded daily in 28 day diaries. Bleeding data were analysed in terms of the number of bleeding and spotting days, the number of bleeding and spotting episodes and bleeding patterns.
using the World Health Organization Menstrual Diary System (Pinol and Machin, 1988). The extent of menopausal symptoms was evaluated by a questionnaire covering the three cycles prior to the screening visit and three cycles prior to each follow-up evaluation (six, 12, 18 and 24 cycles). The symptom chart comprised multiple questions in order to evaluate progestogenic and menopausal symptoms. As no trends were found in those parameters measuring progestogenic symptoms, only those associated with the menopause such as hot flushes, night sweats, vaginal discomfort, feeling tense or wound up and feeling unhappy or depressed are presented. At the time of study termination, both the investigator and the subject assessed the overall tolerability of the treatment as very good, good, moderate, poor or very poor. All other adverse events or symptoms were recorded on specific forms.

Study withdrawal
If the subject had been without an LNG-IUS in situ for >2 weeks or had partially or totally expelled her third IUS during the study or the IUS had partially or totally perforated the uterus or the cervix, the study was terminated. Women were allowed to miss a maximum of seven estrogen tablets in a 28 day cycle.

Statistical methods
Assuming a true incidence of zero, 60 subjects with none showing hyperplasia would give an upper 95% confidence interval (CI) of 4.9%. Allowing for premature terminations, 80 women need to be recruited. Statistical analyses were performed with SAS® System Software. \( P < 0.05 \) was considered to be statistically significant. Intention to treat population was used. Continuous normally distributed variables were analysed by analysis of variance (ANOVA). The normality of distribution of variables measured once was checked with Levene’s test. Residuals were used for repeated measurements. If a variable was not normally distributed even after logarithmic or square transformation, non-parametric Mantel–Haenszel, Wilcoxon rank sum or Fisher’s exact tests were used. The incidence of hyperplasia was calculated by the formula (cumulative number of hyperplasia/women months)*1200. Continuation rates were calculated using Kaplan–Meier estimates.

Results
Demography
The mean age was 47.9 years (SD 3.3) and the mean body mass index was 25.7 kg/m² (SD 4.3).

LNG-IUS insertion/retention
LNG-IUS insertion was attempted in 82 women. Eighty insertions were successful. One woman had a failed insertion due to severe pain. Another subject had her LNG-IUS removed at the entry visit after suffering profound and prolonged cervical shock (vaso-vagal collapse secondary to cervical dilatation) following IUS insertion.

The mean uterine sound measurement was 7.3 cm (SD 0.9, range 5–10).

The investigators assessed 19 insertions (23.2%) as difficult and 63 (76.8%) as easy. Dilatation of the cervix was required for 18 insertions, for which paracervical block using 1% lidocaine was used, and in 17 of these the insertion was deemed difficult. Subjects reported no pain and mild pain in 20 (24.4%) and 46 (56.1%) insertions respectively. Moderate or severe pain was felt in 13 (15.9%) and three (3.7%) cases respectively. In eight of the women experiencing moderate or severe pain the physician assessed the insertion as difficult. Local anaesthesia was not required in any subsequent procedures.

Three partial and two total IUS expulsions occurred during the study. The partial expulsions occurred at 2 weeks, 19 months and 34 months. One complete expulsion occurred unnoticed during the first 6 months and the subject discontinued the study; the second complete expulsion took place after 12 months. A new IUS was successfully reinserted except in the case of unnoticed expulsion. In addition in a sixth subject ultrasonography revealed the IUS to be low-lying in the uterine cavity at 12 months. It was replaced by a new LNG-IUS, and 2 years later the second IUS was partially expelled; this event coincided with study discontinuation, at which time biopsy showed proliferative endometrium.

Figure 1 shows discontinuations by time and reason.

Endometrial histology
Table I shows the results of endometrial histology. At entry, the endometrium was proliferative in 36 women (45%), secretory in 11 (13.8%), inactive in nine (11.3%) and atrophic in one (1.3%). An insufficient sample was obtained in 21 subjects (26.3%). One sample showed diffuse hyperplasia and another an endometrial polyp. This resulted in each case in pre-planned discontinuation during the first six cycles. By the 60 cycle visit, proliferative endometrium was found in two (3.2%), secretory in one (1.6%), inactive in 53 (88.5%) and atrophic in one (1.6%) women.

