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The Relationship Between Saliva 17 Beta-Estradiol Levels with Anxiety and Depression in Menopause Paramedic at Prof I.G.N.G Ngoerah Hospital Denpasar

Petrus Agustinus Seda Sega
Study Program of Psychiatry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia
Corresponding author email: PetrusAgustinus@yahoo.com

Anak Ayu Sri Wahyuni
Department of Psychiatry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia | Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

Ni Ketut Sri Diniari
Department of Psychiatry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia | Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

I Wayan Gede Artawan Eka Putra
Faculty of Public Health, Udayana University, Denpasar, Bali, Indonesia

Abstract---*Background: Hospital Services rely on Medical and Paramedics at the Hospital, Hospital Paramedic services, especially women, are greatly influenced by mood, in women it is especially influenced by hormonal balance, including menstruation and menopause. The drop in estrogen levels after menopause causes many physical and emotional changes. Estradiol is the largest estrogen. It is estimated that the number of women who have menopause will experience a very significant increase of estradiol. Methods: An analytic observational study with a cross-sectional study design on 85 menopausal paramedics at Prof I.G.N.G Ngoerah Hospital Denpasar using a Hospital Anxiety and Depression Scale (HADS) questionnaire and examined salivary levels of 17β estradiol and looked for its relationship with anxiety and depression. Results: Based on the low salivary 17β estradiol level of the sample aged above 50 years (76.5%). Outpatient (75%), underweight (100%), married status (74.4%), and sample >5 years (76.5%). It is also a significant result where the salivary 17β estradiol level is lower in the sample compared to anxiety and depression complaints, with the chi-square test (p-value = <0.001). Conclusion: There is a significant relationship between low salivary 17β estradiol levels and complaints of anxiety and depression in menopausal paramedics.*
Keywords---*17β estradiol salivary levels, anxiety, depression, estradiol, estrogen, hospital anxiety and depression scale (HADS).*

Introduction

Health is a human right and every people has the right to get fair, equitable, and quality services. The services must be supported by optimal services from the Hospital. Women, as a hospital paramedical services, are very much influenced by mood, it is especially influenced by hormonal balance, including menstruation and menopause. Because of that, menopause needs to be seen further as a basis for its relationship with the performance of paramedical services. Starting at the age of 40, women will experience menstrual cycles that are irregular, elongated,

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a little or a lot, and sometimes accompanied by pain. Normal menopause generally occurs between the ages of 45 and 55 years (Deeks et al., 2011). Menopause is preceded by progressive ovarian failure which is characterized by increasing irregular cycles and decreasing estrogen levels. Dropping estrogen levels after menopause causes many physical and emotional changes. Includes vaginal dryness that causes discomfort during sex, and gradual atrophy of the reproductive organs (Sherwood, 2014; Indrias & Maliya, 2015).

Physical changes in menopausal women can have an impact on the onset of disease in menopause, both physically and psychologically. Psychological complaints in menopausal women have more influence on the quality of life compared to physical complaints experienced by menopausal women. The most common psychological complaints are anxiety and depression in menopausal women which are very individual in nature and are influenced by socio-culture, education, environment, and socio-economic status (Indrias & Maliya, 2015; Rostiana & Kurniati, 2009; Jafari et al., 2014; Yun et al., 2015). Entering the perimenopausal period, the activity of the follicles in the ovaries begins to decrease. When the ovaries do not produce ovum and stop producing estradiol, the pituitary gland tries to stimulate the ovaries to produce estrogen, increasing FSH production (Speroff, 1983). Estradiol (E2 or 17β-estradiol, also estradiol) is a sex hormone and also known as the largest estrogen. Estrogen also plays an important role in the physiology of the human oral cavity, so its levels can be measured by collecting saliva samples.[8,9] This study aims to know the relationship between saliva 17 beta-estradiol levels with anxiety and depression in menopause paramedic.

