Conference Paper

Estradiol Serum Levels in Menopausal Women with and without Vasomotor Syndrome in Medan

Fidel Ganis Siregar

Departement of Obstetrics and Gynecology, University of Sumatera Utara, Medan, Indonesia

Abstract

Vasomotor syndrome is the most commonly complained syndrome in menopause women. The main mechanism is the decrease in estrogen which causes increasing of body's core temperature and overactivity of the parasympathetic nervous system. Estradiol is the most abdudant and most potent estrogen derivate that works in major receptors throughout the body. This study aimed to determine difference of estradiol serum levels between women with and without vasomotor syndromes and among the symptoms severity. This study was conducted in 50 menopausal women in the Department of Obstetrics and Gynecology H. Adam Malik Hospital, Medan, Indonesia. Vasomotor symptoms was assessed by interview using three options of answers. Estradiol serum was analyzed using chemiluminescent principle in Prodia Laboratory. Data were tabulated and analyzed by SPSS. This study showed significant difference of mean estradiol serum levels between women with and without vasomotor syndromes (17.5 and 47.5 pg/ml, respectively; p = 0.0001). Women with mild vasomotor syndromes had higher estradiol serum levels (23.9-29 pg/ml) than those with moderate (12-19.7 pg/ml) and severe (11.8 pg/ml) degree of syndromes. By using estradiol level as a marker, the presence vasomotor symptoms even its severeity should have been predicted earlier. Therefore, women can prepare to overcome those debilitating symptoms. Further and larger reseach is needed to make this study applicable in all clinical settings.

Keywords: estradiol, menopause, vasomotor

Corresponding Author: Fidel Ganis Siregar; email: fgsiregar@gmail.com

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1. Introduction

The increasing of life expectancy is proportional with the increasing number of women in the menopausal age 2030 [1-3]. At menopause, there will be a variety of physical and psychological complaints due to declination of estrogen levels [4,5]. Vasomotor syndrome (50-75%) is most common symptoms suffered by menopause women [6-8].

Vasomotor syndrome is different in each persons based on the declination velocity of estrogen level [9-10], depends on the population, geographic area, and personal biological characteristic [11]. Vasomotor syndrome can be uncomfortable even cause disruption in the daily activities and reduce the quality of life [12,13]. We need early marker to predict the presence and severity of vasomotor syndromes, to prepare women facing menopause syndromes, especially vasomotor syndromes [14].

As it is known that reduction of ovary function will reduce estrogen levels to only 5-20 mcg/24 hr in menopause period [15,16]. Estrogen has three derviates, estrone (E1), estradiol (E2), and estriol (E3). Estradiol (E2) is the most abundant and most potent derivates with the greatest number of receptors in variety of organs [17,18]. Estradiol serum level in young woman is more thatn 1000 pg/mL, which will decrease to only

Wahdi (2003) showed that estradiol serum levels wass lower in women with than those without vasomotor syndromes. However, in this study does not explain the difference of estradiol serum levels between the severity of vasomotor symptom [17].

Therefore, author is interested in determining the difference of estradiol serum level between women with and without vasomotor syndrome, also the difference among mild, moderate, and severe degree of syndromes.

2. Materials and Methods

2.1. Study Design

This study was an analytical cross sectional study that conducted in Departemen of Obstetrics and Gynecology H. Adam Malik Hospital and its satellite hospital, Univeristy of Sumatera Utara, Medan, Indonesia. The study has been approved by the local institutional review board.

2.2. Subjects

From February to April 2015, we screened 50 consecutive menopausal women aged 45-65 years old who were working in our institutions. Written informed consents were previously obtained. The inclusion criteria were as follow: not taking hormone replacement therapy; no history of hysterectomy or bilateral oophorectomy; had any malignancy, cardiovascular, diabetes mellitus, osteoporosis, hypertension, or psychiatrics disorder; not smoking or taking alcohol. Subjects who withdrew before the end of the study or if their blood samples were broken, were excluded from this study.

2.3. Study Protocols

Baseline characteristics such as, age, menopause age, body mass index, duration of menopause, and parity were recorded. All eligible subjects were interviewed by a blinded investigators to assess vasomotor symptoms. If the woman denied any symptom of hot flushes, she was said to have no vasomotor syndrome. Conversely, if symptom of hot flushes was presence, the woman was said to have vasomotor syndrome. The syndrome was categorized mild if no sweating occurred, moderate if there was sweating but no limitation of daliy activity, severe if there was sweating with disturbance in daily activity. Estradiol serum was analyezed in Prodia Laboratory using chemiluminescent principle.

