

# Serum Follicle Stimulating Hormone and Estradiol in Peri/Postmenopausal Women attending Siriraj Menopause Clinic: A Retrospective Study

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**Objectives:** To determine serum levels of Follicle Stimulating Hormone (FSH) and Estradiol ( $E_2$ ) in peri/postmenopausal women attending the menopause clinic.

**Study design:** Retrospective descriptive study.

**Setting:** Siriraj Menopause Clinic, Gynecologic Endocrinology Unit, Division of Reproductive Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital.

**Study population:** Peri/postmenopausal women attending Siriraj Menopause Clinic from January 1994 to December 2003.

**Material and Method:** Medical records of women who had a blood test for FSH and/or  $E_2$  prior to hormonal therapy were reviewed.

**Results:** During a 10 year period, there were 116 eligible patients who could be classified into perimenopausal (31 cases), natural postmenopausal (43 cases), and surgical postmenopausal (32 cases) groups. Age at registration of perimenopausal (47.87 ± 4.38 yr) and surgical postmenopausal (48.06 ± 6.49 yr) groups were younger than that of the natural postmenopausal group (55.74 ± 6.80 yr). The perimenopausal group, who still had regular menstruation, was the youngest. The average FSH level of 60.46 ± 33.15 mIU/mL was not different among groups. The estradiol level of perimenopausal (79.05 ± 83.62 pg/mL) and surgical postmenopausal (63.05 ± 136.39 pg/mL) groups were significantly higher than that of natural postmenopausal (25.05 ± 37.663 pg/mL) group ( $p = 0.001$ ). Serum level of FSH or  $E_2$  was not correlated with age or years since menopause. There was significant but minimal negative correlation between serum levels of FSH and  $E_2$ .

**Conclusion:** Serum FSH and/or  $E_2$  levels are not accurate enough by themselves to rule in or rule out perimenopause. The authors suggested that clinicians should diagnose perimenopause based on menstrual history and age, without relying on laboratory testing.

**Keywords:** Serum FSH, Serum estradiol, Perimenopause, Postmenopause

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Perimenopause is a time of transition for women at midlife. The perimenopausal transition is the period of time between the reproductive years and the

menopause, marked by irregularity of menstrual cycles. Women curiously want to know whether they are already in this period, whereas physicians want to know the accuracy of clinical data for identifying perimenopausal women. When women are in their 40s, anovulation becomes more prevalent, and prior to anovulation, menstrual length increases, beginning 2 to 8 years before menopause<sup>(1)</sup>. In one longitudinal

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study, when cycle length exceeded 42 days, menopause predictably followed within 1 or 2 years<sup>(2)</sup>. The duration of the follicular phase is the major determinant of cycle length<sup>(3,4)</sup>. This menstrual cycle change prior to menopause is marked by an elevation of Follicle Stimulating Hormone (FSH) level and a decrease in inhibin level, but a normal level of Luteinizing Hormone (LH) and a slightly elevated level of Estradiol (E<sub>2</sub>)<sup>(5-10)</sup>. During this period, E<sub>2</sub> level remains in the normal range, even slightly elevated, until approximately 1 year before the cessation of follicular growth and development<sup>(3)</sup>. In fact, women in their perimenopausal transition have a higher overall estrogen level than they have during reproductive period. This finding can be logically explained by an increased ovarian follicular response to the increase in FSH secretion during these years<sup>(11)</sup>. In the past, it was assumed that the finding reflected the impairment of ovarian estrogen production, but nowadays it is accepted that the increase in FSH correlates only with a decrease in inhibin-B<sup>(12)</sup>.

Although the changes in reproductive hormones are markers of reproductive aging, hormonal blood tests to confirm the menopausal status are not recommended because of a wide variation in the hormonal level, especially during the perimenopausal period. However, in clinical practice, the serum FSH and E<sub>2</sub> levels are still being tested in the peri/postmenopausal women. The objectives of this study were to determine serum levels of FSH and E<sub>2</sub> in peri/postmenopausal women attending Siriraj menopause clinic and to determine the usefulness of hormonal tests in correlation with clinical presentations of the patients.