The primary reading revealed one case of simple cystic hyperplasia at 60 cycles. However, a subsequent evaluation of the initial sample by two independent pathologists, who were unaware of the treatment regimen or initial report, concluded that it represented fragments of an endometrial polyp without signs of hyperplasia. Moreover, a follow-up hysteroscopy revealed no pathology and the amount of curettings was too small for histological evaluation. The overall exposure to treatment was 3817 women months.

At entry the median endometrial thickness was 6.0 mm (range 0–23) and at 60 cycles it was 4.0 mm (range 1–8). Endometrium was deemed proliferative at baseline in 43 subjects (52.4%). Non-proliferative endometrium was present at the end of cycles 12, 24, 36, 48 and 60 in 98.6, 98.6, 95.5, 96.8 and 95.2% of the participants respectively.

Vaginal bleeding
Bleeding diary analyses were performed on 84 day (third cycle) reference periods. A total of 20 such periods (1680 days) was analysed. Figure 2 shows the median bars for the number of bleeding and spotting days with the study centres combined. There was a statistically significant time effect \( (P = 0.001) \) in the decrease in both the number of bleeding and the number of spotting days.

Likewise the median number of bleeding episodes decreased from the initial three to zero at the end of the first treatment year and thereafter \( (P = 0.001) \). Spotting episodes decreased from the initial median of two episodes to one
episode (range 0–10) in period three; thereafter none occurred from the third 84 day reference period onwards \( (P = 0.001) \).

During the first reference period most women reported either prolonged bleeding (54.2% subjects) or frequent bleeding (36.1%). Amenorrhoea was not reported in the first reference period, but it became more common as the study progressed; 54.3% of women were amenorrhoeic during the reference period 6 and 85.4% during the final reference period of the study; when 1–8 days of spotting were allowed in the analysis the respective proportions of bleeding-free women were 72.9 and 92.7%.

### Continuation rate and discontinuations

The continuation rate per 100 women by Kaplan–Meier estimates at 60 cycles was 79.8 (95% CI 71.0–88.6). Figure 1 outlines the premature discontinuations from the study. A total of eight women discontinued the study due to adverse events and one due to a partial IUS expulsion. Seven women discontinued the study for reasons not related to the treatments.

All subjects started the study with Premarin® 1.25 mg; 73% of subjects continued with this preparation to cycle 12 and 74% to cycle 24, 11% of subjects reduced to Premarin® 0.625 mg from baseline to cycle 12 and 7.4% from cycle 12 to cycle 24. Fifteen per cent of subjects changed to another oral estrogen preparation or discontinued the study to cycle 12 and 18.6% from cycle 12 to 24.

### Adverse events

A total of 1594 adverse events were reported or observed, of which 174 were evaluated to have causality with the study drugs. In order of occurrence the following events were recorded: abdominal pain (n = 31), breast pain (n = 29), dysmenorrhoea (n = 16), IUS complication (n = 12), nausea (n = 12), leukorrhoea (n = 9), dyspepsia (n = 9), edema (n = 7), vaginal bleeding (n = 5), headache (n = 4) and ‘other events’ (n = 40). ‘Other events’ included menstrual disorders, emotional lability, back pain, fatigue, ovarian cyst formation, depression, acne and migraine.

A total of 24 adverse events were classified as both severe by intensity and having a causal relationship to the study treatments. These included breast tenderness (seven events), headache (four events), abdominal pain (three events) and other events (ten events).
bloating (four events), headache and/or migraine (four events), fatigue (two events) ovarian disorder (two events) and one each of abdominal pain, urinary tract infection, backache, profound and prolonged cervical shock due to IUS insertion and a breast lump following increased estrogen.

A total of 18 serious adverse events were reported, of which three were thought to have a possible causality with the study treatment. One subject was hospitalized 685 days from study entry for the excision of a right-sided benign breast lump; she recovered completely and continued in the study. A remote causality with the study treatment was assigned to a basal cell carcinoma suffered by one subject 672 days from study entry; after removal of the carcinoma above the left eye she recovered completely and continued in the study. One subject was diagnosed with ductal carcinoma of the right breast 1539 days from entry. Following partial mastectomy and axillary node sampling she withdrew from the study to commence chemotherapy and radiotherapy. The causality with the LNG-IUS was assessed as none, but causality with estrogen treatment was reported as possible.

