Estradiol and Follicle-stimulating Hormone Levels in Oophorectomized Women using Vaginal Estrogen

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Abstract

To assess the changing estradiol (E_2) and follicle-stimulating hormone (FSH) level in oophorectomized women using vaginal estrogen. Serum estradiol and FSH were evaluated in 32 oophorectomized women using a daily dose of 2 g base of 1.25 mg vaginal conjugated equine estrogen (CEE) cream. The blood sample for hormone assay was collected 8-10 hours from the time of vaginal application. E_2 and FSH levels were measured in the serum sample before and after commencing the study at 4, 8 and 12 weeks using the time-resolved fluoroimmunoassay method. Serum estradiol significantly increased from baseline value at 4, 8 and 12 weeks. (Mean$\pm$SD of E_2 value at 0, 4, 8, 12 weeks : 9.97$\pm$12.13, 249.83$\pm$170.46, 299.38$\pm$190.65, 322.82$\pm$218.31 pmol/L, respectively, $P<0.05$) On the other hand, serum FSH significantly decreased from baseline value at 4, 8 and 12 weeks. (Mean$\pm$SD of FSH value at 0, 4, 8, 12 weeks : 77.64$\pm$27.24, 40.33$\pm$21.64, 38.84$\pm$22.33, 30.90$\pm$24.32 IU/L, respectively, $P<0.05$) In conclusion, a daily dose of 2 g vaginal CEE cream raised the serum estradiol level close to the normal level in the follicular phase of the normal menstrual cycle. However, even though FSH significantly decreased it did not reach the premenopausal level.

It is well accepted that estrogen relieves the symptoms of menopause and protects against osteoporosis, and numerous epidemiologic studies indicate a significant cardioprotective effect[1]. At present, the major useful forms of estrogen therapy are oral and parenteral administration in which the former is more popular in Thailand. Vaginal estrogen cream is one of the specific types of parenteral administration, in which the first-pass effect through the liver is avoided[2]. Even though it is mainly used for treatment of vaginal atrophy, it can also be absorbed into the systemic circulation[2]. However, there is paucity of studies regarding serum estrogen level after use of vaginal conjugated estrogen in oophorectomized women particularly in South East Asian countries which are

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different in population characteristics from women in the West. Hence, the aim of our study was to assess the changing serum level of estradiol and follicle-stimulating hormone in Thai surgically castrated women receiving vaginal conjugated equine estrogen.

MATERIAL AND METHOD

This study was conducted between August 1995 and May 1996 at the menopause clinic, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University. We obtained approval from our Institutional Review Board of Ethical Committee and all participants provided written informed consent before enrollment.

Thirty two oophorectomized women between the age of 40 and 60 were recruited for the study. All patients were in good health and had not been on any hormone therapy for the previous three months. Candidates were excluded from participation if they had a history of the following : breast cancer, endometrial cancer, thromboembolic disease or liver disease. The study took place over 12 weeks. Estradiol (E_2) and follicle-stimulating hormone (FSH) were measured in the serum samples before and after commencing the study at 4, 8 and 12 weeks using the time-resolved fluoroimmunoassay (FIA) method. These were measured by a direct solid phase FIA using commercially available reagents with a sensitivity of FSH and E_2 = 0.05 IU/L and 20 pmol/L respectively. Interassay coefficient of variation for an intermediate serum pool was 3.89 per cent for E_2 and 2.92 per cent for FSH. Average interassay coefficient of variation for all assays was less than 5 per cent. Intra-assay coefficient of variation for an intermediate serum pool was 3.73 per cent for E_2 and 2.15 per cent for FSH. All reagents were from Wallac Oy, Turku, Finland. After baseline measurement of serum hormones, all patients were instructed to use vaginal conjugated equine estrogen (CEE) cream (Premarin cream, Wyeth-Ayerst) applying vaginally with vaginal applicator. The commercially available applicators are marked to dispense 1-4 g of cream (i.e., 0.625-2.5 mg of CEE). Therefore, for the purposes of dispensing 1.25 mg doses, the applicators were calibrated and marked to dispense 2 g of cream. This dose was self-administered by the patient daily at bedtime (10.00-12.00 pm.) Peripheral venous blood from an antecubital vein was collected into heparinized tubes at 8.00 am the following morning. All blood samples were centrifuged and the plasma was withdrawn and stored at -20°C until analyzed. The patients was contacted by telephone before each visit to monitor compliance and adverse effects.