Methods

Research design

This observational study uses a cross-sectional to examine the level of 17 β estradiol among menopause paramedics at Prof I.G.N.G Ngoerah Hospital. The inclusion criteria were, identified menopause by menopause rating scale (MRS), actively working at Prof I.G.N.G Ngoerah Hospital in 2023, not getting menstruation for at least ≥ 12 consecutive months, being willing to participate in the research and has signed a consent form. The exclusion criteria were having a psychiatric disorder, having had surgery to remove the uterus and both ovaries, receiving hormone replacement therapy, suffering from malignancy or chronic disease (cardiac disease, diabetes mellitus, osteoporosis, and SLE).

Location and time of research

The research was conducted at Prof I.G.N.G Ngoerah Hospital from January to August 2023.

Data source determination
Population

The target population in this study were all paramedics that have been menopause, examined by MRS. The affordable population was paramedics that still actively working at Prof I.G.N.G Ngoerah Hospital.

Sample

The sample in this study was measured by using the formula for determining the sample size to test the hypothesis for two population proportions, using the formula by Sopiyudin M.[10] The required sample size from this calculation method for the nominal data scale. In looking at the relationship between at least 50% who are anxious and depressed in menopause in previous studies, with a power of 90%, a minimum sample of 41 multiplied by two is obtained 82.

Research procedure
Method and Data Collection Technique

The research begins by distributing the consent to take part in the research to the women paramedics. Then doing MRS screening to make sure the sample is already menopause and HADS screening is to divide the sample into anxiety group and depression group. The buccal salivary swab was taken at 07.00-10.00 in the morning, before gargling/toothpaste and fasting an hour before it was taken; the buccal salivary swab should avoid food residue, blood, pus, or other dyes. The salivary specimen will be examined in the clinical pathology laboratory using a

competitive immunoenzymatic color metric method for the quantitative measurement of 17 beta-estradiol using enzyme-linked immunosorbent assay (ELISA) method (BT LAB ELISA kit Human 17 beta Estradiol saliva).

Outcomes Measure

The primary outcome measure was the relationship of 17β estradiol salivary level with anxiety and depression. Secondary outcomes included the characteristics and relationship of 17β estradiol salivary level and anxiety and depression with age, workplace, BMI, marital status, and length of menopause (McKay et al., 2006; Cassano & Fava, 2002).

Statistical Analysis

Descriptive statistical analysis aims to describe the characteristics of the subject and research variables. Different proportions analysis using the chi-square test was used to compare anxiety and depression disorder, based on level 17β estradiol. Regression Logistic analysis was used to assess the association between anxiety and depression based on salivary levels, and an adjusted odds ratio was used after controlling the confounding factors. The CI was 95% and P α = 0,05. All statistical analysis was done with SPSS 26 version (Mitchell et al., 2010; Bryant et al., 2012).

Results

Background characteristics of research subjects

A total of 85 paramedics were assessed in this research (Figure 1), from the HADS examination the samples were divided into anxiety, depression, anxiety, and depression groups. There are 64 depressed, 21 not depressed and 62 anxious, and 23 not anxious. Only depression 3 samples, only anxiety 1 sample, not anxiety and not depression 20 samples (Figure 2)

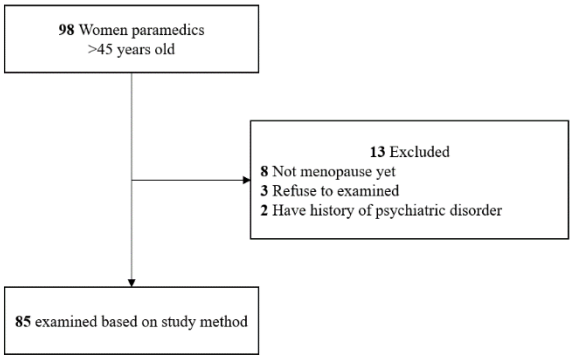

Figure 1. Study Flowchart

The level of 17β estradiol from the saliva was divided into a high level of 17β estradiol (22 samples; 25.9%) and a low level of 17β estradiol (67 samples; 74.1%). The highest level of 17β estradiol is 20.56 pg/dl and the lowest is 8,14 pg/dl.