Two out of 14 women experiencing a serious adverse event discontinued the study, one after breast carcinoma, as described above, and another for an elective varicose vein operation.

Menopausal symptom relief

Hot flushes, sweating at night and vaginal discomfort (dryness/pain on intercourse) all improved significantly during the first 24 months of the study, see Table II. There was a similar improvement in the psychological symptoms of feeling tense or wound up and unhappy or depressed.

Overall assessment of tolerability

At termination or discontinuation of the study the subjects assessed treatment as very good and good in 60 (75.9%) and 13 (16.5%) cases respectively, one (1.3%) rated the tolerability as moderate, one (1.3%) as poor and one (1.3%) as very poor. Subjects discontinuing due to adverse events gave the poor and very poor assessments.

Although not designed as a contraceptive efficacy study, many subjects relied on the LNG-IUS to protect them from pregnancy during the study; no conceptions occurred during the 318 woman years of exposure to the study treatment.

Table I. Endometrial histology by time-point (intent to treat population)

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Total number</th>
<th>No sample obtained</th>
<th>Insufficient sample</th>
<th>Atrophic endometrium</th>
<th>Inactive endometrium</th>
<th>Secretory endometrium</th>
<th>Proliferative endometrium</th>
<th>Other</th>
<th>Endometrial hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>-</td>
<td>21</td>
<td>26.3</td>
<td>1</td>
<td>1.3</td>
<td>9</td>
<td>11.3</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>-</td>
<td>23</td>
<td>31.1</td>
<td>5</td>
<td>6.8</td>
<td>44</td>
<td>59.5</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>73</td>
<td>-</td>
<td>10</td>
<td>13.7</td>
<td>1</td>
<td>1.4</td>
<td>62</td>
<td>84.9</td>
<td>-</td>
</tr>
<tr>
<td>36</td>
<td>67</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>16.4</td>
<td>1</td>
<td>53</td>
<td>79.1</td>
<td>-</td>
</tr>
<tr>
<td>48</td>
<td>62</td>
<td>1</td>
<td>1.6</td>
<td>14</td>
<td>22.6</td>
<td>2</td>
<td>45</td>
<td>72.6</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>62</td>
<td>-</td>
<td>4</td>
<td>6.5</td>
<td>1</td>
<td>1.6</td>
<td>53</td>
<td>85.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Two screened subjects who had begun treatment were excluded, one because of complex endometrial hyperplasia on entry biopsy and another because of endometrial polyp. Inactive endometrium was also seen in one, one and four women who discontinued the study at 6, 30 and 54 months respectively. Complex hyperplasia with cytological atypia was suspected, but not confirmed, in an endometrial polyp within inactive endometrium in another woman discontinuing at 42 months.

One subject discontinuing at cycle 54 had inactive endometrium and endometrial polyp. *Histological classification as atrophic inactive etc.
The data from this study demonstrate that the use of the LNG-IUS in combination with conjugated oral equine estrogen effectively prevents the endometrium from becoming hyperplastic in estrogen-exposed perimenopausal women over a period of 5 years. Furthermore, the endometrium consistently showed lack of proliferation in >95% of subjects from cycles 12 to 60. Our results are in accordance with previous reports in peri- (Andersson et al., 1992; Suhonen et al., 1997) and postmenopausal women (Raudaskoski et al., 1995; Suhonen et al., 1995 and 1997; Suvanto-Luukkonen et al., 1997; Suvanto-Luukkonen and Kaupilla, 1999; Varila et al., 2001). Oral or transdermal estradiol was used in these studies. The LNG-IUS has even been successfully used for the treatment of all types of endometrial hyperplasia (Perino et al., 1987; Scarselli et al., 1988). Hyperplastic changes in the endometrium have been reported with sequential (Lindgren et al., 1992; Ross et al., 1993; Writing Group for the PEPI Trial, 1996) but not continuous (Pike et al., 1997; Wells et al., 2002) combined therapy.