### Material and Method

This observational study took place in Siriraj Menopause clinic, Gynecologic Endocrinology Unit, Division of Reproductive Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. Medical records of pre/postmenopausal women who attended Siriraj Menopause Clinic from January 1994 to December 2003 and who had blood tests for FSH and/or E<sub>2</sub> prior to hormone therapy, were reviewed. The data included menstrual patterns, age at registration, age at menopause, reasons for attending the clinic and the levels of FSH and E<sub>2</sub> were analysed.

The hormonal assays were performed by the Department of Clinical Pathology. Serum FSH level was determined by two-site sandwich immunoassay using direct chemiluminometric technique. The lower limit of detection was 0.3 mIU/mL with an inter- and an intra-

assay coefficients of variation of 5% and 5.2%, respectively. Serum E<sub>2</sub> level was determined by competitive immunoassay using direct chemiluminometric technique. The lower limit of detection was 1 pg/mL with an inter- and an intra-assay coefficients of variation of 5%. In the perimenopausal group, blood test was obtained randomly because there were 3 menstrual patterns that made it difficult to specify the day of menstrual cycle.

### Statistical analysis

Descriptive statistics were used to describe the data. Values were expressed in mean  $\pm$  Standard Deviation (SD) or number (%). Unpaired t-test (or Mann-Whitney U test) was used to compare continuous data between 2 study groups. Chi-square test and ANOVA (or Kruskal Wallis H test) were used to compare among groups in the categorical and the continuous data, respectively. A linear regression analysis was used to test the coefficient of determination between age and hormonal levels, and between FSH and E<sub>2</sub> levels. A p-value of < 0.05 was considered statistically significant.

### Results

From January 1<sup>st</sup>, 1994 to December 31<sup>st</sup>, 2003, 2,979 patients registered at the Siriraj Menopause Clinic. One hundred and sixteen patients had blood tests for serum FSH and/or E<sub>2</sub> before or at the time of registration. There were 10 cases excluded, 5 cases of natural postmenopausal women post hysterectomy, 4 cases of surgical postmenopausal women taking hormonal replacement therapy before the blood test, and 1 case of unknown menopausal status. One hundred and six cases were included in the analysis.

The patients were classified into perimenopausal (31 cases), natural postmenopausal (43 cases) and surgical postmenopausal (32 cases) group. In the perimenopausal group, the menstrual pattern was classified into regular cycle, irregular cycle and amenorrhea. The menstrual pattern and timings in climacteric period are shown in Table 1. At registration, the perimenopausal and surgical postmenopausal groups were younger than the natural postmenopausal group. The perimenopausal group who still had regular menstruation was the youngest.

Fig. 1 shows the prevalence of reasons for attending the menopause clinic, classified by menstrual pattern. The prevalence of menopausal symptoms was highest in the perimenopausal group compared to other groups ( $p = 0.002$ , Chi-square test).

