Gynecological Endocrinology, April 2009; 25(4): 269–275

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healthcare

HORMONE THERAPY

An open-label study of subdermal implants of estradiol-only *versus* subdermal implants of estradiol plus nomegestrol acetate: effects on symptom control, lipid profile and tolerability

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(Received 25 April 2008; accepted 15 October 2008)

Abstract

Objective. To compare the effects of continuous 17-β estradiol-only silastic implants with those of continuous 17-β estradiol plus continuous nomegestrol acetate silastic implants on symptom control, lipid profile and tolerability in postmenopausal women.

Methods. This was an open-label, parallel-group study. Women with and without uterus and no contraindications to hormone therapy (HT) in this study, we consider as HT the replacement of Estrogens-only and Estrogens + Progestogens Therapy, were enrolled. Each subject was assigned to receive four 17-β estradiol-only silastic implants (women without uterus), or four 17-β estradiol plus one nomegestrol acetate silastic implant (women with intact uterus), for 1 year.

Results. A total of 40 subjects were enrolled and received, the silastic implants of which 40 (100.0%) subjects completed the study ($n = 20$, estradiol only; $n = 20$, estradiol plus nomegestrol acetate). The incidence of postmenopausal symptoms decreased significantly. No significant decreases in total cholesterol (1.3%), low-density lipoprotein cholesterol (1.1%), triglycerides (1.2%) and fasting glucose ((1.3%) serum levels were observed in both groups, whereas high-density lipoprotein (HDL) cholesterol increased significantly (2.8%), during the study in both groups. The incidences of adverse events were similar in both treatment groups.

Conclusions. Women treated with 17-β estradiol-only silastic implants or 17-β estradiol plus nomegestrol acetate silastic implants showed significant improvement of postmenopausal symptoms, including urogenital and sexual health symptoms and a significant increase in HDL cholesterol and no significant differences in other lipid profiles and tolerability.

Keywords: *Implant, hormone therapy, symptom control, lipid profile, tolerability*

Introduction

Alterations in lipid metabolism that typically occur during menopause includes increases in concentration of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and decreases in concentrations of high-density lipoprotein (HDL) cholesterol. These alterations substantially increase the risk of cardiovascular morbidity and mortality [1,2].

Unopposed estrogen therapy, however, increases the incidence of endometrial hyperplasia [3–6] and the risk of endometrial carcinoma [7]. Addition of a progestin to estrogen replacement therapy has been shown to reduce this risk to the endometrium [8,9].

Unfortunately, adverse effects of some progestins on the lipid profile have been documented, including reductions in HDL cholesterol concentration [10–13], which suggests that combination therapy could potentially reduce some of the cardiovascular benefits obtained with estrogen alone.

The publication of the first results from the Women's Health Initiative (WHI) in 2002 led to a dramatic headline in the media around the world [14]. The media reports also made much of the first reported tend to increase cardiovascular events with EPT (Estrogens + Progestogens therapy), in contrast to the expected decrease in cardiovascular disease seen in observational studies of women using

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ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.1080/09513590802632480

hormone therapy (HT) around menopause. Few in the media reported the publication from the WHI 1 year later which showed that a significant increase in the cardiovascular events was only seen in women initiating EPT more than 20 years after the menopause and that there was a non-significant decrease in such events (hazard ratio 0.89) when EPT was initiated within 10 years of menopause.

Effects of HT on lipid profile depend on the type of estrogen and progestogens, and the dose and route of administration. Many progestogens affect serum lipoprotein metabolism: those structurally related to testosterone, such as levonorgestrel and norethisterone, may reverse the high-density lipoprotein (HDL)-raising effect of oral estrogens, due mainly to an increase in HDL catabolism [10–13]. In contrast, progestogens such as nomegestrol acetate progesterone and dydrogesterone have little or no effect on serum lipoprotein metabolism [15–19]. Some authors have previously expressed concern about the addition of progestogens to estrogen replacement regimens [20,21], the main problem being the potentially adverse effects of added synthetic progestogens on lipid and lipoprotein metabolism. Although the oral route is the most common form of estrogen replacement therapy in postmenopausal women, parenteral estrogens and estrogens + progestogens replacement therapy offers several theoretical advantages. Perhaps the most important advantage of parenteral over oral estrogens + progestogens replacement therapy is that the former route avoids the first-pass effect. Implants are independent of user's compliance for effectiveness.