One case of simple cystic hyperplasia without atypia was found during the study, though subsequent assessment suggested a benign endometrial polyp. The acceptable incidence of endometrial hyperplasia in HRT users has been determined to be 1–2% [European Agency for the Evaluation of Medical Products (EMEA, 1997)], and so even if this one case were to be categorized as diffuse hyperplasia the incidence (1.7%) over a 5 year period would be acceptable. However classified, all the histopathologists were agreed that the risk of atypical hyperplasia or endometrial carcinoma in this patient would be negligible, in view of the demonstrable progestogen effects causing prominent decidualization with small inactive glands.

Endometrial micropolyps have been previously reported in fertile women using the LNG-IUS for contraception (Silverberg et al., 1986). One out of several other studies using the LNG-IUS in combination with oral or transdermal estrogen has reported cases of endometrial polyps (Varila et al., 2001). The mechanism underlying the development of an endometrial polyp is unclear. Endometrial polyps were first reported by Staland (1981), which introduced continuous combined estrogen–progestogen therapy; polyps were found in 11% of endometrial biopsies. Endometrial polyps were seen in 5.6% of women in another study of continuous combined therapy (Williams et al., 1990) and one study of fertile women showed endometrial polyps in 24% of women (Van Bogaert, 1988).

Endometrial samples taken from women using the LNG-IUS as a contraceptive show uniform changes of endometrial glandular atrophy and stromal decidualization (Silverberg et al., 1986; Zhu et al., 1989) and immunoreactivity of the proliferation marker Ki67 has been shown to decline (Salmi et al., 1998). Similar histological effects have been seen when the LNG-IUS is used in combination with estrogen replacement therapy (Andersson et al., 1992). The LNG-IUS has been shown to cause alterations in the endometrial insulin-like growth factor (IGF) system both in fertile and menopausal women (Pekonen et al., 1992; Suvanto-Luukkonen et al., 1995; Suhonen et al., 1996; Rutanen et al., 1997). With the LNG-IUS in utero, IGF-I mediated estrogenic effects are inhibited. The suppression of IGF-I and abundant production of IGF binding protein-1 by decidualized stromal cells may be one of the molecular mechanisms responsible for the suppression of endometrial growth when the LNG-IUS is used alone or in combination with postmenopausal estrogen replacement (Pekonen et al., 1992; Suvanto-Luukkonen et al., 1995; Suhonen et al., 1996; Rutanen et al., 1997). The use of LNG-IUS also results in the inhibition of angiogenesis (Hague et al., 2002). The doses of LNG found to suppress angiogenesis were based on those found in LNG-IUS-exposed endometrium.

The proportion of amenorrhoeic women increased from 54.4% at 12 cycles to 92.7% at the end of the study. During the first 3 months the amenorrhoea rate was low. These results are consistent with previous reports about the LNG-IUS combined with estrogen in perimenopausal women at 1 year (Andersson and Rybo, 1990) and postmenopausal women over a 5 year period (Suvanto-Luukkonen et al., 1999). However, in this study the early amenorrhoea rate was lower than that reported in postmenopausal studies. Interestingly, replacement of the LNG-IUS during HRT after 5 years induced temporarily a few additional bleeding days (Varila et al., 2001). Menstrual-like bleeding and spotting are commonly experienced during the first few months of treatment using various combinations of continuous estrogen and progestin HRT (Staland, 1981; Mattsson et al., 1982). When sequential HRT is used in postmenopausal women, long-term compliance is relatively low as a result of menstrual-like bleeding (Hahn, 1989). This pattern is often not acceptable to perimenopausal