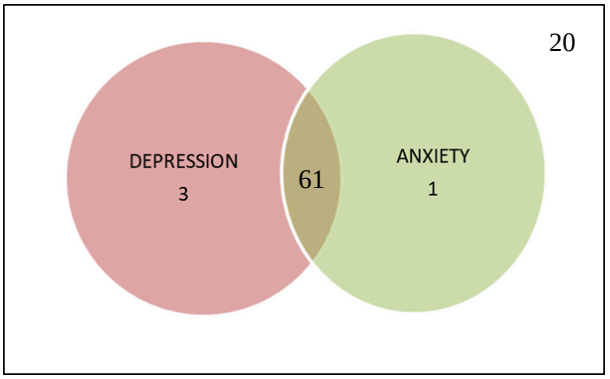

Figure 2. Distribution of anxiety and depression in the sample

Distribution of Anxiety and Depression Based on Subject Characteristics

Statistical analysis was carried out for all the obtained data, such as describing the characteristics of age, length of menopause, workplace, marital status, and body mass index of the study sample compared to anxiety and depression based on the HADS assessment (Table 1).

Table 1
Distribution of Anxiety and Depression Based on Subject Characteristics

Characteristics	Total							
	Anxiety		No anxiety		Depression		No Depression	
	N	%	N	%	N	%	N	%
Age:	25	73.5	9	26.5	25	73.5	9	26.5
45 – 50	37	72.5	14	27.5	39	76.5	12	23.5
>50								
Workplace	25	75.8	8	24.2	24	72.7	9	27.3
In-Patient	37	71.2	15	28.8	40	76.9	12	23.1
Out-patient								
BMI	4	100	0	0	4	100	0	0
Underweight	58	75.3	19	24.7	60	77.9	17	22.1
Normal	0	0	4	100	0	0	4	100
Overweight								
Marital status								
Married	60	73.2	22	26.8	61	74.4	21	25.6
Widow	2	66.7	1	33.3	3	100	0	0
Length of menopause								
< 5 years	25	73.5	9	26.5	24	70.6	10	29.4
> 5 years	37	72.5	14	27.5	40	78	11	21.6
TOTAL:	62	72,9	23	27.1	64	75.3	21	24.7

Distribution of level saliva 17β estradiol Based on Subject Characteristic

Level of 17β estradiol in menopausal women in the range of 10 pg/dl – 20 pg/dl, Researchers divided it into two groups: <15 pg/dl as low level and >15 pg/dl as high level (Table 2).

Table 2
Distribution of level saliva 17β estradiol Based on Subject Characteristic

Characteristics	Total	Level of saliva 17β estradiol			
		High		Low	
		N	%	N	%
Age:					
45 – 50	34 (40%)	10	29.4	24	70.6
>50	51 (60%)	12	23.5	39	76.5
Workplace					
In-Patient	33 (38,8%)	9	27.3	24	72.7
Out-Patient	52 (61.2%)	13	25	39	75
BMI :					
Underweight	4 (4.7%)	0	0	4	100
Normal	77 (90.6%)	18	23.4	59	76.6
Overweight	4 (4.7%)	4	100	0	0
Marital status					
Married					
Widow	82 (96.5%)	21	25.6	61	74.4
	3 (3.5%)	1	33.3	2	66.7
Length of Menopause					
< 5 years	34 (40%)	10	29.4	24	70.6
> 5 years	51 (60%)	12	23.5	39	76.5
TOTAL	85 (100%)	22	25.9	63	74.1

Association Between Level of 17β *Estradiol with Anxiety in Menopause Paramedics*

Data analysis using non-parametric ordinal data, because comparing high and low without looking at the level. So researchers used the Mann-Whitney test (Table 3).

Table 3
Association Between Level of 17β Estradiol with Anxiety in Menopause Paramedics

Variable	Anxiety		PR	CI 95%	p-value
	Yes	No			
Estradiol Saliva:					
Low	61 (96,8%)	2(3,2%)	21,3	3,137	<0.001
High	1 (4,5%)	21(95,5%)		144,634	

Association Between Level of 17β Estradiol with Depression

Data analysis using non-parametric ordinal data, because comparing high and low without looking at the level. So researchers used the Mann-Whitney test (Table 4).