To date, there have been no studies comparing the effects of subdermal implants containing 17-β estradiol-only with subdermal implants containing 17-β estradiol plus a progestogen on lipid profiles, postmenopausal symptoms, including urogenital and sexual health symptoms and tolerability. The present study aims to compare the effects of subdermal implants containing estradiol-only on lipid profiles, postmenopausal symptoms, including urogenital and sexual health symptoms, tolerability and to determine the effect of adding a subdermal implant containing nomegestrol acetate. To accomplish this, standard laboratory tests, evaluation of postmenopausal symptoms, including urogenital and sexual health symptoms and tolerability were assessed in each group at the end of months 3, 6, 9 and 12 of therapy.

Methods

This was an open-label study to compare the effects of subdermal silastic implants containing estradiol-only with those of subdermal silastic implants containing estradiol plus a subdermal silastic implant containing nomegestrol acetate on symptom control, bleeding patterns, lipid profile and tolerability in postmenopausal women. The protocol was approved by the ethic committee and informed consent was obtained from patients prior to enrollment. The study center was specialised menopause service located in University hospital.

Subjects

Generally healthy postmenopausal women between the ages of 45 and 65 years with and without intact uterus were recruited if they had: undergone a natural menopause at least 6 months prior to the screening evaluation; an absence of endometrial hyperplasia; serum follicle stimulating hormone (FSH) > 40 IU/I; and an average of four or more hot flushes daily during the pre-study evaluation. Subjects were excluded for the following reasons: history or presence of clinically significant physical disease; undiagnosed vaginal bleeding; hypertension; obesity; excessive smoking; alcohol or drug abuse; Pap smear class III or greater; use of estrogens, progestogens, androgens, tibolone or lipid-lowering agents within 90 days of the screening evaluation; and known sensitivity to an investigational or a related drug.

Medication

Eligible subjects were assigned to receive four 17-β estradiol-only silastic implants (women without uterus), that release $\sim$100 μg daily in the first 5 months and 80 μg in the last 7 months, or four 17-β estradiol plus one nomegestrol acetate silastic implant (women with intact uterus), for 1 year. Nomegestrol acetate implant releases $\sim$100 μg daily during the first 3 months of use. This rate declines to 70 μg daily during the last 9 months of use.

Implants were handmade using segments of surgical-grade, semipermeable Silastic® tubing (Technical Products, Decatur, GA), steam-sterilised in an autoclave at 121°C for 10 min and allowed to dry inside the autoclave for a further 10 min. Implants were submitted to microbiological and endotoxin control. Concomitant medication (other than oral vitamins, calcium and antihypertensive drugs) was allowed for the treatment of intercurrent medical conditions at the discretion of the investigator. Prior established regimens other than those that could interfere with the study evaluation were also permitted.

Assessments

Prior to the initiation of treatment, patients underwent a screening visit assessment that included a complete medical and gynecological history, physical and gynecological examinations, vital signs, standard laboratory tests, serum FSH and estradiol, and

endometrial biopsy (women with intact uterus). A pretreatment diary card was maintained for at least 14 but no more than 21 days prior to study entry to record the number and severity of hot flushes, the presence and severity of other menopausal symptoms (headache, dizziness, palpitations, body aches and pains, weakness, tiredness, sleep interruptions, insomnia, night sweats, paresthesia, irritability, nervousness, depressed mood, crying spells and loss of concentration), urogenital symptoms (vaginal dryness and painful intercourse), sexual health symptoms (decreased sexual interest and frequency of sexual intercourse episodes) and bleeding. A total score of hot flushes for each subject in each month was calculated as the sum of the mean number of hot flushes per day multiplied by the respective score (1 = mild, 2 = moderate, 3 = severe). Regarding the other symptoms, the intensity was scored as absent (0), mild (1), moderate (2) or severe (3).