2.4. Estradiol Serum Analysis

We took 5 cc of blood sample from median cubital vein. The sample was then We took 5 cc blood sample from mediana cubiti vein. The sample was then centrifuged. About 80 uL sample and 75 uL reagen Ancillary pack was being put inside cuvettel and incubated at 370C for 4.5 minutes. 75 uL Reagent Lite was taken and incubated at 370C for 2.75 minutes. 25 uL Ancillary well was added to 100 uL solid phase reagent and incubated at 370C for 5.5 minutes. Cuvette was then separated, aspirated, and washed by Wash 1 liquid. Then, 300 uL each acid and base reagents were added to initiate chemiluminescent reaction. The estradiol was counted inversely to relative light units detected by system.

2.5. Data Analysis

Data were analyzed descriptively to see the frequency distribution of the characteristics. All data was tested for the normality of distribution to determine the choice of statistical analysis. To analyze the difference between serum estradio level between both study groups, we used Mann-Whitney test. Meanwhile, the correlation characteristics of postmenopausal women with estradiol serum level were determined using Spearman correlation. The degress of confidence was 95%.

3. Results

In this study, about 26 of 50 menopausal women (52%) had vasomotor syndromes. Subjects who experience vasomotor syndrome mostly aged 45-50 years old (84.6%), had parity ≥ 4 (85.3%), normoweight (100%), menopausal age 45-50 years old (96.1%), and duration of menopause 1-2 years (100%).

Age, parity, menopause, age, and duration of menopause were strong negatively correlated with estradiol serum levels. Body mass index was proportionally correlated with estradiol serum levels.

As shown in Table 3, women with mild vasomotor syndromes had higher estradiol serum level (23.9-29 pg/ml) than those with moderate (12-19.7 pg/ml) and severe (11.8 pg/ml) degree. There was significant difference of mean estradiol serum level between women with and without vasomotor syndromes (17.5 pg/ml and 47.5 pg/ml, respectively; p = 0.0001).

4. Discussion

Menopause is the cessation of menstruation for at least 12 months due to loss of ovarium function [7,8]. The declination of ovaries cause deficiency of estrogen production, which will bring many menopausal symptoms. The menopase syndrome consists of vasomotor syndrome (hot flushed, sweating, palpitation, headache, insomnia), psychologic disorders (moody, fatigue, low libido), urogenital symptoms (dryness of

Characteristics	Vasomotor syndrome	No vasomotor syndrome	Total
Age (years old)			
45-50	0 (0%)	22 (84.6%)	22 (36.7%)
51-55	11 (32.4%)	4 (15.4%)	15 (25%)
56-60	14 (41.2%)	0 (0%)	13 (23.3%)
61-65	9 (26.4%)	0 (0%)	9 (15.0%)
Parity			
0	0 (0%)	1 (4%)	1 (1.7%)
1-3	5 (14.7%)	25 (96%)	30 (50%)
≥4	29 (85.3%)	0 (0%)	29 (48.3%)
IMT			
Normoweight	34 (100%)	0 (0%)	34 (56.7%)
Obese	0 (0%)	22 (84.6%)	22 (36.7%)
Overweight	0 (0%)	4 (15.4%)	4 (6.7%)
Menopause age (years old)			
45-50	0 (0%)	25 (96.1%)	25 (41.7%)
51-55	24 (70.6%)	1 (3.9%)	25 (41.7%)
56-60	10 (29.4%)	0 (0%)	10 (16.7%)
Duration of menopause			
1-2	5 (14.7%)	26 (100%)	31 (51.7%)
3-4	9 (26.5%)	0 (0%)	9 (15.0%)
≥5	20 (58.8%)	0 (0%)	20 (33.3%)

Table 1: Baseline characteristics of subjects.

Characteristics	Estradiol serum level	
	r	*p value*
Age	-0.859	<0.001
Body mass index	0.699	0.316
Parity	-0.907	0.002
Menopausal age	-0.830	<0.001
Duration of menopause	-0.880	<0.001

Table 2: Correlation between menopausal women characteristics and estradiol serum level.