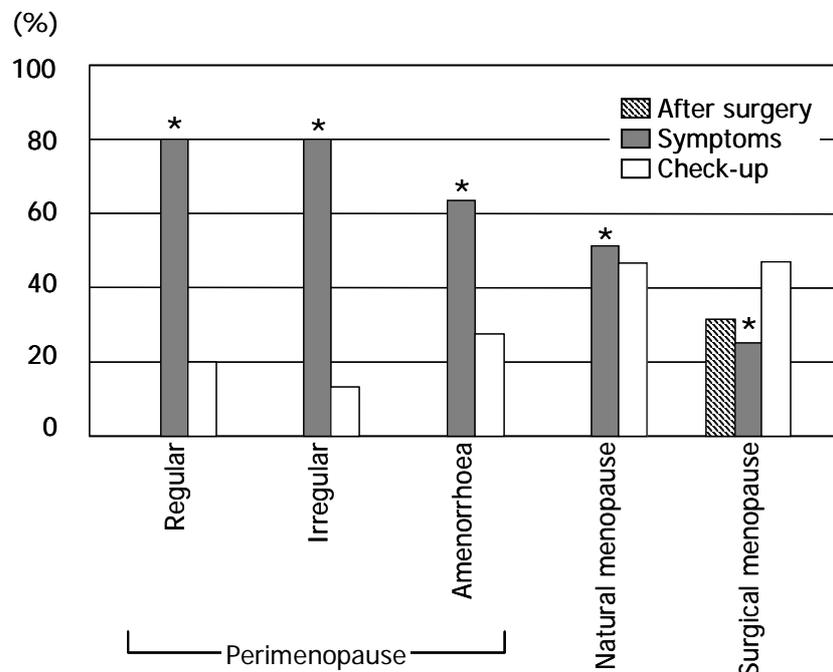
The serum FSH and E<sub>2</sub> in women with different menstrual patterns are presented in Fig. 2. The average

FSH level was  $60.46 \pm 33.15$  mIU/mL. The FSH levels were not statistically different among groups ( $p = 0.566$ , ANOVA). In the perimenopausal group, the mean FSH level of  $69.5 \pm 33.5$  mIU/mL in amenorrhic women was higher than the  $46.3 \pm 59.8$  mIU/mL in the regular cycle and the  $49.3 \pm 30.86$  mIU/mL in the irregular cycle

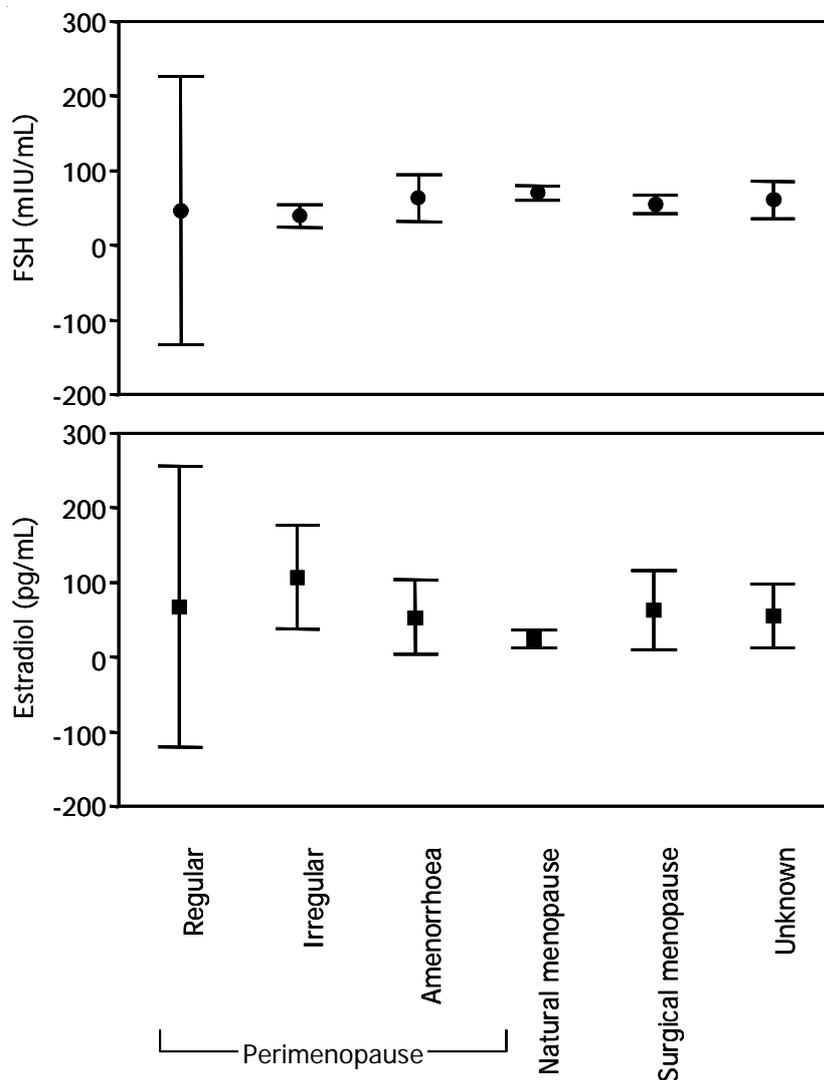
**Table 1.** Menstrual pattern and timings in climacteric period (n = 106)