Premarin contains conjugated equine estrogen extracted from the urine of pregnant mares. The preparation consists of 50 to 58 per cent sodium estrone sulphate, 25 to 35 per cent of sodium equilin sulphate and other equine estrogens in smaller amounts.

Pretreatment and posttreatment findings were compared. Each patient served as her own control. Analysis of variance and paired *t*-test was used to examine the difference in pre- and posttreatment hormone level as appropriate.

RESULT

The characteristics of the studied population are shown in Table 1. Serum level of E_2 and FSH at 0, 4, 8 and 12 weeks is illustrated in Fig. 1-2. The results revealed that after daily use of 1.25 mg vaginal CEE cream, serum E_2 significantly increased from baseline value at week 4, 8 and 12. ($P<0.0001$) Though, there was no statistically significant difference of the serum value between week 4, 8 and 12 ($P>0.05$). On the other hand, FSH level significantly decreased from baseline value at week 4, 8 and 12 ($P<0.0001$). However, FSH level continued to decrease at week 8 and 12 with statistically significant difference between week 4-12 and 8-12 ($P<0.05$).

DISCUSSION

In this study, we recruited only those women who underwent hysterectomy and bilateral oophorectomy to lessen the confounding factors

Table 1. Characteristics of the studied population (N=32).

Characters	Mean±SD	Range
Age (years)	47.91±4.66	40-60
BW (kg)	54.38±9.27	31-75
Height (cm)	154.34±6.63	138-175
BMI	22.68±2.69	16.28-24.97
Parity	1.94±1.68	0-6
TSM (months)	13.00±10.52	1-37

BW = Body weight, BMI = Body mass index
TSM = Time since menopause

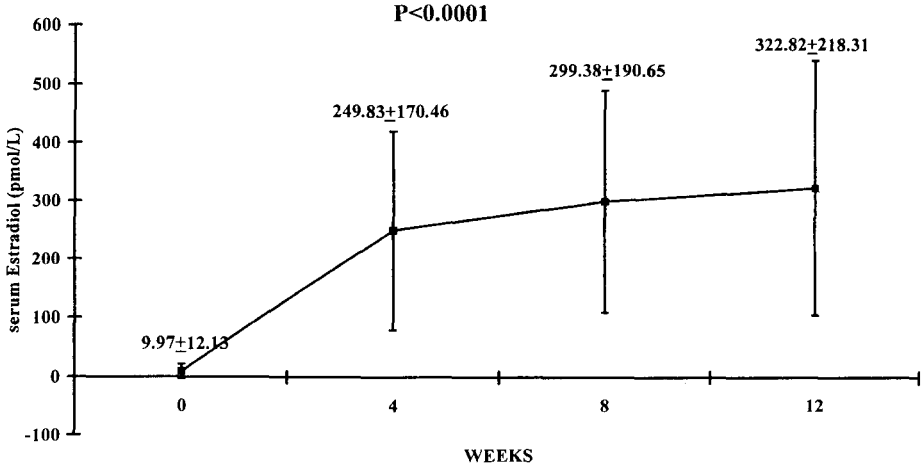

Fig. 1. Serum estradiol level at week 0 (baseline value) and week 4, 8 and 12 after commencing vaginal conjugated equine estrogens.