During the study, subjects were seen for follow-up visits at the end of months 3, 6, 9 and 12. Subjects maintained diary cards throughout the study to record hot flushes, other menopausal symptoms, sexual activity and bleeding patterns (women with intact uterus). Fasting glucose and plasma levels of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were obtained at baseline and months 6 and 12. Safety evaluations included the recording of adverse events, vital signs and weight. Physical and gynecological examinations, laboratory tests and an endometrial biopsy were performed at baseline and month 12.

Statistical analysis

Statistical tests were two-sided and significance was accepted at $p < 0.05$. To evaluate baseline equivalence of the two groups, the χ^2 test and Fisher's exact test were used to compare the distribution of nominal attributes, Student's *t*-test for ordinal attributes with normal distribution, and the non-parametric Mann–Whitney test for ordinal attributes without normal distribution.

Significant changes over time in the number of hot flushes and frequency of sexual intercourse episodes within each group were evaluated using Student's *t*-test for paired observations, and the groups were compared by Student's *t*-test for independent observations. Other postmenopausal symptoms were evaluated within each group by the Wilcoxon signed ranks test, and the groups were compared using the Mann–Whitney test. Incidences of urogenital symptoms (vaginal dryness, painful intercourse) and sexual health variables (decreased sexual interest) were evaluated within each group by the McNemar test, and between groups by the χ^2 test. Significant changes over time in weight, vital signs and laboratory values within each group were evaluated using Student's *t*-test for paired observations, and the groups were compared using Student's *t*-test for independent observations. Comparison between groups with respect to adverse events was performed using the χ^2 or Fisher's exact test.

Results

A total of 40 subjects were enrolled and received four 17-β estradiol-only silastic implants or four 17-β estradiol silastic implants plus one nomegestrol acetate silastic implant of which 40 (100.0%) subjects completed the study ($n = 20$, four 17-β estradiol-only silastic implants; $n = 20$, four 17-β estradiol silastic implants plus one nomegestrol acetate silastic implant). Baseline demographic and clinical characteristics were similar in both treatment groups (Table I).

Vasomotor symptom control

The intensity (Figure 1) and mean number of hot flushes decreased significantly, compared with baseline, in both treatment groups over time, indicative of improvement. No significant differences were observed between treatment groups in the relief of hot flushes. Both treatment groups reported a significant decrease in the incidence of other postmenopausal symptoms (headaches, dizziness, palpitations, body aches and pains, sleep interruptions, night sweatness, tiredness, insomnia, paresthesia, depressed mood, irritability, nervousness and loss of concentration) over time. Although significant differences from baseline and also between treatment groups were observed at a few cycles for a few symptoms, no consistent or clinically significant trends were observed.

Urogenital symptom control

Regarding urogenital symptoms (Figure 2), vaginal dryness decreased significantly over time, compared

Table I. Baseline demographic and clinical characteristics.

Characteristic	Estradiol only ($n = 20$)	Estradiol + progestogen ($n = 20$)
Mean age (years)	53.2	51.1
Mean weight (kg)	61.5	60.5
Height (m)	1.56	1.57
Time since last menstrual period (years)	5.23	4.14
Sexual activity (*n* (%))		
No	8 (40.0)	6 (30.0)
Yes	12 (60.0)	14 (70.0)
Frequency of sexual activity per month (*n* (%))		
1–3	6 (50.0)	8 (57.1)
4–5	4 (33.3)	4 (28.6)
8	2 (16.6)	1 (7.1)
16	0 (0.0)	1 (7.1)