	Menstrual pattern	Age		p <sup>(a)</sup>
		n	Mean $\pm$ SD	
Age at registration (yr)	Regular cycle	5	43.40 $\pm$ 4.83	0.000
	Irregular cycle	15	48.60 $\pm$ 2.69	
	Amenorrhoea	11	49.27 $\pm$ 5.06	
	Menopause	43	55.74 $\pm$ 7.98	
	Surgical menopause	32	48.06 $\pm$ 6.49	
Age at menopause (yr)	Regular cycle	NA	NA	0.000
	Irregular cycle	NA	NA	
	Amenorrhoea	NA	NA	
	Menopause	43	47.53 $\pm$ 5.27	
	Surgical menopause	32	42.47 $\pm$ 6.29	
Years since menopause (yr)	Regular cycle	NA	NA	0.064
	Irregular cycle	NA	NA	
	Amenorrhoea	NA	NA	
	Menopause	43	8.21 $\pm$ 6.55	
	Surgical menopause	32	5.59 $\pm$ 5.03	

Note <sup>(a)</sup> = One way ANOVA; NA = not applicable



**Fig. 1** Prevalence of reasons for attending menopause clinic, classified by menstrual pattern at registration (\* prevalence of menopausal symptoms in perimenopausal group is higher than other groups,  $p = 0.002$ , Chi-square test)



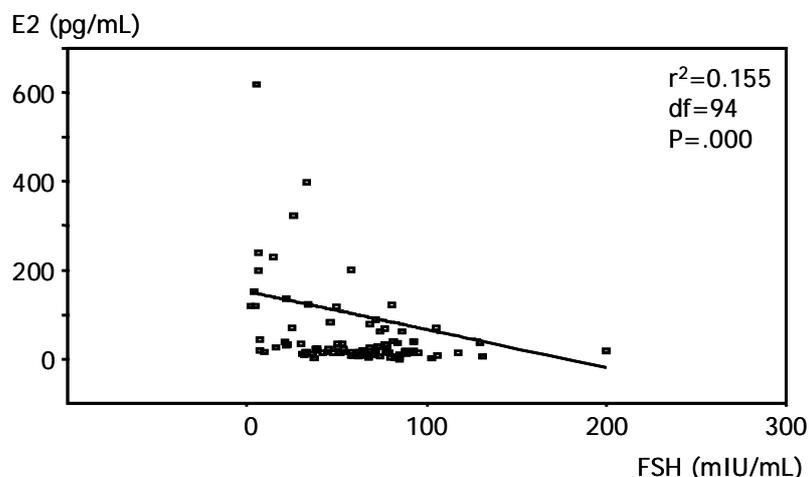
**Fig. 2** Reproductive hormones in middle age women with different menstrual pattern (FSH = follicle stimulating hormone)

groups. The differences were not statistically significant ( $p = 0.474$ , Kruskal Wallis H test).

The  $E_2$  levels of perimenopausal, surgical postmenopausal, and natural postmenopausal groups were  $79.05 \pm 83.62$  pg/mL,  $63.05 \pm 136.39$  pg/mL, and  $25.05 \pm 37.663$  pg/mL, respectively. The  $E_2$  level of the perimenopausal and surgical postmenopausal groups were significantly higher than that of the natural postmenopausal group ( $p = 0.001$ , ANOVA). In the perimenopausal group, the mean  $E_2$  level was highest in the women who had irregular cycles ( $95.04 \pm 98.55$  pg/mL) and lowest in those who had amenorrhoea ( $18.78 \pm 5.44$  pg/mL) but the differences were not

statistically significant ( $p = 0.22$ , Kruskal Wallis H test).

