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MENOPAUSAL TRANSITION

Potential health benefits of continuous LNG-IUS combined with parenteral ERT for seamless menopausal transition and beyond – a commentary based on clinical experience

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Abstract

Objective: To comment on the acceptability and potential health benefits of the continuous use of the levonorgestrel-releasing intrauterine system (LNG-IUS), combined with estrogen substitution, for seamless transition through the menopause, in women with climacteric symptoms.
Design and method: Evaluation of the recent hormone replacement therapy literature and the acceptability of the combined parenteral estrogen and intrauterine LNG-IUS regimen in a group of approximately 100 women, above 48 years of age, using LNG-IUS for contraception, who developed climacteric symptoms requiring estrogen substitution. Main outcome measures: acceptability and continued use of the method for the treatment of climacteric symptoms and for prevention.
Results: The combination of intrauterine progestogen delivery to suppress the endometrium, in combination with systemic estrogen, is highly acceptable resulting in a high continuation of use due to the absence of side effects and erratic bleeding in the large majority of women.
Conclusion: The study suggests that parenteral estrogen replacement therapy combined with intrauterine progestogen delivery for endometrial suppression in the perimenopause is highly practical and beneficial, providing enhanced quality of life. There are strong arguments to categorize the regimen as probably the most effective, safest and best accepted route resulting in high patient compliance as well as potentially providing maximal benefits for peri- and postmenopausal women.

Keywords

Hormone replacement therapy, menopause, uterus

History

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Introduction

Data from observational studies, conducted in the 1990s, suggested protective effects of hormone replacement therapy (HRT) on chronic diseases such as coronary heart disease (CHD), osteoporosis, colorectal cancer and dementia. Studies suggested significant reduced risk of coronary events and repeat events [1]. Oral estrogen replacement therapy (ERT) was found to slow the progression of atherosclerosis [2] and even to improve the skin texture [3]. Other population-based studies noted benefits of estrogen on peripheral arterial diseases [4]. Sherwin et al. found consistent evidence from epidemiological studies conducted in the late 1990s that ERT significantly reduces the risk of Alzheimer's disease (AD) [5]. Interestingly, this author suggested that the immediate postmenopausal period may constitute a critical window for treatment with ERT that maximizes its potential to protect against cognitive decline with aging and/or to reduce the risk of AD. Other studies also found protection against AD and commented that ERT may delay the onset and decrease the risk of AD [6,7]. The use of ERT should however be relatively long.

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However, surprisingly, the Women's Health Initiative (WHI) study, published in 2002 [8] sought to evaluate the risks and benefits for women taking estrogen (E) and progestogen (P) in combination, and E only, and the Million Women Study published in 2003 (MWS) [9], showed an increase in breast cancer, cardiovascular disease and venous thromboembolic events among postmenopausal HRT users. Major criticism followed the publication of the WHI study results as the WHI study was conducted in women with an average age of 66 years that were at least 13 years after menopause, which is usually not the age women consult for climacteric symptoms.

It was later found that the increase in breast cancer was not present in long-term users of ''estrogen-only'' therapy (a slight increase was seen in the MWS) [10]. Other studies such as the Swedish Cohort Study [11] concluded that the increased incidence of breast cancer was attributed to the progestogen component of the HRT regimen and indicated the need for the development of safer progestogens and alternative routes of administration to avoid adverse effects. It has been known for some time that progestogens can compromise the cardioprotective effect of estrogens [12]. It was therefore suggested, that for women with uterus, intrauterine systems, which deliver a progestogen direct to the uterus, should be developed.

Recently, several remarkable papers were published indicating the benefits of ERT (and adverse effects of systemic progestogen) as described in the earlier observational studies. An extended

follow-up of the WHI trial, published in the *Lancet Oncology*, evaluated the impact of estrogen-only therapy on breast cancer against placebo, and found a 23% reduction in the incidence of breast cancer [13].

A 10-year randomized trial conducted in 1006 women between 45 and 58 years of age receiving HRT early after menopause had a significantly reduced risk of mortality, heart failure and myocardial infarction without any apparent increased risk of breast cancer, venous thromboembolism or stroke [14].