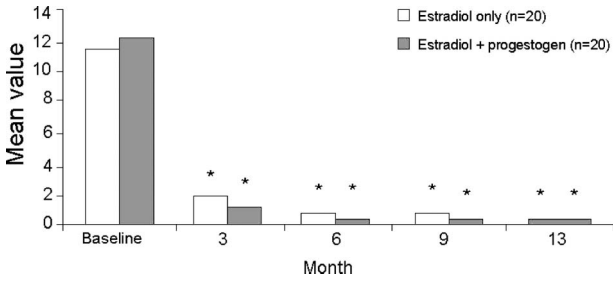

Figure 1. Total score of hot flushes calculated as sum of mean number of hot flushes per day multiplied by respective score (1 = mild, 2 = moderate, 3 = severe). *Significantly different from baseline; Estradiol only; estradiol plus nomegestrol acetate silastic implants.

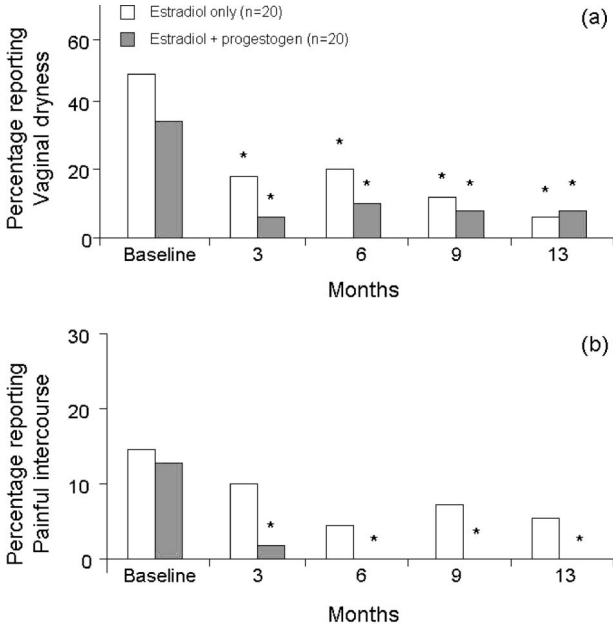

Figure 2. Incidence of urogenital symptoms: (a) vaginal dryness, (b) painful intercourse. *Significantly different from baseline; estradiol only; estradiol plus nomegestrol acetate silastic implants.

with baseline, in both treatment groups. At month 1, vaginal dryness was significantly lower in the 17-β estradiol-only silastic implants group. Painful intercourse decreased significantly from baseline at all months in both groups.

Sexual health symptom control

Two sexual health variables (Figure 3) were evaluated (decreased sexual interest and frequency of sexual intercourse episodes). Decreased sexual interest improved significantly over time, compared with baseline, in both treatment groups, and no significant differences were observed between treatment groups. The frequency (mean number/month) of sexual intercourse episodes remained unchanged in the 17-β estradiol-only silastic implants group at every month, compared with baseline, and increased