Serum level of FSH or  $E_2$  was not correlated with age at menopause or Years Since Menopause (YSM). There was a statistically significantly negative correlation between FSH or  $E_2$  levels with other parameters in the climacteric period (Fig. 3). However, there was no correlation between FSH or  $E_2$  levels with other parameters in either the perimenopausal, the natural postmenopausal, or the surgical postmenopausal groups (Table 3). In addition, there was no difference in the FSH or  $E_2$  level between women with or without menopausal symptoms (Table 2).



**Fig. 3** Correlation between FSH and E<sub>2</sub> in climacteric period (FSH = follicle stimulating hormone, E<sub>2</sub> = estradiol)

**Table 2.** Serum follicle stimulating hormone (FSH) and estradiol (E<sub>2</sub>) levels in pre/postmenopausal women with or without menopausal symptoms

Hormone levels	Menopausal symptoms				p <sup>(a)</sup>
	Presence		Absence		
	N	Mean ± SD	N	Mean ± SD	
FSH (mIU/mL)	58	61.91 ± 35.06	57	58.73 ± 29.60	0.601
Estradiol (pg/mL)	47	53.33 ± 80.62	53	48.48 ± 95.35	0.786

Note <sup>(a)</sup> unpaired t-test

**Table 3.** Coefficient of determination (r<sup>2</sup>) between serum follicle stimulating hormone (FSH) or estradiol (E<sub>2</sub>) and age or year since menopause (YSM) (n = 106)

	r <sup>2</sup>	df	p <sup>(a)</sup>
Perimenopausal group			
FSH vs Age	0.019	30	0.456
E <sub>2</sub> vs Age	0.000	22	0.941
Natural postmenopausal group			
FSH vs Age	0.055	41	0.130
FSH vs YSM	0.005	41	0.665
E <sub>2</sub> vs Age	0.053	38	0.152
E <sub>2</sub> vs YSM	0.088	38	0.064
Surgical postmenopausal			
FSH vs Age	0.037	30	0.290
FSH vs YSM	0.031	30	0.337
E <sub>2</sub> vs Age	0.137	26	0.053
E <sub>2</sub> vs YSM	0.034	26	0.345

Note <sup>(a)</sup> Linear regression analysis

## Discussion

The age of menopause can be determined using the definition of the WHO but the age of pre/perimenopause cannot be clearly defined. In the longitudinal Massachusetts Women's Health Study<sup>(13)</sup>, women who reported the onset of menstrual irregularity were considered to be in their perimenopausal period. The median age for the onset of this transition was 47.5 years. Only 10% of women abruptly stop menstruation without a period of prolonged irregularity menstrual periods. The perimenopausal transition from reproductive to postreproductive status was, for most women, approximately 4 years in duration. In a cross-sectional study by Treloar<sup>(14)</sup>, the average age for entry into the perimenopausal transition was 45.1, and the age range that included 95% of women was 39-51. In that study, the mean duration of the perimenopausal transition was 5 years, with a range of 2 to 8 years. In the present study, the age of the perimenopausal group was within the age range reported in other

literature<sup>(1,13,14)</sup>. Almost 50% of the perimenopausal women had irregular cycles, and only 16% (5 of 31) of the women in this group still had regular menstrual cycles.

