

The Relation of Serum Inhibin B, Estradiol and FSH Levels to Menometrorrhagia in Perimenopausal Women

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Abstract

Objective: To determine whether serum estradiol, follicle stimulating hormone (FSH), and inhibin B levels are associated with menometrorrhagia in perimenopausal women.

Materials and Methods: Forty-two perimenopausal women with menometrorrhagia and 42 age-matched regular-cycling women participated in this prospective study. Blood samples to measure serum estradiol, FSH, and inhibin B were collected in perimenopausal women with menometrorrhagia when they had vaginal bleeding. In women with regular cycles, blood samples were collected between days 3 and 8 of the cycle. The *t* test was used for statistical comparisons between the 2 groups.

Results: Mean inhibin B levels were lower in patients in the study group compared with patients in the control group (16.8 pg/ml vs 22.4 pg/ml), but this difference was not statistically significant. Mean FSH values were not significantly different between patients in the study and control groups (17.4 IU/L vs 11.6 IU/L). However, mean estradiol values were significantly higher in patients in the study group than they were in the control group (127.1 pg/ml vs 39.3 pg/ml).

Discussion: High serum estradiol levels are associated with menometrorrhagia in perimenopausal women. However, a significant relation was not demonstrated between menometrorrhagia in perimenopausal women and levels of FSH and inhibin B.

Keywords: estradiol, inhibin B, FSH, menometrorrhagia, perimenopausal women

Özet

Perimenopozal Menometrorajinin Serum İnhibin B, Östradiol ve FSH Düzeyleri ile İlişkisi

Amaç: Çalışmanın amacı, perimenopozal kadınlarda menometrorajinin serum östradiol, FSH ve inhibin B düzeyleri ile ilişkisini araştırmaktır.

Materyal ve Metot: Menometroraji şikâyeti olan 42 hasta ve yaşları uyumlu 42 regüler siklik kanaması olan kadın kontrol grubu olarak çalışmaya dahil edildi. Kan örnekleri menometrorajisi olan kadınlarda kanamalı iken, kontrol grubunda ise siklusun 3-8. günleri arasında alındı. Gruplar arasındaki istatistiksel karşılaştırma *t* testi ile yapıldı.

Sonuçlar: Ortalama serum inhibin B düzeyi istatistiksel olarak anlamlı olmasa da çalışma grubunda (16.8 pg/ml) kontrol grubuna (22.4 pg/ml) göre düşük bulundu. FSH düzeyinde de, iki grup arasında anlamlı fark bulunmazken (çalışma ve kontrol gruplarında sırasıyla; 17.4 IU/L ve 11.6 IU/L), östradiol düzeyi çalışma grubunda istatistiksel olarak anlamlı ölçüde yüksek bulundu (127.1 pg/ml ve 39.3 pg/ml).

Tartışma: Yüksek östradiol düzeyi perimenopozal menometroraji ile ilişkilidir. Ancak çalışmada FSH ve inhibin B düzeylerinin perimenopozal menometroraji ile anlamlı bir ilişkisi görülmemiştir.

Anahtar sözcükler: östradiol, inhibin B, FSH, menometroraji, perimenopoz

Introduction

Menometrorrhagia is a pattern of dysfunctional uterine bleeding defined as excessive uterine bleeding during menses and at irregular intervals. Menometrorrhagia is an uncomfortable and

annoying disorder that in some perimenopausal women leads to anxiety about cancer. Because an increased frequency of inadequate luteal function or anovulation occurs during perimenopause (which leads to progesterone deficiency and causes estrogen withdrawal or estrogen breakthrough bleeding), dysfunctional uterine bleeding and menometrorrhagia are the most common complaints among women during the perimenopause. Moen and associates demonstrated high serum estradiol levels in perimenopausal women with

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menometrorrhagia and suggested these increased levels as the cause of menometrorrhagia (1).

Estradiol, follicle stimulating hormone (FSH), and inhibin interact with each other and affect menstruation (2). FSH stimulates estradiol production, and depending on serum levels, estradiol has either a positive or negative effect on the release of FSH. Inhibin, a dimeric glycoprotein composed of an α subunit and a β A subunit (inhibin-A) or a β B subunit (inhibin B), was initially identified on the basis of its ability to suppress FSH secretion (3,4). Inhibin is synthesized by granulosa cells in response to FSH, which is secreted to follicular fluid and ovarian venous effluent. Inhibin is an important inhibitor of FSH secretion. FSH stimulates the secretion of inhibin from granulosa cells, and in turn, is suppressed by inhibin. There is a reciprocal relationship.