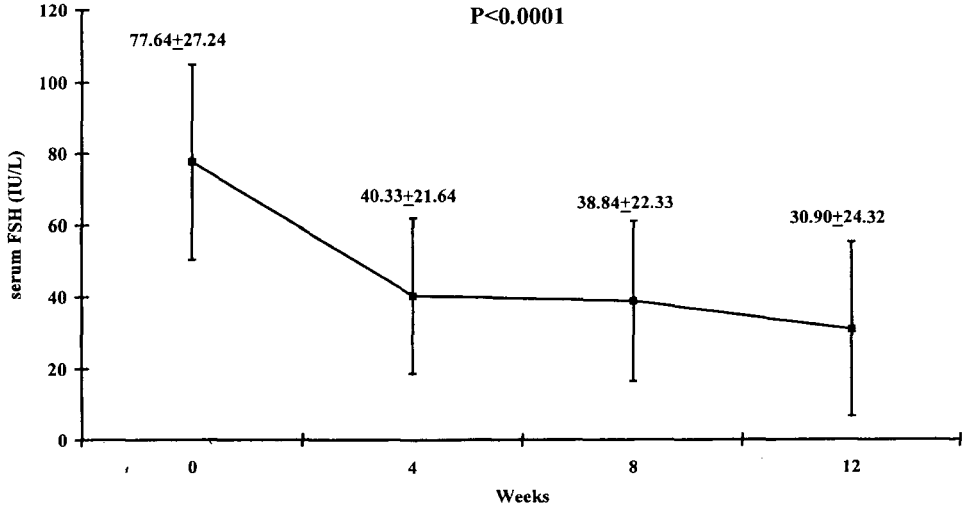

Fig. 2. Serum follicle-stimulating hormone (FSH) level at week 0 (baseline value) and week 4, 8 and 12 after commencing vaginal conjugated equine estrogens.

that might stem from some ovarian hormones i.e. androgen which is still secreted after menopause, in which it can be conversed to estrogen[1]. Another reason was to prevent the unopposed estrogen from stimulating endometrial proliferation in menopausal women with intact uterus.

The results of this study showed that a daily dose of 2 g base of 1.25 mg vaginal CEE cream increased serum E_2 level close to the level in the follicular phase of a normal menstrual cycle. During the normal menstrual cycle, the minimal E_2 level is approximately 40 pg/ml (147 pmol/L) with a peak of 250 pg/ml (919 pmol/L) at midcycle and 100 pg/ml (367 pmol/L) during the luteal phase[3]. Some have suggested that this should be the therapeutic guideline for estrogen replacement therapy[4].

Regarding postmenopausal bone loss, there is evidence that estrogen administration with average levels of E_2 in the early to midfollicular range (60 pg/ml or 220 pmol/L) is adequate to normalize urinary calcium and creatinine excretion and protect bone in most women[5]. With this E_2 level, frequency of vasomotor flushes was reported to be reduced by more than half[6,7]. Beside this, the amount of estrogen required to treat symptoms of vaginal atrophy is much lower than the amount needed to eliminate vasomotor flushes in a young women after bilateral oophorectomy[2,4]. Some studies reported approximate serum estrone and estradiol levels after various doses and formulations of estrogen replacement, in which one showed that 1.25 mg of CEE in the form of 2 g vaginal cream increased the serum E_2 level to 35 pg/ml (128 pmol/L)[4,8-10]. This value is lower than the level shown in this study. This is probably due to the difference in research methodology i.e. the difference in time-interval from hormone application to blood sample collection, application technique, the difference of vaginal absorption capability of drug in different ethnic groups or due to between hormone assay methods variability[11]. Further study with evaluation of both estrone (E_1) and estradiol (E_2) level may be more appropriate with this vaginal CEE cream, however E_1 kit test is not available in our laboratory, so far.

In this study, we collected blood samples 8-10 hours after vaginal application, though some studies showed that the peak serum level of E_2 after vaginal application of 1.25 mg CEE was around 6 hours[12]. This was because the bedtime of the studied population was around 10.00-12.00 pm and the most convenient time for the subjects to have blood sample collection was around 8.00 am the following morning.