Table 4
Association Between Level of 17β Estradiol with Depression in Menopause Paramedics

Variable	Depression		PR	CI 95%	p-value
	Yes	No			
Estradiol Saliva:					
Low	63(100%)	0 (0%)	22	3,242	<0.001
High	1(4,5%)	21(95,5%)		149,298	

Discussion

Characteristics of Anxiety and Depression Based on Age

The observational study consisted of 85 menopause paramedics at Prof. IGNG Ngoerah Hospital. Anxiety and depression were found mostly in the age of 45-50 years sample with complaints of anxiety at 73.5%, and depression 73.5%. while in sample with age group >50 years with complaints of anxiety 72.5%, depression 76.5%. This finding is also consistent with research by Windarwati et al. (2020), that reported menopausal complaints with depression was at the age of 51-56 years (41.2%), and at the age of <50 years, whereas in previous studies it was found that most experienced anxiety complaints (25.0%) (Windarwati et al., 2020). Menopause based on age, appears when women at age 45-65 years old. The first complaint felt is a vasomotor complaint. The severity of complaints varies for each woman. Vasomotor complaints appear in the form of hot flushes that are felt from the chest to the neck and head. The skin in these areas looks reddish. Immediately after the onset of hot flushes, the area affected by hot flushes is uncomfortable and accompanied by profuse sweating, this makes anxiety complaints increase at the beginning of menopause (Indrias & Maliya, 2015; Windarwati et al., 2020; Goodman et al., 2011).

Characteristics of Anxiety and Depression Based on Workplace

Anxiety appears more in the in-patient department (75.8% *vs* 71.2%) and depression in the out-patient department (76.9% *vs* 72.7%). Complaints of anxiety and depression may correlate with a load of work and daily routine activity, where the workload is heavier dealing with various patient cases in paramedics who are at in-patient and the same daily routine activity does not occur, so the more visible is anxiety, but compared to paramedics in outpatient care the workload is lighter with case-control patients lighter, with a mild level of emergency, and the same daily routine, so that outpatient paramedics tend to look more depressed than anxious (Ruotsalainen et al., 2014).

Characteristics of Anxiety and Depression Based on BMI

BMI is divided into three groups: underweight, normal and overweight. In the underweight sample, 100% of them complain about anxiety and depression; All sample in the group of overweight didn't complaint about anxiety and depression. This finding is also consistent with Emaus et al. (2008), that most of the conversion of androgens to estrogens occurs in adipose tissue, so it is often assumed that overweight women have more circulating estrogens, and will have milder or fewer menopausal complaints. However, there are also certain menopausal complaints, such as vasomotor disturbances, which increase weight in overweight women. Based on the thermoregulatory model, high adiposity is a potent insulator that will inhibit heat loss and increase vasomotor symptoms, reducing symptoms of anxiety and depression (Emaus et al., 2008).

Characteristics of Anxiety and Depression Based on Marital Status

Depression appears more in the widow than married (100% *vs* 74.4%) and anxiety appears more in the married than widow (73.2% *vs* 66.7%). Several researchers found that women with widow status have a higher risk to have depression than those married. When compared with anxiety complaints, women that still married tend to have anxiety in the menopause period. This may be caused by loss of social support or close interpersonal relationships, change in economic status, and also the obligations of women in terms of sexual relationship (Jafari et al., 2014).

Characteristics of Anxiety and Depression Based on Length of Menopause

At the beginning of menopause (perimenopause) there are more anxiety complaints (73.5% *vs* 72.5%) and at the end of menopause (postmenopause) there are more depression complaints (78.4% *vs* 70.6%). Complaints in menopause will peak around 1-2 years after menopause, at which time irregular ovarian function occurs and decreased estrogen levels. In 70% of women will experience vasomotor disturbances in one to two years after menopause and after 5 years only 25% remain, that's what makes at the beginning of menopause (perimenopause) experience more anxiety while at the end of menopause (postmenopause) more depression (Fischl, 2001).