Vasomotor syndrome severity degree	Estadiol serum level (pg/ml)	Total
Mild	23.9-29.0	4 (11,8%)
Moderate	12.0-19.7	15 (44,1%)
Severe	11.8	15 (44,1%)
Total		34 (100,0%)

Table 3: Estradiol serum level based on vasomotor syndrome severity degres.

Group	N	Estadiol serum level	P value*
Vasomotor syndrome	34	17.50 pg/ml	
No vasomotor syndrome	26	47.50 pg/ml	0,0001
Total	60		
* Mann-Whitney test			

Table 4: Difference of estradiol serum level between women with and without vasomotor syndrome.

vagina, dyspareunia), osteoporosis, dryness of skin, and increases incidence of cardiovascular disorders [13].

Vasomotor syndrome is the most common syndrome suffered by menopause women [4,20-22]. There are three severity degress of vasomotor syndrome such as mild if there was presence of hot flushes without sweating, moderate if both symptoms were presence, and severe if both symptoms have caused limitations of daily activities.

This syndrome was found since climacteric until post menopause. Some studies reported that 75%-80% women have complained of vasomotor syndromes since several years before menopause [17,23]. In Bandung, Indonesia, study showed that higher proportion of menopause women (88.3%) complained of vasomotor syndrome during her life. About 85% women that suffering from vasomotor syndrome will continue to have it in entire year and 25-50% will continue untul 5 years later [24]

However, characteristics of vasomotor complaints differ depending on the geography area [7,9,25]. Blumel showed that in poulation with severe vasomotor symptoms, they mostly had low education level, nulliparity, surgical menopause, and had also severe both psychological and urogenital disorders [26]. In this study, subjects who experience vasomotor syndrome mostly aged 45-50 years old (84.6%), had parity ≥ 4 (85.3%), normoweight (100%), menopausal age 45-50 years old (96.1%), and duration of menopause 1-2 years (100%).

High parity is associated with menopause which previously described by Kuzmarek [27] but there is no theory that can explain the association. In the other hand, Kriplani in India showed controversial results about this [28].

In obesity, fat causes greater peripheral conversion of adrenal androgen to estrogen. Besides that, lower sex hormone binding globulin increase protection against hot flushes [29]. The decline of estrogen in menopause does not occur suddenly. Estrogen is still presence in blood from peripheral conversion. The adrenal gland is the main source of estrone. Most estrone generated from peripheral aromatization of androstenendion. Aromatization of androstenendion can occur in fat, muscle, liver, bone marrow. But only 30-40% of this conversion are derived from fat cells and muscles. Therefore, obese women have a higher number of estrogen levels than lean women [16,19,28].

This results was similar to that of Study of Women's Health Across the Nation (SWAN) study. In 3.302 menopause women with vasomotor syndrome, women with BMI 28 kg/m2 had more severe vasomotor syndrome than women with BMI 31 kg/m2 [30].

This association was remained significant after controlled of other risk factors. However, Amabebe showed positive correlation between the high BMI and severity of syndrome [31].

Early menopause age is associated with more significant morbidity and mortality of symptoms. However, mostly women menopause at 45-50 years old [32]. Stanford reported that median menopause age in developing countries was 50-51 years old [33]. Kwawukume showed that in developing countries, natural age of menopause is 4 years earlier thatn that of developing countries [34]. In a large study by Oloran, they showed mean menopause age was 48.5 +/- 4.6 years old [35].

Age, parity, menopause, age, and duration of menopause were strong negatively correlated with serum estradiol levels. Body mass index was proportionally correlated with serum estradiol levels. These results were similar to theories, as ovaries follicles decreased by aging while estradiol increased by the increasing fats [17].

Before a woman experiences menopause, there have been anatomical changes in the ovary as a result of the aging process that cause sclerosis and reduction in the number of primordial follicles, as well as a decrease in the activity of steroid hormone synthesis. The decline of estrogen levels will mark the beginning of climacteric and continue decreasing during menopause, reaching lowest level during the post menopause period. This cause negative feedback on the hypothalamus, which in turn causes increased production of gonadotropins, resulting in hipergonadotropin-hypogonadism condition. With declining estrogen levels in the body, then all physiological functions of sex hormones will be disturbed, causing neurovegetative disorders, psychological disorders, somatic disorders and menstruation disorder [4,17].

