Estradiol and Follicle-Stimulating Hormone Levels in Oophorectomized Women Applying Percutaneous 17 ß-Estradiol Over the Medial Surface of the Left Arm

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Abstract

To assess the changing estradiol (E_2) and follicle stimulating hormone (FSH) level in oophorectomized women applying percutaneous 17 ß estradiol over the medial surface of the left arm. Thirty-nine women, who had undergone total abdominal hysterectomy and bilateral oophorectomy after 4 weeks, were enrolled into the study. All subjects received a daily dose of 1.5 mg percutaneous 17 ß-estradiol in 2.5 g of the gel, applied over the medial surface of the left arm in the limited area of 150 cm^2. Serum E_2 and FSH were measured before and after commencing the study at weeks 4, 8 and 12. The measurment was performed 12-14 hours after the gel application, using time-resolved fluoroimmunoassay (FIA) method. Serum E_2 significantly increased from the baseline value at weeks 4, 8 and 12 (Median of E_2 value at weeks 0, 4, 8 and 12 = 47.30, 86.78, 128.00 and 163.15 pmol/L, respectively, $P<0.05$). While the serum FSH level significantly decreased. (Median of FSH value at weeks 0, 4, 8 and 12 = 66.05, 60.40, 53.35 and 48.40 IU/L, respectively, $P<0.05$). In conclusion, this dose, duration and route of estrogen administration increased the serum E_2 level close to the early to mid-follicular phase of the normal menstrual cycle. While FSH level significantly decreased but did not reach the premenopausal range.

Key word : Estradiol, FSH, Oophorectomized Women, Percutaneous 17 ß-Estradiol, Medial Surface of Left Arm

Surgical oophorectomy before menopause dramatically alters hormonal dynamics[1]. Compared to natural menopause when the ovary gradually decreases in secreting hormones[2]. Hence, the magnitude of menopausal problems, for instance, bone loss, seem to be more abrupt in those who have undergone surgical oophorectomy.

Benefits of hormone replacement therapy have been shown to strongly outweigh the risks,[3-5] especially in those with good selection criteria. It has been widely agreed that the ideal estrogen replacement therapy regimen should approximate the premenopausal state, have a sustained and controlled delivery consistent with

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normal ovarian secretory patterns, and cause as few side effects as possible, including minimal alteration of hepatic enzmes[6]. Eventhough, there are no available formulations which meet all the expectations, percutaneous estrogen has certain advantages over oral preparations[6]. Estrogen is known to be well absorbed through the skin in which the first-pass effect through the liver is avoided. The concentration of estrogen reaching the liver is physiologic[7]. Oestrogel® (International Pharmaceuticals Ltd.) is a percutaneous estradiol gel. The usual daily dose is 1.5 mg of estradiol which is dissolved in 2.5 g of the gel. It is recommended to apply the gel over a large area of the abdomen and thighs[7]. Serum level of estradiol are approximately 70 pg/ml (257 pmol/L), similar to estradiol levels achieved with 2 mg of oral estradiol[8,9]. However, after applying the gel, patients should allow the gel to dry for a few minutes before allowing clothing to come in contact with the skin[7].

Thailand is a tropical country with high temperatures and humidity, particularly in summer. Applying the gel over the recommended area may take more time before the gel becomes dry which is not so convenient. Hence, we conducted a study to assess the serum estradiol level in surgically castrated women who applied the gel at the medial surface of the left arm. This may be a more convenient site for gel application if serum estradiol can be increased to the physiologic level.

MATERIAL AND METHOD

This study was conducted from 1 August 1995 to 31 March 1996 at the menopause clinic, Department of Obstetrics and Gynecology, Chulalongkorn Hospital. We obtained approval by our Institutional Board of Ethical Committee and all participants provided written informed consent before enrollment. Thirty nine women who underwent total abdominal hysterectomy and bilateral oophorectomy at Chulalongkorn Hospital after 4 weeks were recruited for the study. These women had had regular periods before the surgery. The body mass index (BMI) was not more than 25 Kg/m^2. All patients were in good health and had not been on any hormone regimen for the previous three months. Candidates were excluded from participation if they had a history of the following : breast cancer, endometrial cancer, endometriosis, thromboembolic disease or liver disease. None had skin disease or history of alcohol or hormone allergy. 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 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 apply 2.5 g base of 1.5 mg percutaneous 17 ß-estradiol, (Oestrogel®, International Pharmaceuticals Ltd.) at the medial surface of the left arm in the limited area of 150 cm^2. A broad plastic band with central spacing was designed for the women to wrap it around their arm before applying the hormone. This ensured that the application was confined to the limited area and it was the same procedure in every subject. The application was done by the women daily at night (8.00 pm). Peripheral blood from an antecubital vein was collected into heparinized tubes on the following morning (8.00-10.00 am), 12-14 hours after percutaneous application. All blood samples were centrifuged and plasma was withdrawn and stored at -20°C until analyzed. The subjects were contacted by telephone before each visit to monitor compliance and side effects.