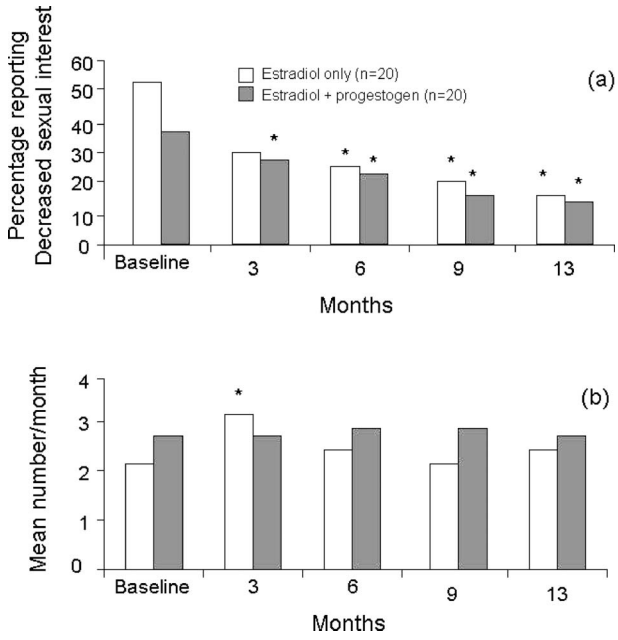

Figure 3. Sexual health variables; (a) decreased sexual interest, (b) frequency of sexual intercourse episodes. *Significantly different from baseline; estradiol only; estradiol plus nomegestrol acetate silastic implants.

significantly at 1–3 and remained unchanged thereafter in the 17-β estradiol silastic implants plus one nomegestrol acetate silastic implant group, compared with baseline.

Bleeding patterns

The bleeding patterns were analysed in those women with an intact uterus. The bleeding episodes were characterised by spotting or mild bleeding, and the duration of bleeding episodes was most commonly 1–3 days in duration.

Lipid profile

No significant decreases in total cholesterol (1.3%), LDL cholesterol (1.1%), triglycerides (1.2%) and fasting glucose (−1.3%) serum levels were observed during the study, compared with baseline in both groups, whereas HDL cholesterol increased significantly (2.8%), during the study in both groups (Table II).

Weight gain

No significant difference in the mean weight gain from baseline to month 12 was observed between the treatment groups (0.96 kg *vs.* 1.02 kg increase in the groups, 17-β estradiol-only silastic implants group and 17-β estradiol silastic implants plus one nomegestrol acetate silastic implant group, respectively).

Table II. Comparison of continuous 17-β estradiol-only silastic implants with those of continuous 17-β estradiol plus continuous nomegestrol acetate silastic implants.

	Estradiol only ($n = 20$)	Estradiol + progestogen ($n = 20$)
Glucose (mg/dL)	87.7 $\pm$ 0.7 (-1.24)	89.5 $\pm$ 18.8 (-1.30)
Total cholesterol (mg/dL)	194.9 $\pm$ 40.8 (-1.3)	199.4 $\pm$ 46.1 (-1.2)
HDL cholesterol (mg/dL)	50.1 $\pm$ 12.1 ($+2.8$)	49.8 $\pm$ 12.7 ($+2.79$)
LDL cholesterol (mg/dL)	123.8 $\pm$ 41.8 (0.9)	128.6 $\pm$ 50.8 (0.7)
Triglycerides (mg/dL)	105.1 $\pm$ 54.5 (-1.19)	113.9 $\pm$ 47.5 (-1.2)

Effects on fasting serum glucose and lipoprotein levels in 40 postmenopausal women. Values are expressed as mean $\pm$ SD at month 12 (mean percentage change from baseline to month 12).

Tolerability

No significant difference between treatment groups regarding the incidence of adverse events was observed. No clinically significant changes in vital signs or laboratory values were observed in either treatment group, and no significant difference between treatment groups with respect to the incidence of abnormalities at month 12 was reported. In the 17-β estradiol silastic implants plus one nomegestrol acetate silastic implant group, two patients presented abnormalities as follows: mastodynia ($n = 1$) and hyperemic vagina ($n = 1$).

Compliance with study medication was similar, and high during the entire treatment study.

Discussion

The introduction of subdermal implants represents a milestone in the continued research effort on delivery systems to ensure sustained release of steroids at low, stable concentrations for years without compromising effectiveness and safety.

Implants are independent of user's compliance for effectiveness. Although the oral route is the most common form of estrogen replacement therapy in postmenopausal women, parenteral estrogens and estrogens + progestogens replacement therapy offers several theoretical advantages. Perhaps the most important advantage of parenteral over oral estrogens + progestogens replacement therapy is that the former route avoids the first-pass effect.