Other studies found that by circumventing the first-pass liver metabolism of estrogens, using transdermal estrogen administration, a significantly lower risk of venous thromboembolism (VTE) may occur when compared with oral ERT. This suggested that parenteral ERT may be safer [15].

Two important conclusions could be made, on the basis of the recent literature, regarding the most probable optimal HRT regimen, as this regimen would result in less risk (e.g. cardiovascular, breast cancer, VTE) for women. First, the timing of initiation of HRT: in clinical trials, early initiation and prolonged HRT did not result in an increased risk of breast cancer and stroke [13]. Second, the use of systemic progestogen: because of the impact of the hormone on breast and other organ tissues, systemic progestogen administration should probably be avoided [16,17]. An intrauterine progestogen or progesterone-releasing system may be safer and result in less side effects [18].

In their recent article, Herman Depypere and co-authors assessed the use of LNG-IUS from contraception to HRT through the so-called transitional phase [19]. They stressed the importance of seamless transition by adding estrogen in women requesting relief of climacteric symptoms to enhance the quality of life of women. They concluded that the results indicate that continuing with the LNG-IUS from contraception to ERT has no adverse effect on the vaginal bleeding profile, and that the combination of estrogen with LNG-IUS shows a positive effect on quality of life.

The current report provides further clinical evidence on the long-term experience of continuous parenteral ERT combined with intrauterine levonorgestrel administration using an intrauterine system and provides further comments as to the health benefits of the LNG-IUS alone or combined with estrogen replacement, in the transitional phase of life of women and beyond.

Design and method

The recent relevant literature was evaluated with the aim to find arguments, which we thought could support our thesis that the combined parenteral estrogen supplementation with intrauterine hormonal suppression of the endometrium, in women with uterus, could potentially be the most acceptable and safest regimen for women providing high adherence and, therefore, a high preventive potential.

Of the 440 women who participated in a long-term contraceptive study with the Femilis® LNG-IUS (Contrel Drug Delivery Research, Ghent, Belgium) (Figure 1) which started in 2002, 212 women exceeding 48 years of age were selected for the current evaluation.

From this group of perimenopausal women, 102 were symptomatic and received percutaneous 17 β-estradiol, 1.5 mg daily (Oestrogel®, Besins International, Brussels, Belgium), or an equivalent dose by patch or orally, on a continuous basis (Figure 2). The T-shaped LNG-IUS remained *in situ* to prevent hyperplasia. Women continued to be followed-up on a yearly basis.

Prior to prescribing ERT, women were thoroughly informed about the immediate and long-term health benefits and potential risks of the combined regimen.

Figure 1. Femilis LNG-IUS.

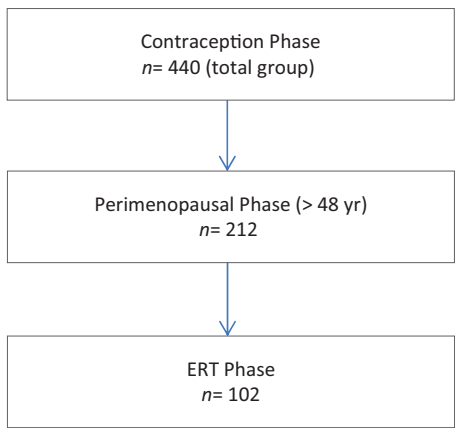

Figure 2. Flowchart of the study.

Table 1. Patient characteristics (age) ($n = 102$ perimenopausal/menopausal women in ERT phase) and duration of use.

	Age (years)	Duration of use (months)
Average	57	83
Range	48–67	22–122

Results

The average age of women in the ERT phase was 57 years (range 48–67) and the average duration of use of the regimen was 83 months (range 22–122) (Table 1).

Of the 102 women included in this ERT phase, all women are continuing to use the combined regimen. 97.09% of women were in amenorrhea at the time of analysis. Only 2.91% (3/102) had still some slight bleeding as they approached menopause. No significant adverse experiences, related to the regimen, were recorded.