Descriptive statistics were used where it was appropriate. Each subject served as her own control. Median was used to average hormone level at weeks 0, 4, 8 and 12. Friedman two-way ANOVA was used to examine the difference in pre- and post treatment hormone level. P-value of less than 0.05 was considered statistically significant.

RESULTS

Of all 39 subjects, 38 completed the 12 week study period. One case dropped out due to poor compliance (<85%). The demographic characteristics of the studied population are shown in Table 1. Serum estradiol (E_2) and follicle stimulating hormone (FSH) level at weeks 0, 4, 8 and 12 are demonstrated in Table 2 and 3. When considering the prevalence of women who had serum E_2

of 150 pmol/L or more after the hormonal application, the results were as follows : the prevalence shown in per cent at weeks 4, 8 and 12 was 31.58 per cent, 44.74 per cent and 55.26 per cent respectively.

DISCUSSION

There is evidence that estrogen administration with average levels of estradiol (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[10]. This E_2 level was also reported to reduce frequency of vasomotor flushes by more than half[11,12]. Moreover, the amount of estrogen required to treat symptoms of vaginal atrophy was much lower than the amount needed to eliminate vasomotor flushes in young women after bilateral oophorectomy[7,13]. The serum level of estradiol after the usual daily dose of percutaneous estradiol gel applied over the abdomen and thighs has shown to approximate the level in the early to mid-follicular phase[8,9]. In this study, after applying the daily dose of 1.5 mg percutaneous estradiol in 2.5 g gel over the medial surface of the left arm in the limited area of 150 cm^2, the median serum estradiol level was close to the level in the early to mid-follicular phase, though it was not as high as that in previous reports[8,9]. This difference may be due to the smaller surface area of the left arm assigned in this study compared to the larger area of the abdomen and thigh. In addition, hormone assay methods variability,[14] difference in research methodology i.e. time-interval from hormone application to blood sample collection, appli-

Table 1. Demographic characteristics of studied population (N=38).

Character	Mean±SD
1. Age (yr)	46.47±5.40
2. BMI (kg/m^2)	23.28±1.81
3. Parity	2.37±2.14

BMI = Body mass index

Table 2. Serum estradiol (E_2) level before and after percutaneous application of 17 ß-estradiol at week 4, 8 and 12.

At week	Serum E_2 (pmol/L)		
	Median	5 percentile	95 percentile
0	47.30	6.0	94.90
4*	86.78	20.00	281.80
8*	128.00	45.20	580.10
12*	163.15	50.00	500.50

*P<0.05 between week 0-4, 0-8, 0-12, 4-8, 4-12
Non significant between week 8-12

Table 3. Serum follicle stimulating hormone (FSH) level before and after percutaneous application of 17 ß-estradiol at week 4, 8 and 12.

At week	Serum FSH (IU/L)		
	Median	5 percentile	95 percentile
0	66.05	32.80	106.80
4*	60.40	24.40	98.40
8*	53.35	17.80	89.90
12*	48.40	18.00	94.00

*P<0.05 between week 0-4, 0-8, 0-12, 4-8, 4-12, 8-12

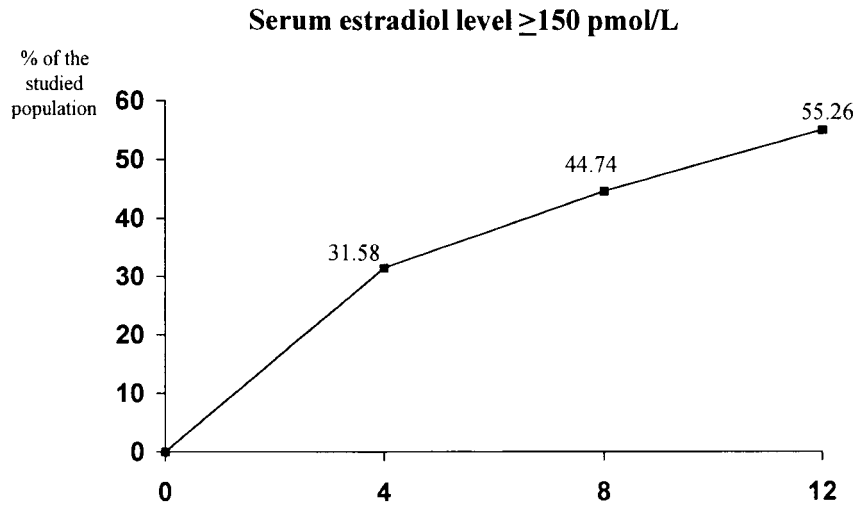

Fig. 1. Percentage of the studied population who had serum estradiol level ≥ 150 pmol/L at week 4, 8 and 12.

cation technique, etc may influence the value obtained in various studies. Whether there is a difference in skin absorption capability of these different sites of gel application, still needs to be investigated.