The role of serum estradiol levels in perimenopausal women with menometrorrhagia has been demonstrated. In this prospective study, we investigated the relation between menometrorrhagia and levels of estradiol, FSH, and inhibin B in perimenopausal women with menometrorrhagia.

Materials and Methods

Seventy perimenopausal women with menometrorrhagia who presented at the Başkent University Alanya Hospital Gynecology Outpatient Clinic between August 2005 and October 2006 participated in this study. Written informed consent was obtained from all participants, and the Ethics Committee of Başkent University approved the study protocol prior to its inception. Perimenopausal women with menometrorrhagia were included in the study: Perimenopausal women with menometrorrhagia caused by anatomic factors (e.g. those with myoma uteri upon transvaginal ultrasonography or endometrial biopsy results indicating polyps, hyperplasia, or cancer) and those treated with any kind of sex hormone in the 3 weeks preceding the hormonal assessment were excluded from the study. Women older than 39-years having moderately irregular cycles (that is, with reported change in menstrual cycle frequency in the preceding year and with at least one menstruation in the preceding 3 months before admission) were considered perimenopausal.

Of the 70 perimenopausal women, 42 were included in the study group. These women were matched for age with 42 women with regular cycles (controls). Blood samples to measure serum estradiol, FSH, and inhibin B were collected in perimenopausal women when they had menometrorrhagia; in women with regular cycles, samples were collected between the 3rd and 8th days of the cycle. All samples were stored at -70°C before analysis.

Estradiol and FSH levels were measured on an Immulite Analyser (Diagnostic Products Corporation, Los Angeles, CA, USA) using reagents and calibrators supplied by manufacturer. Serum estradiol levels were determined using a solid-phase

competitive chemiluminescent enzyme immunoassay. Serum FSH levels were determined using a solid-phase 2-site chemiluminescent immunometric assay. Intra-assay and interassay coefficients of variation for estradiol and FSH were 9.3% and 10.6%, and 1.4% and 5.9%, respectively.

Inhibin B levels were measured by a double-antibody ELISA (Diagnostic Systems Laboratories, Inc., Webster, TX, USA). The assay standards provided by the manufacturer were calibrated using the World Health Organization's First International Standard for inhibin B (recombinant human inhibin, Lot 96/784). The limit of detection for inhibin B assay was 7.0 pg/ml. Intra-assay and interassay coefficients of variation for inhibin B were 4.6% and 6.7%, respectively. All samples from a given patient were run within the same assay.

Statistical analysis was performed by using SPSS 11.5 for Windows (SPSS, Inc, Chicago, IL, USA) statistical software. The *t* test was used to compare basic characteristics, serum estradiol, FSH, and inhibin B levels between the study and the control groups. Data were expressed, as mean \pm SD and *p* value of less than 0.05 were considered significant.

Results

The mean age of the women was not significantly different between the study and control groups, 43.2 ± 4.3 yrs vs. 42.0 ± 4.2 yrs respectively. The mean BMI was also not different between the study and control groups, 28.7 ± 5.1 vs 28.3 ± 5.5 respectively.

The mean estradiol value for women in the study group was 127.1 ± 92.0 pg/ml (range, 1.9-193 pg/ml), and for women in the control group it was 39.3 ± 31.0 pg/ml (range, 30-371 pg/ml); this difference was significant. The mean values of FSH for women in the study and in the control groups were 17.4 ± 16.4 IU/L and 11.6 ± 11.0 IU/L, respectively ($p > 0.05$). Mean values for inhibin B were lower among women in the study group compared with controls (16.8 ± 11.1 pg/ml vs 22.4 ± 22.4 pg/ml); however, this difference was not significant (Table 1).

In perimenopausal women with menometrorrhagia, the mean estradiol and inhibin B levels were 116.3 pg/ml and 16.4 pg/ml, respectively, for women with BMIs < 30 ($n=25$) and 143.0 pg/ml and 17.5 pg/ml, respectively, for women with BMIs ≥ 30 ($n=17$). These differences also were not significant.