Concerning FSH level in this study, it showed that FSH significantly decreased as time went by. However, the level was not lowered to the same level as in the premenopausal range, at least at 12 weeks after commencing the vaginal cream. This is probably because, before entering menopause, the ovary, not only secretes estrogen, but also produces inhibin which suppresses the FSH level to the premenopausal range[1]. Approaching menopause, the ovary secretes less inhibin causing the FSH level to rise before the E_2 level starts to drop[1]. With HRT, even though FSH can be suppressed by the hormone used, but not reaching the premenopausal range, probably due to lack of inhibin. Nevertheless, whether long term HRT decreases the FSH level to the premenopausal range, still needs to be studied.

In conclusion, the result of this study implies that, not only for treatment of urogenital symptoms in menopausal women, vaginal CEE cream might also be used as an alternative route for hormone replacement therapy for prevention and treatment of other menopausal problems. However, owing to the variable vaginal absorption in different individuals, more studies are needed to demonstrate its beneficial effects, particularly in prevention of cardiovascular disease and osteoporosis.

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ระดับของอิสตราดิออลและฟอลลิเคิล-สติมูเลติงฮอร์โมนในสตรีตัดรังไข่เมื่อใช้อิสโตเจนทางช่องคลอด

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ได้ศึกษาถึงการเปลี่ยนแปลงของระดับฮอร์โมน Estradiol (E_2) และ Follicle stimulating hormone (FSH) ในสตรีที่ได้รับการตัดรังไข่ทั้งสองข้าง และได้รับฮอร์โมน Estrogen ทางช่องคลอด โดยวัด Estradiol และ FSH ในซีรั่มของสตรีที่ได้รับการตัดรังไข่ทั้งสองข้าง 32 ราย ซึ่งใช้ครีมใส่ช่องคลอดปริมาณ 2 กรัม ซึ่งประกอบด้วยตัวยา Conjugated equine estrogen (CEE) 1.25 มิลลิกรัม การเก็บเลือดเพื่อวิเคราะห์ทางฮอร์โมนได้กระทำภายหลังจากใส่ยาทางช่องคลอด 8-10 ชั่วโมง การตรวจระดับ E_2 และ FSH จะกระทำก่อนและหลังได้รับยาในสัปดาห์ที่ 4, 8 และ 12 ด้วยวิธี Time-resolved fluoroimmunoassay ผลการศึกษา พบว่า ระดับซีรั่ม Estradiol ลดลงอย่างมีนัยสำคัญทางสถิติในสัปดาห์ที่ 4, 8 และ 12 เมื่อเทียบกับค่าของฮอร์โมนเมื่อจุดเริ่มต้น (ค่าเฉลี่ย±ส่วนเบี่ยงเบนมาตราฐานของค่า E_2 ในสัปดาห์ที่ 0, 4, 8 และ 12 : 9.79±12.13, 249.83±170.46, 299.38±190.65, 322.68±218.31 pmol/L, ตามลำดับ, $P<0.05$) ในทางตรงกันข้าม FSH ลดลงอย่างมีนัยสำคัญทางสถิติในสัปดาห์ที่ 4, 8 และ 12 เมื่อเทียบกับค่าของฮอร์โมนเมื่อจุดเริ่มต้น (ค่าเฉลี่ย±ส่วนเบี่ยงเบนมาตราฐานของค่า FSH ในสัปดาห์ที่ 0, 4, 8 และ 12 : 77.64±27.24, 40.33±21.64, 38.84±22.33, 30.90±24.32 IU/L, ตามลำดับ, $P<0.05$) โดยสรุป การใช้ครีม CEE ขนาด 2 กรัม ใส่ทางช่องคลอดทุกวัน ช่วยเพิ่มระดับ Estradiol สูงขึ้นใกล้เคียงกับระดับปกติในระยะ Follicular ของรอบระดูปกติ อย่างไรก็ตาม ถึงแม้ว่า FSH จะลดลงอย่างมีนัยสำคัญ แต่ก็ไม่ลดลงเท่าในระดับที่สตรียังมีระดูตามปกติ

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