Discussion

The climacteric symptoms, particularly hot flushes, night sweats, sleeping disturbances and depressive moods elicited by the decline in circulating estrogens, can cause considerable distress to women. These are usually more severe in perimenopausal than postmenopausal women. Up to 85% of perimenopausal women report suffering from vasomotor symptoms and their well-being is negatively correlated to the frequency of hot flushes [20]. The primary results of the early estrogen prevention trial (KEEPS),

recently presented at the Annual meeting of the North American Menopause Society, that focused on quality-of-life parameters, showed favorable effects of hormone therapy [21]. The trial tested two different types of estrogen compared with placebo: a low-dose oral conjugated estrogen at a dose of 0.45 mg/d, and a transdermal estradiol patch at a dose of 50 μg/d. Both forms of estrogen were taken with cyclic micronized progesterone (Prometrium®, Abbott Laboratories, Abbott Park, IL, USA) for 12 days per month. The trial was, however, not large enough to assess effects on clinical outcomes, such as heart attacks and strokes.

The perimenopause is the period of physiological change surrounding the final menstruation in women's life and is characterized by a decline in ovarian function and estrogen/progesterone deficiency symptoms, including vasomotor symptoms and menstrual bleeding disorders. The postmenopause follows the perimenopause and starts 12 months after the last menstrual period. The ovarian function during the perimenopausal phase is not absent as it is mostly in the postmenopause. This decline is unpredictable in time and has been estimated to occur approximately 2–8 years before menopause. The use of LNG-IUS during this period is highly beneficial as up to 90% of women may experience menstrual changes during the transition to menopause [22]. Abnormal uterine bleeding is the most frequent gynecological complaint in the perimenopause and the incidence increases as women approach menopause [23]. Heavy menstrual bleeding occurs frequently. The bleeding is often menorrhagic and is, therefore, an important reason for hysterectomy in the perimenopause [24]. Heavy bleeding is caused by dysfunction of the corpus luteum in approximately half of perimenopausal women as no significant uterine pathology could be demonstrated in 50% among them [25]. Consequently, there is a risk for endometrial hyperplasia and endometrial cancer due to the decline in luteal phase progesterone excretion. Although, there is a reduced frequency of ovulation in the perimenopause, contraception is still necessary. Unplanned pregnancies and induced abortions are frequent in women over the age of 40 and are second only to unintented pregnancies in adolescents in the USA [26].

Various regimens for hormone substitution are available. One of the major problems with combined oral estrogen/progestogen HRT is progestogen/progesterone-induced premenstrual tension (e.g. mood changes, headache, sleepiness, mastalgia, nausea) [27]. Also metabolic changes can occur, as evidenced in the WHI study. Progestogens have an essentially anti-estrogenic effect and can potentially counteract the beneficial effects of co-administered estrogens. This is a major concern as the cardioprotective action of estrogens on the arterial physiology, preventing ischemic events, and on the lipid and lipoprotein profile, could be adversely altered by progestogens in a dose and duration-dependent manner [28,29]. Natural progesterone does not produce the same unacceptable metabolic profile as synthetic progestogens. Micronized progesterone does not appear to affect carbohydrate metabolism, liver function or clotting mechanism [30]. However, the manufacturer warns for certain serious and less serious side effects (e.g. changes in vision and speech, sudden severe headaches and pains in chest and legs, weakness and fatigue) [31]. Women using systemic E/P HRT continue to have regular withdrawal periods, which is not acceptable to many among them.

The most obvious approach, therefore, at least from a physiological point of view, seems to release the progestogen locally in the uterine cavity. This is logical since the major reason for progestogen use in non-hysterectomised women is for endometrial protection against estrogenic hyperstimulation. Intrauterine-administered progestogen, such as levonorgestrel, delivered to the target cells of the endometrium has a profound suppressive effect on endometrial growth rendering the endometrium inactive and, simultaneously eliminates uterine bleeding. The advantage of this route of administration could be even more important as it was recently hypothesized by Horwitz and Sartorius that systemic progestogens could reactivate dormant breast tumors by inducing progesterone receptors [32]. Women who develop breast cancer while on conventional systemic HRT could have undiagnosed breast cancer before the start of HRT, and the progestogen component could activate inactive breast cancer stem cells. Once reactivated, estrogen could expand the tumor cells.