The prevalence of menopausal symptoms varies from studies to studies but it is consistent that the prevalence is high during menopausal transition and declined with time after menopause. In a large longitudinal study, 10% of women experienced hot flashes before menopause, while in other studies as many as 15-25% of premenopausal women reported hot flashes<sup>(13,15-17)</sup>. A large American cross-sectional survey reported that 49% of early postmenopausal women and 57% of perimenopausal women experienced significant hot flashes<sup>(18)</sup>. In a community based Australian survey, 6% of premenopausal women, 26% of perimenopausal women, and 59% of postmenopausal women complained of hot flashes<sup>(19)</sup>. In the present hospital based study, the prevalence of menopausal symptoms in the perimenopausal women was higher than those reported in the community based studies; whereas the prevalence of the symptoms in the natural postmenopausal group was similar to other reports. Women in the surgical postmenopausal group should have more menopausal symptoms since the estrogen level declined abruptly. However, in the present study the surgical menopausal group had fewer symptoms than the perimenopausal group. This finding could be explained by the duration since surgery, which was almost 6 years before the patient registered to the clinic. The longer the time since menopause, the fewer the symptoms would be present<sup>(13)</sup>.

The levels of FSH were not different among groups with different menopausal status. The mean FSH levels in each group were higher than 40 mIU/mL; therefore the FSH level could not be used to differentiate between the perimenopausal transition and postmenopausal status. The levels of E<sub>2</sub> in the perimenopausal and the surgical postmenopausal groups were significantly higher than that of the natural postmenopausal group. Actually the E<sub>2</sub> level in surgical and natural postmenopausal groups should be similar<sup>(20)</sup>. However, most of circulating estradiol after menopause was derived from the peripheral conversion of estrone, which in turn was mainly derived from the peripheral conversion of androstenedione. Therefore, increasing body weight results in increasing production of estrogen from androstenedione<sup>(21-23)</sup>. One possible factor that may explain the finding in the present study was the difference in body weight. The perimenopausal women had normal to slightly elevated E<sub>2</sub> level, except

for those with amenorrhoea who had the FSH and E<sub>2</sub> levels within the postmenopausal range. The result was similar to other reports<sup>(12,24)</sup> and indicated that the follicular growth and development cease even though the timing does not reach the definition of menopause.

The levels of FSH and E<sub>2</sub> in women with or without menopausal symptoms were not different. In addition, hot flashes could occur in a number of premenopausal women<sup>(13,15-17,19)</sup>. Thus, menopausal symptoms combined with the serum levels of FSH and/or E<sub>2</sub> could not be used to rule in or rule out the perimenopausal transition. This finding was consistent with the conclusion of a study by Bastian<sup>(25)</sup>. Bastian LA. et al performed a systematic review of the accuracy of self-assessment, symptoms, signs, and laboratory tests in diagnosing women in perimenopause. They found that the self assessment of going through the transition, e.g. symptoms of hot flashes, night sweating, vaginal dryness, high FSH levels, and low inhibin B levels yielded the greatest positive likelihood ratios. However, a single symptom or test is not accurate enough by itself to rule in or rule out perimenopause. The authors agree with their conclusion. However, from the present result, if the FSH is in the menopausal range and the E<sub>2</sub> levels are still in the normal range or slightly elevated, perimenopause can be diagnosed (except for the surgical postmenopausal women). It is important to note that the level of E<sub>2</sub> can be affected by certain factors including peripheral conversion of androstenedione, ethnic variation, host factors such as body size and smoking behavior<sup>(26-28)</sup>.

In conclusion, serum FSH and/or E<sub>2</sub> levels are not accurate enough to differentiate between perimenopause and postmenopause. The authors suggest that clinicians should diagnose perimenopause based on menstrual history and age without relying on laboratory test results.

#### Acknowledgement

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ระดับ follicle stimulating hormone และ estradiol ในซีรัมของสตรีก่อนและหลังวัยหมดระดูที่มารับ  
การตรวจในคลินิกวัยทอง โรงพยาบาลศิริราช: การศึกษาย้อนหลัง

สุรศักดิ์ อังสุวรรณ, ประสงค์ ตันมหาสมุทร, มณี รัตนไชยานนท์, จงดี แดงรัตน์, กิติรัตน์ เตชะไตรศักดิ์,  
สุชาดา อินทวิวัฒน์, พิชัย ลีระศิริ