In this study, both treatment therapies significantly reduced hot flushes, as well as urogenital and sexual health symptoms. Statistically significant differences ($p < 0.05$) were detected between groups regarding some of the postmenopausal symptoms (other than hot flushes) at different months, but these differences did not persist across all months or show any specific pattern to denote major clinical significance. Findings from the present study regarding the relief of vasomotor and central nervous system-related symptoms are consistent with the well-documented literature for oral combined HT [22–25].

Both treatment groups showed improvement of urogenital symptoms (vaginal dryness and painful intercourse). The incidence of vaginal dryness decreased significantly over time, compared with baseline, in both treatment groups.

Similarly, both treatments were effective in improving sexual interest over time, compared with baseline, with no significant difference between groups at any treatment month (despite the observation that a higher proportion of women in the estradiol-only group were more symptomatic at baseline, compared with those in the estrogen + progestogen group). These findings regarding improved libido are supported by the published literature for oral combined HT [26–30].

Although the present study did not utilise the McCoy Sex Scale, the findings are consistent with those of numerous other published studies that have documented a strong correlation between improved libido and relief of vaginal dryness and painful intercourse, two physical factors that may affect sexual health [26–29]. Furthermore, it is counter-intuitive to believe that diminished libido can significantly improve in a population of women still experiencing notable vaginal dryness or painful intercourse. Studies have consistently shown that other estrogen/progestin combinations are effective in relieving both of these symptoms [26,27,31] and, not surprisingly, these HT regimens have also been shown to improve libido and other sexual health parameters significantly over time, with no significant differences from each group provided that the severity of baseline sexual health parameters is comparable between treatment groups [26].

The mean number of sexual intercourse episodes increased significantly in the estrogen + progestogen group during the first 3 months of therapy, but did not persist beyond month 3, and no change in the mean number of episodes was reported at any month in the estrogen-only group. This finding is not surprising, because other important factors must be taken into account when evaluating frequency of intercourse that were not included in the design of the present study, such as availability of a partner and physical, psychological and sexual health of the partner, as well as individual sexual fantasies, enjoyment and frequency of orgasms. Although this is a limitation for further conclusions, differences between groups regarding those factors, if present, did not seem to have any major influence on the final outcome.

The present bleeding results are also consistent with the published literature regarding the incidence, characteristics and duration of breakthrough bleeding episodes among women taking oral HT regimens

[22–24,32]. Likewise, bleeding episodes were generally characterised as spotting or mild bleeding with a duration most commonly of 1–3 days.

The lipid profiles of both treatment groups from this study are consistent with the well-documented literature regarding the effects of estradiol gel and estradiol delivering patch on serum lipids [33–35]. Considering all of the lipid parameters evaluated, estradiol-only and estradiol plus nomegestrol acetate implants promoted favourable changes in lipid profile, and the addition of nomegestrol acetate did not appear to mitigate the favourable impact of the estradiol on the overall lipid profile.

This study has demonstrated that both therapies are neither associated with a significant weight gain, regardless of the duration of therapy, nor this is a reason for premature discontinuation.

Both treatment groups had acceptable safety profiles, with no clinically significant changes in vital signs or laboratory results. One woman in the estradiol + progestogen treatment group showed endometrial hyperplasia without atypia at the month 12 endometrial biopsy. The small number of women treated in the present study, however, and the isolated occurrence of one case of hyperplasia, do not permit further conclusions about inadequacy of the progestin dose.

The results of the present study are in accordance with those of previous publications and the biological rationale of the study drugs evaluated. Both treatments showed significant improvement of menopausal vasomotor symptoms, urogenital symptoms and decreased libido, with no persistent significant differences between treatment groups. The facts that the present study had no placebo group and was open-label are limitations, although lipid results were certainly unaffected by these, and more subjective aspects, such as libido, demonstrated more similar results in both groups than might have been expected. HT is a first-choice treatment for the improvement of postmenopausal symptoms and protection against osteoporosis.

Acknowledgement

Financial support from Rockefeller Foundation under the South-to-South Programme is gratefully acknowledged.

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