Characteristic of 17β Estradiol Salivary Level
Characteristic of 17β Estradiol Salivary Level based on Age

Based on age, in this study, the group with low 17β estradiol salivary levels was mostly from the group >50 years old (76.5%) compared to the sample age group of 45-50 years (70.6%). Then, with high 17β estradiol salivary levels relative to marital status, the group with high 17β estradiol salivary levels mostly came from the 45-50 year-old sample group (29.4%) compared to those from the group >50 years old (23.5%). Entering the perimenopausal period, the activity of the follicles in the ovaries begins to decrease. When the ovaries do not produce ovum and stop producing estradiol, the pituitary gland tries to stimulate the ovaries to produce estrogen, increasing FSH production. There is a 10-20 fold increase in FSH levels and a threefold increase in LH levels, which reaches a maximum level 1-3 years after menopause, the estradiol level at the beginning of menopause is still at 20 pg/dl and then continues to decrease due to degenerative processes and continues to stabilize in levels of 10 pg/dl (Metintas et al., 2010).

Characteristic of 17β Estradiol Salivary Level based on Workplace

The group with low 17β estradiol salivary levels was the outpatient group (75%) compared to the inpatient group (72.7%). Then, with high 17β estradiol salivary levels, the largest group came from the inpatient group (27.3%) compared to those from outpatient care (25%). In women who work in outpatient care, the tendency is the same, so estradiol in outpatient care tends to be stable, whereas, in women who work in inpatient care, the possibility is unstable because it tends to be higher (Ruotsalainen et al., 2014).

Characteristic of 17β Estradiol Salivary Level based on BMI

The underweight group has a low 17β estradiol salivary level and the overweight group has high 17β estradiol salivary level. Estradiol levels in postmenopausal women are lower than in women of reproductive age and the early phase of menopause. In postmenopausal women, estradiol and estrone are derived from the conversion of adrenal androgens in the liver, kidney, brain, adrenal glands, and adipose tissue. Aromatization processes that occur in the periphery are associated with female body weight. Obese women have higher levels of estrogen than thin women because of increased peripheral aromatization. Circulating estradiol levels after menopause are about 10-20 pg/ml, most of which come from the peripheral conversion of estrone, which in turn comes mainly from the peripheral conversion of androstenedione (Agha-Hosseini et al., 2009; Lee et al., 2020).

Characteristic of 17β Estradiol Salivary Level based on Marital Status

The married group has a low 17β estradiol salivary level and the widow group has high 17β estradiol salivary level. Other studies have shown women who are married, have a higher risk of experiencing stress compared to women who are widows, women who are still married are more likely to experience problems during menopause, so that severe stress causes estradiol to decrease in the systemic circulation and saliva. This may be caused by the loss of social support or close interpersonal relationships, changes in economic status, and also the obligations of women in terms of sexual relations (Jafari et al., 2014).

Characteristic of 17β Estradiol Salivary Level based on Length of Menopause

At the beginning of menopause (perimenopause) 17β estradiol salivary levels are high and at the end of menopause (postmenopause) the salivary 17β estradiol levels are low. Entering the perimenopausal period, the activity of the follicles in the ovaries begins to decrease. When the ovaries do not produce ovum and stop producing estradiol, the

pituitary gland tries to stimulate the ovaries to produce estrogen, increasing FSH production. There is a 10-20 fold increase in FSH levels and a threefold increase in LH levels, which reaches a maximum level 1-3 years after menopause, the estradiol level at the beginning of menopause is still at 20 pg/dl and then continues to decrease due to degenerative processes and continues to stabilize in levels of 10 pg/dl,[17] Changes in the ovarian vascular system as a result of the aging process and the occurrence of sclerosis in the ovarian vascular system are thought to be the cause of ovarian vascular disorders. The aging process and decreased ovarian function cause the ovaries to be unable to respond to pituitary stimulation to produce steroid hormones (Baziad, 2008).