Table 1. Mean hormone levels of the study and the control groups

	Study group (n=42)	Controls (n=42)	p*
Estradiol (pg/ml)	127.1 \pm 92.0	39.3 \pm 31.0	<0.05
FSH (IU/L)	17.4 \pm 16.4	11.6 \pm 11.0	NS
Inhibin b (pg/ml)	16.8 \pm 11.1	22.4 \pm 22.4	NS

*Student *t*-test (Statistical Significance: $p < 0.05$).
•Data are mean \pm SD; NS: not significant.

Discussion

In this study, the potential roles of serum estradiol, FSH, and inhibin B levels were studied in perimenopausal women with menometrorrhagia. Serum estradiol levels were statistically significantly higher in perimenopausal women with menometrorrhagia compared with age-matched women with regular cycles. However, an association between menometrorrhagia in perimenopausal women and serum FSH and inhibin B levels was not found.

Santoro and associates, and Shideler and associates had not previously shown an association between hyperestrogenism and menstrual irregularities, but Moen and associates were the first researchers to demonstrate an association between hyperestrogenism and menometrorrhagia, before our report (1,5,6). Santoro and associates have mentioned that a hyperestrogenic status and irregular cycles coexist with decreased progesterone secretion, and that this suggests luteal insufficiency during the perimenopausal phase (5). Similarly, Burger and associates showed that an increased frequency of anovulatory cycles, which heralds the occurrence of a final menstrual period, is associated with menstrual irregularities (7). Thus, women with anovulatory cycles show a long duration, abnormal bleeding, or both.

Moen and associates compared 28 perimenopausal women with menometrorrhagia (duration of bleeding disturbance varied from a short time to several years) with 28 age-matched women with regular cycles with regard to serum estradiol and FSH levels. They found that serum estradiol levels were significantly higher in perimenopausal women with menometrorrhagia when compared with women with regular cycles (i.e. 0.55 ± 0.57 nmol/L compared with 0.24 ± 0.13 nmol/L). However, despite the fact that mean FSH levels in women with menometrorrhagia were almost 2 times those of women with regular cycles (21.2 ± 23.1 IU/L compared with 11.8 ± 3.7 IU/L), FSH levels were not found to be statistically significantly different (1). Thus, our study has confirmed the role of serum estradiol in perimenopausal women with menometrorrhagia demonstrated in Moen's study. Although, the interaction between menstrual status and levels of FSH, estradiol, and inhibin are known (2,8-10), Moen and associates were unable to evaluate the inhibin levels in their study (1).

Although, we failed to demonstrate a statistically significant relation between menometrorrhagia of perimenopausal women and serum levels of inhibin B in our study, levels of inhibin B may be of use in further investigations. Also, it should be borne in mind that ours was the first study to report inhibin B levels in perimenopausal women with menometrorrhagia.

Several studies have examined inhibin levels in women at different levels of perimenopause. Burger and associates studied the serum FSH, estradiol, and inhibin A and B levels in 110 perimenopausal women. Burger and associates found levels of inhibin B to be 48 ng/L and 13.5 ng/L, respectively, in women

with regular cycles and women with irregular cycles (reported as a change in menstrual cycle frequency in the preceding year with a bleeding in the preceding 3 months). In the same study, FSH levels rose from 13.5 IU/L to 21.4 IU/L, but estradiol levels did not change significantly between women with regular and irregular cycles (11).

Freeman and associates also studied serum levels of FSH, estradiol, inhibin B, and luteinizing hormone in women during perimenopause. They found that with changes in cycle length that occurred well before 3 months of amenorrhea, inhibin B levels were significantly lower and FSH levels were significantly higher than premenopausal levels. Estradiol levels also did not differ significantly from the premenopausal levels until women had been through menopause (2).

Additionally, fluctuations in sex hormones across a woman's lifespan have been shown to be related with obesity (12). In perimenopausal women with menometrorrhagia, mean estradiol and inhibin B levels in those with BMIs ≥ 30 were not found to be significantly different from those who had BMIs < 30 , in our study; however, this association requires further investigation.

According to our results, serum estradiol levels were significantly higher in perimenopausal women with menometrorrhagia. This indicates that high serum estradiol levels are associated with menometrorrhagia in perimenopausal women. Larger prospective studies are needed to confirm the relation between menometrorrhagia and FSH and inhibin B levels in perimenopausal women.

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