Estrogen therapy will stabilize osteoporosis or prevent it from occurring. The critical blood level of estradiol that is necessary to maintain bone is 40-50 pg/ml or 150-180 pmol/L[15]. In this study we considered the prevalence of subjects who had a serum estradiol level higher than 150 pmol/L at week 4, 8 and 12. It was found that the prevalence increased respectively (At weeks 4, 8 and 12 = 31.58%, 44.74% and 55.26% respectively, Fig. 1). This might be due to better compliance of the gel, because there is no known report showing the accumulation effect of this percutaneous gel.

Considering FSH level, after the gel application, the median level significantly decreased from the baseline value. However, it did not reach the normal level in the reproductive period. This is probably because the functioning ovary not only secretes estrogen, but also produces inhibin which suppresses FSH level to the premenopausal range[15]. After menopause, the ovary stops producing both estrogen and inhibin. Hence, without inhibin, this usual dose of estrogen might not be enough to bring FSH down to the reproductive range, at least within the 12 weeks interval of gel application. Whether a higher daily dosage or longer duration of gel application will suppress FSH to the premenopausal range, is a matter for future investigation

In conclusion, the daily dose of percutaneous 1.5 mg estradiol in 2.5 g of the gel, applied over the medial surface of the left arm, increased the serum estradiol level close to the level in the follicular phase of a normal menstrual cycle. However, it may be less efficient than using the gel applied over the abdomen and thighs which have a larger surface area. With this daily dosage and duration of treatment, FSH did not come down to the premenopausal range, eventhough it did significantly decrease.

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ระดับฮอร์โมนเอสตราดิออลและเอฟเอสเอ็ช ในสตรีที่หมดระดูจากการตัดมดลูกและรังไข่ทั้งสองข้างซึ่งได้รับฮอร์โมน 17 β-estradiol ทาบริเวณต้นแขนซ้ายด้านใน

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การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อประเมินค่าการเปลี่ยนแปลงของระดับฮอร์โมน Estradiol (E_2) และ Follicle-stimulating (FSH) ในสตรีที่หมดระดูจากการตัดมดลูกและรังไข่ทั้งสองข้าง ซึ่งได้รับฮอร์โมน 17 β-estradiol ทาผิวหนังบริเวณต้นแขนซ้ายด้านใน สตรีที่ได้รับการคัดเลือกเข้าโครงการวิจัย เป็นสตรีจำนวน 39 ราย ที่ได้รับการผ่าตัดมดลูกและรังไข่ทั้งสองข้างมาได้ 4 สัปดาห์ กลุ่มสตรีดังกล่าวได้รับยาทาชนิดเยล ที่มีฮอร์โมน 17 β-estradiol ขนาด 1.5 มิลลิกรัม ในเยล 2.5 กรัม ทาบริเวณต้นแขนซ้ายด้านในพื้นที่ที่กำหนด 150 ตารางเซนติเมตร โดยได้ทำการตรวจวัดระดับฮอร์โมน E_2 และ FSH ก่อนและหลังเริ่มต้นการศึกษาที่ 4, 8 และ 12 สัปดาห์ โดยตรวจเลือดภายหลังทายาแล้ว 12-14 ชั่วโมง และตรวจวัดโดยวิธี Time-resolved fluoroimmunoassay (FIA) ผลการศึกษาพบว่า ระดับ E_2 เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติในสัปดาห์ที่ 4, 8 และ 12 (ค่ามัธยฐานของ E_2 ในสัปดาห์ที่ 0, 4, 8 และ 12 = 47.30, 86.78, 128.00 และ 163.15 pmol/L ตามลำดับ, $P<0.05$) ในขณะที่ระดับ FSH ลดลงอย่างมีนัยสำคัญทางสถิติ (ค่ามัธยฐานของ FSH ในสัปดาห์ที่ 0, 4, 8 และ 12 = 66.05, 60.40, 53.35 และ 48.40 IU/L ตามลำดับ, $P<0.05$) โดยสรุป การใช้ฮอร์โมน Estrogen ชนิดทาในขนาดและระยะเวลาดังกล่าวสามารถเพิ่มระดับของ E_2 ในกระแสเลือดได้ใกล้เคียงกับระดับ ในระยะ Mid-follicular ของรอบระดูปกติ อย่างไรก็ตามถึงแม้ระดับ FSH จะลดลงอย่างมีนัยสำคัญ แต่ก็ยังไม่ถึงระดับปกติในวัยเจริญพันธุ์

คำสำคัญ : เอสตราดิออล, เอฟเอสเอ็ช, สตรีหมดระดูจากการตัดรังไข่, ฮอร์โมน 17-β เอสตราดิออล, ทาบริเวณต้นแขนซ้ายด้านใน

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