**วัตถุประสงค์:** เพื่อศึกษาระดับ follicle stimulating hormone (FSH) และ estradiol ( $E_2$ ) ในซีรัมของสตรีก่อนและ  
หลังวัยหมดระดูที่มารับการตรวจในคลินิกวัยทอง

**ลักษณะการศึกษา:** การศึกษาแบบพรรณนาย้อนหลัง

**สถานที่ทำการศึกษา:** คลินิกวัยทอง หน่วยต่อมไร้ท่อทางนรีเวช สาขาวิชาเวชศาสตร์การเจริญพันธุ์ ภาควิชาสูติศาสตร์  
นรีเวชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

**กลุ่มประชากรที่ทำการศึกษา:** สตรีก่อนและหลังวัยหมดระดูที่ลงทะเบียนในคลินิกวัยทองระหว่างเดือน มกราคม  
พ.ศ. 2537 ถึง เดือนธันวาคม พ.ศ. 2546

**วัสดุและวิธีการ:** ทบทวนเวชระเบียนของสตรีที่ได้รับการตรวจวัดระดับฮอร์โมน FSH และ  $E_2$  ในซีรัมก่อนได้รับ  
ฮอร์โมนทดแทน

**ผลการศึกษา:** ในช่วงระยะเวลา 10 ปี มีผู้ป่วย 116 ราย แบ่งเป็นกลุ่มสตรีวัยใกล้หมดระดู 31 ราย สตรีวัยหมดระดู  
ตามธรรมชาติ 43 ราย และสตรีวัยหมดระดูจากการผ่าตัด 32 ราย อายุของผู้ป่วยเมื่อมาเข้าคลินิกของกลุ่มสตรีวัย  
ใกล้หมดระดู ( $47.87 \pm 4.38$  ปี) และสตรีวัยหมดระดูจากการผ่าตัด ( $48.06 \pm 6.49$  ปี) น้อยกว่ากลุ่มสตรีวัยหมดระดู  
ตามธรรมชาติ ( $55.74 \pm 6.80$  ปี) สตรีวัยใกล้หมดระดูที่ยังมีระดับฮอร์โมน FSH สูงกว่ากลุ่มที่มีอายุน้อยที่สุด ค่าเฉลี่ยของ  
ระดับฮอร์โมน FSH คือ  $60.46 \pm 33.15$  มิลลิยูนิตต่อมิลลิลิตร ค่าเฉลี่ยของระดับฮอร์โมน FSH ไม่มีความแตกต่างกัน  
ในแต่ละกลุ่ม ระดับฮอร์โมน estradiol ในกลุ่มสตรีวัยใกล้หมดระดู ( $79.05 \pm 83.62$  พิโคกรัมต่อมิลลิลิตร) และสตรี  
วัยหมดระดูจากการผ่าตัด ( $63.05 \pm 136.39$  พิโคกรัมต่อมิลลิลิตร) สูงกว่ากลุ่มสตรีวัยหมดระดูตามธรรมชาติ ( $25.05$   
 $\pm 37.66$  พิโคกรัมต่อมิลลิลิตร) อย่างมีนัยสำคัญทางสถิติ ( $p = 0.001$ ) ระดับฮอร์โมน FSH และ  $E_2$  ไม่สัมพันธ์กับอายุ  
หรือ จำนวนปีตั้งแต่วัยหมดระดู พบมีความสัมพันธ์ทางลบในระดับเล็กน้อยแต่มีนัยสำคัญทางสถิติ ระหว่างระดับฮอร์โมน  
FSH และ  $E_2$

**สรุป:** ระดับฮอร์โมน FSH และ/หรือ  $E_2$  ในซีรัมไม่มีความแม่นยำพอในการวินิจฉัยภาวะสตรีวัยใกล้หมดระดู แพทย์  
ควรวินิจฉัยภาวะนี้โดยอาศัยประวัติระดูและอายุ โดยไม่ต้องใช้ผลการตรวจทางห้องปฏิบัติการ

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