The use of the levonorgestrel-releasing intrauterine system does not appear to be associated with an increased risk of breast cancer, seemingly similar to the absence of adverse breast effects in women using estrogen-only therapy [18]. It could be argued that women who are predisposed for breast cancer should be excluded from systemic HRT. Horwitz et al. recommend local progestogen delivery in these women as the locally delivered hormones could provide the desired protective effect in the uterus without their possible harmful effects in the breast. Given the above arguments, the advantage of this route of administration could therefore be substantial.

In addition to the beneficial effects of ERT on the cardiovascular system, recent studies also recognize preventive effects of ERT on Alzheimer's disease if taken during the critical window near the menopause, as suggested by Sherwin many years ago [5]. A recent update of the Cache County Study suggests that hormone therapy may have neuroprotective effects that depend on when the therapy is initiated and if ERT is opposed by progestogens or not [33]. The WHIMS trial found a higher risk of AD with opposed ERT [34]. Women were also much older. Maki et al. suggest that the initiation of hormone therapy early in the perimenopausal or postmenopausal stage might confer benefit to verbal memory and the neural systems underlying memory, whereas late-life initiation confers no benefit or harm, particularly if the progestogen is given locally through an IUD to mimic estrogen-only therapy (personal communication) [35]. Regarding the neuroprotective effect of ERT it appears that the timing, route of administration of the progestogen component and the duration of ERT may be essential. To obtain this effect, adherence and consistent use of the regimen are essential.

Continuation of use, however, seems to be difficult for many women and, therefore, the regimen proposed here may offer significant advantages. Indeed, a high number of women will not continue the use of the orally administered treatment regimens necessary to derive long-term health benefits. As low as 40% or less of women taking oral HRT will continue it for more than a year [36–39]. Re-initiation of bleeding, breakthrough bleeding and hormonal side effects, caused by systemic progestogen absorption, are usually the reason for discontinuing the therapy. These women could be offered a non-systemic progestogen method, with the concomitant advantage of providing contraception and effective treatment of erratic or heavy bleeding. Hormonal side effects and abnormal bleeding are the most important symptoms to avoid as they will determine if the woman will continue the method or not. With conventional estrogen/progestogen combinations, sequential or continuous combined regimens, the likelihood of continuous or erratic breakthrough bleeding has been reported to be as high as 64% and is the major reason to discontinue the method in over 30% of women [36].

The current study confirms that continuous combined regimen with intrauterine progestogen delivery leads to an optimal patient compliance as the abovementioned factors are fully dealt with. These privileged women will then be able to receive the full impact of HRT's preventive health benefits.

Strengths and weaknesses of the parental ERT + LNG-IUS regimen

This commentary is based on clinical research in many hundreds of peri- and postmenopausal women since 1997. These studies were conducted with parenteral estradiol combined with an intrauterine levonorgestrel-system releasing 14 or 20 μ/d. The current study highlights the possibility for women to pass through an often difficult phase in life using a regimen that can enhance quality in life as well as provide additional health benefits. An opportunity that too many women neglect because of misinformation by the media and even by their health care provider or pharmacist. Up to this day, the majority of women starting to use the combined parenteral-intrauterine regimen at the time of menopause continue to use it, suggesting the high acceptability of the regimen. As they have taken the regimen continuously for many years, ignoring the media upheaval surrounding the publication of the WHI study, they constitute a highly interesting group for further study. The weaknesses of the regimen are few and relate to the insertion of the intrauterine system which can sometimes be painful in sensitive women. Premedication and counseling is therefore recommended.

Conclusion

The study suggests that continuous parenteral ERT combined with intrauterine progestogen delivery for endometrial suppression in the perimenopause is highly practical and beneficial, providing enhanced quality of life, as it combines the benefits of prevention of endometrial proliferation and treatment of menorrhagia and hyperplasia, if present, together with a suppression of climacteric symptoms. In addition, the contraceptive effect of locally administered LNG is highly desirable as many perimenopausal women run considerable risk of unintended pregnancy. The review of the recent literature suggests that there are strong arguments to categorize the combined systemic/parenteral estrogen and intrauterine progestogen or progesterone administration as probably the most effective, safest and best accepted route resulting in high patient compliance as well as potentially providing maximal benefits for peri- and postmenopausal women.

Declaration of interest

Dirk Wildemeersch, MD, PhD, is head of research at Contrel Drug Delivery Research, an organization involved in devising controlled release systems for contraception and gynecological treatment.

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