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**Table II. Experience of menopausal symptoms during study**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Study entry</th>
<th>Cycle 6</th>
<th>Cycle 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Flushing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hot flushes experienced</td>
<td>29</td>
<td>35.4</td>
<td>65</td>
</tr>
<tr>
<td>Nocturnal sweating</td>
<td>27</td>
<td>32.9</td>
<td>66</td>
</tr>
<tr>
<td>Vaginal discomfort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘None’</td>
<td>39</td>
<td>50.0</td>
<td>63</td>
</tr>
<tr>
<td>‘A little’</td>
<td>29</td>
<td>37.2</td>
<td>7</td>
</tr>
<tr>
<td>‘Quite a bit’</td>
<td>8</td>
<td>10.3</td>
<td>4</td>
</tr>
<tr>
<td>‘Extremely’</td>
<td>2</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>Feeling tense/wound up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘None’</td>
<td>7</td>
<td>8.5</td>
<td>–</td>
</tr>
<tr>
<td>‘A little’</td>
<td>27</td>
<td>32.9</td>
<td>–</td>
</tr>
<tr>
<td>‘Quite a bit’</td>
<td>28</td>
<td>34.1</td>
<td>–</td>
</tr>
<tr>
<td>‘Extremely’</td>
<td>20</td>
<td>24.2</td>
<td>–</td>
</tr>
<tr>
<td>Feeling unhappy/depressed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘None’</td>
<td>25</td>
<td>30.5</td>
<td>–</td>
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<tr>
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<td>20</td>
<td>24.2</td>
<td>–</td>
</tr>
<tr>
<td>‘Quite a bit’</td>
<td>27</td>
<td>32.9</td>
<td>–</td>
</tr>
<tr>
<td>‘Extremely’</td>
<td>10</td>
<td>12.2</td>
<td>–</td>
</tr>
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</table>

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**Discussion**

This study shows that the combination of intrauterine levonorgestrel and oral estrogen provides an effective HRT regimen in perimenopausal women, achieving amenorrhoea and a continuation rate at 60 cycles of 79.8%.

The proportion of amenorrhoeic women increased from 54.4% at 12 cycles to 92.7% at the end of the study. During the first 3 months the amenorrhoea rate was low. These results are consistent with previous reports about the LNG-IUS combined with estrogen in perimenopausal women at 1 year (Andersson and Rybo, 1990) and postmenopausal women over a 5 year period (Suvanto-Luukkonen et al., 1999). However, in this study the early amenorrhoea rate was lower than that reported in postmenopausal studies. Interestingly, replacement of the LNG-IUS during HRT after 5 years induced temporarily a few additional bleeding days (Varila et al., 2001). Menstrual-like bleeding and spotting are commonly experienced during the first few months of treatment using various combinations of continuous estrogen and progestin HRT (Staland, 1981; Mattsson et al., 1982). When sequential HRT is used in postmenopausal women, long-term compliance is relatively low as a result of menstrual-like bleeding (Hahn, 1989). This pattern is often not acceptable to perimenopausal
women (Mattsson et al., 1982). Continuous combined estrogen–progestogen therapy was introduced 20 years ago (Staland, 1981) aiming to produce continuous suppression of the endometrium and amenorrhoea. With time, most postmenopausal women using this regimen became amenorrhoeic (Staland, 1981; Magos et al., 1985; Weinstein et al., 1990; Mattsson and Sporrong, 2003; Pickar et al., 2003; Mattsson et al., 2004). The results of our study suggest a more acceptable bleeding pattern, which may be the principal reason for good compliance as evidenced by the high continuation rate at 5 years, in contrast with only 20% of women who continued estrogen replacement after 4 years in a Canadian study (Pilon et al., 2001).

Insertion was assessed as easy in 76.8% of cases. The cervix was not pre-treated with estrogen as in some other studies, and paracervical block was not used routinely. The proportion of easy insertions in this study was close to that found in younger, fertile women (Andersson et al., 1994).

Menopausal symptoms were alleviated markedly a few months into the study and improvement was maintained throughout. The high tolerability ratings and high continuation rate are to be expected for a regimen providing good relief of menopausal symptoms, high rates of amenorrhoea and highly effective low compliance contraception. Many of the study participants had not previously used an intrauterine device, yet satisfaction with the method was high among a population where background use of IUD is low (5% of women aged 16–49 years).

The LNG-IUS offers women who have no fertility goals a highly effective method of contraception that eliminates heavy perimenopausal bleeding and to which can be added estrogen supplementation to relieve vasomotor symptoms with suppression of endometrial proliferation resulting in amenorrhoea. The treatment regimen is well tolerated with an acceptable incidence of adverse effects. This regimen provides an alternative strategy for perimenopausal women with the likelihood of increasing compliance.

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