Relationship of 17β Estradiol Salivary Level with Anxiety and Depression
Relationship of 17β Estradiol Salivary Level with Anxiety

Table 3 shows low salivary 17β estradiol levels in the sample group with the most anxiety complaints, (61 samples; 96.8%), while 17β estradiol salivary levels were low in the group without anxiety complaints, (2 samples; 3.2%). It can also be seen that the salivary 17β estradiol level is high in the sample group without anxiety complaints, (21 samples;95.5%), while the 17β estradiol salivary level is high in the sample group with anxiety complaints, (1 sample;4.5%). Based on the statistical analysis there's a positive correlation between 17β Estradiol Salivary Level with Anxiety (PR: 21.2; CI 95%: upper 144.643 and lower 3.137; p<0.001).

Relationship of 17β Estradiol Salivary Level with Anxiety

Table 4 shows low salivary 17β estradiol levels in the sample group with the most depression complaints, (63 samples; 100%), while 17β estradiol salivary levels were low in the group without depression complaints, (0 samples; 0%). It can also be seen that the salivary 17β estradiol level is high in the sample group without depression complaints, (21 samples;95.5%), while the 17β estradiol salivary level is high in the sample group with depression complaints, (1 sample;4.5%). Based on the statistical analysis there's a positive correlation between 17β Estradiol Salivary Level with Depression (PR: 22; CI 95%: upper 142.298 and lower 3.242; p<0.001) (Azcoitia et al., 2011; Bimonte & Denenberg, 1999).

A study by Hosseini *et al.* found that there was a significant difference in the concentration of salivary 17β estradiol levels between groups. The salivary concentration of 17β Estradiol (pg/ml-1) was lower in the case group (17.60 ± 1.54) than in the control group (21.64 ± 1.12, P=0.036). Individuals in the case group also showed lower 17β Estradiol (pg/ml-1) (5.98 ± 0.67) compared to individuals in the control group (8.56 ± 0.95, P=0.031). The results of this study illustrate that sex steroid hormones appear to have an important role in the physiology of the human oral cavity. It appears that the soft tissues of the mouth are sensitive to changes in female blood levels of sex steroid hormones. The decrease in estrogen levels during menopause is thought to affect the maturation process of the oral epithelium, causing the epithelium to become atrophic and thin. Then the decrease in female sex hormones indicates a role in the maintenance of oral tissue. Previous studies have shown that estradiol is the predominant estrogen receptor subtype in the human oral epithelium and salivary glands. Estrogen can directly regulate the physiology of oral tissues by binding to the estradiol subtype (17β Estradiol) (Kushner et al., 2000; Cauley, 2015).

This study aimed to evaluate whether salivary 17β Estradiol is correlated with anxiety and depression. The literature states that when a woman has entered menopause, the function of the ovaries to produce the hormone estrogen will decrease. Other complaints that will arise besides vasomotor complaints are also psychological in the form of feelings of fear, anxiety, anxiety, irritability, irritability, difficulty concentrating, changes in behavior, depression, and disturbances of libido.[3] In the urogenital system, complaints of painful intercourse, vaginal dryness, vaginal discharge, and infection appear. The skin becomes dry and thin, itches, and wrinkles. Complaints of discomfort appear in the oral cavity, in the form of persistent dry mouth and a feeling of burning or heat. In the long term, the impact of estrogen deficiency is the increased incidence of osteoporosis, dementia, coronary heart disease, stroke, and colon cancer (Speroff, 1983).

Conclusion

The findings suggest that anxiety appears more in the groups of age 45-50 years old, in-patient department, underweight and married status, and have a length of menopause <5 years. Depression appears more in the groups of age >50 years old, out-patient department, underweight, widow status, and length of menopause >5 years. Low levels of 17- β estradiol were found in the groups of age >50 years old, out-patient department, underweight, married status, and length of menopause >5 years. Taken together anxiety and depression have a relationship with the

Salivary levels of 17- β estradiol. Its levels become decreased in patients with anxiety and depression versus the control group.

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