The age of menopause is determined by the number of follicles present in the ovaries. When the fetus was 20 weeks, the follicles were estimated to contain 7 million of ovaries. In puberty, follicles will reach its peak level and then decrease linearly until the age of 40 years old. At the age of 40-45 years old, the average number of primordial follicles decreases to 8.300 [15]. These processes occur continuously during a woman's life, until ovaries become very tired at the age of 49-51 years old. Furthermore, the number of follicles decline of the sharply. After menopause, there were no more follicles [17]. This condition resulted in disorder of ovaries metabolism and growth, leading to ovarian atrophy and thickening of albuginea. All these processes are genetically aroused. So it is clear that the process of aging and decreased ovarian function dimish the pituitary to produce steroid, which cuase related symptoms [16].

Estrogen is composed three derivates, estrone (E1), estradiol (E2), estriol (E3). Estrone (E1) is an estrogen compound with $C_{18}H_{22}O_2$ chemical groups, found on the body as a metabolite of estradiol, secreted primarily in the ovaries. Estradiol (E2) is a natural hormone estrogen with phenolic alcohol $C_{18}H_{24}O_2$ chemical groups that are generally secreted by the ovaries, with the greatest number, and the most potent activity [5].

Estrogen deficiency leads to loss of estrogen-catecholamines precusors, resulting in decreased sympatho-hypothalamic control. Core body temperature will raised. Initially, thereis a compensatory increase in the secretion of adrenaline to synchronize the central temperature to the high peripheral temparature. Along with this, there will also

an increase in the activity of parasympathetic nervous system. This is in accordance with the pathophysiology in which hot flashes and headaches occured and followed by vasodilation due to subsequent increase followed by decrease in serum adrenaline. Vasodilation limited to the face, arm and hand. The other issued raised hypothesis that decreased of ovarium funnction caused decrease of opioid tonus at ypothalamus and instablity of temperature regulation [8,17,23].

Hot flushes is the classic sign of vasomotor syndrome. Its mechanisms remained controversial. It was presumed that hormonal, metabolic, and psychologic factors induce vasodilatation and increase body core temperature. Some women reported that hot flushes begin with headache that extend to entire body, especially around face and uppert trunk, then their skin will redden, hot, begin sweating, and palpitations. At this time, skin temperature increases 5-9°C and core temperature decreases 0.6°C. Therefore, this was like a compensation to reduce core temperature. The frequency of each hot flush varies 1-2 times per hours to 1-2 times per week. In some situations, severe symtpoms can last for 54 minutes [23].

There was significant difference of mean estradiol serum level between women with and without vasomotor syndromes (17.5 pg/ml and 47.5 pg/ml, respectively; $p = 0.0001$). Wahdi (2003) also showed significant difference of serum estradiol level between both groups ($p < 0.01$) with 9.557 pg/ml in women with vasomotor symptoms compared to 14,160 pg/mL in women without vasomotor symptoms [17]. In this study, it was shown that there was a tendency of low serum estradiol level in lower severity of syndrome.

Wahdi (2003) showed that estradiol serum levels wass lower in women with than those without vasomotor syndromes. However, in this study does not explain the difference of estradiol serum levels between the severity of vasomotor symptom. He also showed that 63% subjects in his study overcomed vasomotor symptoms 1-2 years after menstrual cessation, 30% had symptoms after 1-2 years before menstrual cessation, and 7% had symptoms immediate after menstrual cessation [17].

To manage vasomotor symptoms, first, one's should change her lifestyle to be more healthy and avoid of psychoogic stress. Evaluation was done 3 months later. If symptoms were decreased, follow up was done annually. If symptoms were persist, clinicians should decide of prescribing drugs. Phytoestrogen is the first line therapy for mild vasomotor syndrome but being the second line in moderate to severe syndrome. Estrogen and hormon replacement therapy are the first line drugs for moderate to severe vasomotor syndrome. The other alternative drugs are clonidine or gabapentin [45].

5. Conclusion

This study showed significant difference of serum estradiol level between women with and without vasomotor syndrome. There was a tendency of lower serum estradiol level in lower severity of syndrome. Further research is needed to make this marker applicable in all clinical settings.

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